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REVIEW

Precision medicine in sepsis and septic shock: From omics to clinical tools

Juan Carlos Ruiz-Rodriguez, Erika P Plata-Menchaca, Luis Chiscano-Camón, Adolfo Ruiz-Sanmartin, Marcos Pérez-Carrasco, Clara Palmada, Vicent Ribas, Mónica Martínez-Gallo, Manuel Hernández-González, Juan J Gonzalez-Lopez, Nieves Larrosa, Ricard Ferrer

ORCID number: Juan Carlos Ruiz-Rodriguez 0000-0001-7392-8617; Erika P Plata-Menchaca 0000-0002-9050-2658; Luis Chiscano-Camón 0000-0003-0037-0610; Adolfo Ruiz-Sanmartin 0000-0001-5587-5419; Marcos Pérez-Carrasco 0000-0001-7086-083X; Clara Palmada 0000-0003-0463-4070; Vicent Ribas 0000-0002-7266-6106; Mónica Martínez-Gallo 0000-0002-7340-2161; Manuel Hernández-González 0000-0002-6932-5853; Juan J Gonzalez-Lopez 0000-0003-2419-5909; Nieves Larrosa 0000-0001-8808-0233; Ricard Ferrer 0000-0002-4859-4747.

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Juan Carlos Ruiz-Rodriguez, Luis Chiscano-Camón, Adolfo Ruiz-Sanmartin, Marcos Pérez-Carrasco, Clara Palmada, Ricard Ferrer, Intensive Care Department, Vall d'Hebron Hospital Universitari, Vall d'Hebron Barcelona Hospital Campus, Barcelona 08035, Spain

Juan Carlos Ruiz-Rodriguez, Erika P Plata-Menchaca, Luis Chiscano-Camón, Adolfo Ruiz-Sanmartin, Marcos Pérez-Carrasco, Ricard Ferrer, Shock, Organ Dysfunction and Resuscitation Research Group, Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Barcelona Hospital Campus, Barcelona 08035, Spain

Juan Carlos Ruiz-Rodriguez, Luis Chiscano-Camón, Adolfo Ruiz-Sanmartin, Ricard Ferrer, Departament de Medicina, Universitat Autònoma de Barcelona, Bellaterra 08193, Spain

Erika P Plata-Menchaca, Department of Intensive Care, Hospital Clínic de Barcelona, Barcelona 08036, Spain

Vicent Ribas, Data Analytics in Medicine, Digital Health Unit, Eurecat, Centre Tecnològic de Catalunya, Barcelona 08005, Spain

Mónica Martínez-Gallo, Manuel Hernández-González, Immunology Division, Vall d'Hebron Hospital Universitari, Vall d'Hebron Barcelona Hospital Campus, Barcelona 08035, Spain

Mónica Martínez-Gallo, Manuel Hernández-González, Diagnostic Immunology Research Group, Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Barcelona Hospital Campus, Barcelona 08035, Spain

Mónica Martínez-Gallo, Manuel Hernández-González, Department of Cell Biology, Physiology and Immunology, Universitat Autònoma de Barcelona, Bellaterra 08193, Spain

Juan J Gonzalez-Lopez, Nieves Larrosa, Department of Clinical Microbiology, Vall d'Hebron Hospital Universitari, Vall d'Hebron Barcelona Hospital Campus, Barcelona 08035, Spain

Juan J Gonzalez-Lopez, Nieves Larrosa, Department of Microbiology and Genetics, Universitat Autònoma de Barcelona, Bellaterra 08193, Spain

Corresponding author: Juan Carlos Ruiz-Rodriguez, MD, PhD, Consultant Physician-Scientist, Intensive Care Department, Vall d'Hebron Hospital Universitari, Vall d'Hebron Barcelona Hospital Campus, 119, Passeig de la Vall d'Hebron, Barcelona 08035, Spain.
jcruiz@vhebron.net

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Abstract

Sepsis is a heterogeneous disease with variable clinical course and several clinical phenotypes. As it is associated with an increased risk of death, patients with this condition are candidates for receipt of a very well-structured and protocolized treatment. All patients should receive the fundamental pillars of sepsis management, which are infection control, initial resuscitation, and multiorgan support. However, specific subgroups of patients may benefit from a personalized approach with interventions targeted towards specific pathophysiological mechanisms. Herein, we will review the framework for identifying subpopulations of patients with sepsis, septic shock, and multiorgan dysfunction who may benefit from specific therapies. Some of these approaches are still in the early stages of research, while others are already in routine use in clinical practice, but together will help in the effective generation and safe implementation of precision medicine in sepsis.

Key Words: Sepsis; Septic shock; Organ dysfunction; Precision medicine; Biomarkers; Phenotype; Endotype

Core Tip: Sepsis is a heterogeneous disease with different clinical courses and several clinical phenotypes. Precision medicine in sepsis allows the identification of specific subgroups of patients who may benefit from a personalized approach with interventions targeted towards specific pathophysiological mechanisms.

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INTRODUCTION

Sepsis requires a structured and protocolized treatment, which have been thoroughly reviewed in the literature[1-3]. The last version of the Surviving Sepsis Campaign (SSC) guidelines was released in 2021[4], and the hour-1 bundle was updated in 2018 [5]. The implementation of the SSC recommendations and bundles[6] is associated with a sustained reduction in the risk of death. Still, mortality from sepsis remains unacceptably high[7].

All patients with sepsis are candidates for receipt of the main pillars of sepsis treatment: Infection control, initial resuscitation, and multiorgan support. However, specific subgroups of patients not responding to conventional therapies may benefit from other therapies, which can be considered therapeutic rescue strategies.

Currently, sepsis is defined as organic dysfunction associated with a dysregulated response of the host to infection[8]. The host response is initiated when bacterial endotoxin or other bacterial structures interacting with the host´s immune system stimulate the production of a cascade of immune mediators that activate and target leukocytes, leading to organ dysfunction.

SEPSIS: A HETEROGENEOUS DISEASE

We have to ask ourselves whether all septic patients' clinical courses are predictable. Does dysregulated host response to infection progress and manifest similarly in all patients? The answer is clear and resounding: No. In sepsis, there is significant heterogeneity between individuals. In a certain way, such heterogeneity is foreseen based on

the existing differences in age, causative microorganisms, types of sepsis foci, and comorbidities. Pathophysiologically, there are also significant differences. The inflammatory response occurs in two distinct stages: The pro-inflammatory and the anti-inflammatory phases. These phases vary among individuals and within the same individual, depending on a particular moment within the clinical course. This could explain the observed heterogeneity in responses to available immunomodulating treatments (*e.g.*, corticosteroids, elimination of cytokines, and anti-cytokine antibodies).

Therefore, patients with a low risk for adverse outcomes are candidates to receive conventional treatments. In contrast, patients with a high risk of clinical deterioration could benefit from specific therapies addressing their particular pathophysiological characteristics. This gives rise to so-called 'precision medicine'. This term comes from oncology and described the adaptation of a treatment to each patient's traits based on the genomic study and the molecular characteristics of tumors.

In this narrative review, we explain the different strategies to create and implement precision medicine for sepsis, with the intent of supporting individualization of patients' management (Figure 1). In the first part of this manuscript, we will review the technologies developed to identify endotypes and phenotypes (omics-based biomarkers, bioinformatics, and biomarkers commonly used in the clinic). In the second part of the manuscript, we will describe the different endotypes with their specific potential treatments (*e.g.*, immunoglobulins, endotoxin- and cytokine-hemadsorption, restoration of immunoparalysis) (Table 1). Omics-based biomarkers research is still in the early stages, while other biomarkers are now available and in use in the clinic.

TECHNOLOGIES DEVELOPED TO IDENTIFY ENDOTYPES AND PHENOTYPES

Omics technologies

Novel technologies have been developed in recent years to detect different evolutionary patterns or other patterns in response to different therapies in sepsis. Omics-based biomarkers and bioinformatics can select various endotypes and phenotypes of sepsis patients indistinguishable from the clinical point of view at the bedside. Therefore, they help in the adaptation of specific therapies to patients according to their individual characteristics[9].

Genomics and epigenomics: Genomics is defined as the study of genes and their functions. The different clinical presentations and prognoses of sepsis patients have already been associated with particular genetic variants. A genetic polymorphism is an allelic variant that exists in an unalterable state in a population, with a frequency (generally > 1%) that cannot be accounted for by new mutations. Various polymorphisms have been described in the genes that encode pro-inflammatory and anti-inflammatory cytokines. This is also true for cytokine receptors, cellular recognition pathways, intracellular signaling pathways, and hemostasis molecules. All these pathways are involved in the severity and risk of mortality in sepsis[10].

Epigenomics studies the additional changes that alter gene expression without changing the DNA sequence. These include DNA methylation, non-coding (nc)RNAs, histone variants, and histone post-translational modifications. Epigenetic modifications can respond to environmental stimuli by activating or inhibiting gene transcription. Lorente-Sorolla *et al*[11] showed that sepsis patients undergoing widespread changes in the methylome of their circulating monocytes had associated aberrant levels of interleukin (IL)-10 (IL-10) and IL-6, and a high occurrence of organ dysfunction. Changes in histone modifications, especially histone acetylation, can lead to abnormal expression of IL-10 mRNA[12]. An ncRNA is a functional RNA molecule transcribed from DNA, though not translated into a protein. ncRNAs regulate gene expression at the transcriptional and post-transcriptional levels. The three major classes of short ncRNAs are known as micro (mi)RNAs, short interfering (si)RNAs, and piwi-interacting (pi)RNAs. Plasma levels of miR-133a are higher in critically ill patients with sepsis than in patients with non-infectious inflammation, and predict intensive care unit (ICU) and long-term mortality[13]. Consequently, epigenetic biomarkers could help detect patients with clinical deterioration and unfavorable evolution[11-14].

Table 1 Clinical applicability of precision medicine strategies

Precision medicine strategy	Target (s)	Clinical application
Genomics and epigenomics	Genetic variants	Prognosis, severity
	Genotypes	Susceptibility to sepsis
Transcriptomics	Gene expression profiles, activity and regulation	Susceptibility to sepsis
	Sepsis response signatures	Severity, prognosis
Metabolomics	Small molecules produced by cells	Prognosis
	Metabolomic profile	Response to treatment
Proteomics	Proteins expressed by the genome under certain conditions	Diagnosis, Prognosis
	Biomarkers	Diagnosis, prognosis
Bioinformatics	Machine learning techniques	Diagnosis
		Prediction of clinical trajectories
		Assessment and treatment of organ dysfunction
		Clinical phenotypes
Biomarkers	Levels of molecules (mostly inflammatory)	Phenotypes
		Antimicrobial stewardship
		Prediction of organ dysfuntion
		Allocation of hospital resources
		Diagnosis
		Severity
Immunoglobulins	Immunoglobulin levels	Detection and treatment of sepsis-associated hypogammaglobulinemia
Endotoxin and hemoadsoption	Endotoxin levels and elimination by hemoadsoption	Rescue therapy
Cytokines and hemoadsoption	Cytokine levels and elimination by hemoadsoption	Rescue therapy
Immunoparalysis	mHLA-DR expression	Immunoparalysis detection
		Immunoadjuvant treatment
		Stratification of patients
		GM-CSF therapy

GM-CSF: Granulocyte-macrophage colony-stimulating factor.

Individualized treatment based on the genetic characteristics of the host has not yet been implemented in clinical practice, even though it is undoubtedly one of the most promising research fields for the future management of patients with sepsis and septic shock.

Transcriptomics: The transcriptome is the set of messenger RNAs and ncRNA molecules in a specific cell or tissue. Transcriptomics is the study of the transcriptome of one particular cell or tissue in a specific circumstance, based on the analysis of gene expression profiles. It aims at monitoring gene activity and regulation. Transcriptomic studies have made possible the characterization of different gene expression profiles in sepsis.

Interindividual transcriptome variation in sepsis has been evaluated in several large cohorts. Maslove *et al*[15] identified two subtypes in septic patients. The subtype 1 gene expression profile is characterized by a significantly increased expression of genes involved in inflammatory and Toll-like receptor (TLR)-mediated signaling pathways. This profile is associated with a higher prevalence of sepsis. Davenport *et al* [16] analyzed peripheral blood leucocyte global gene expression of 265 critically ill

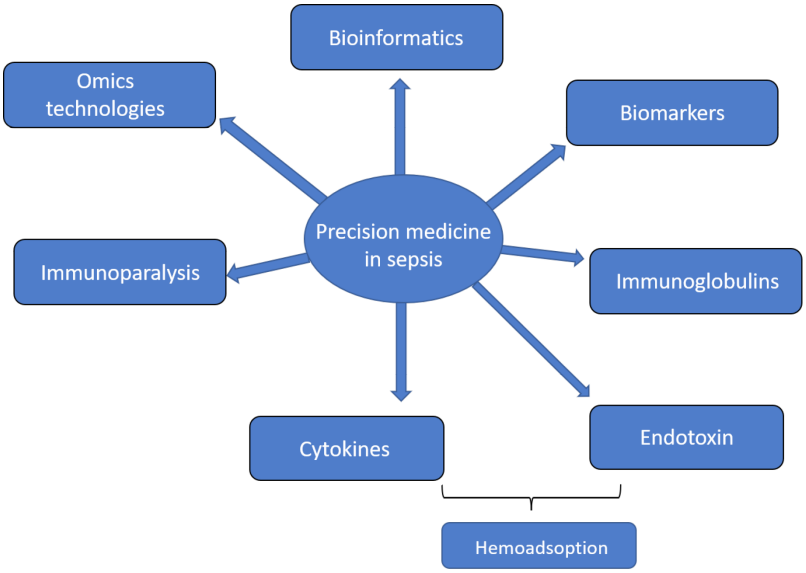

Figure 1 Strategies to create precision medicine in sepsis.

patients with community-acquired pneumonia and organ dysfunction. That transcriptomic study showed two distinct sepsis response signatures: *SRS1* and *SRS2*. *SRS1*, present in 41% of patients, identified patients with an immunosuppression phenotype that included features of endotoxin tolerance, T cell exhaustion, and down-regulation of human leucocyte antigen class II. *SRS1* was associated with higher 14-, 28- and 60-d mortality than *SRS2*. Sweeney *et al*[17] performed an unsupervised clustering analysis on pooled transcriptomic profiles from 14 datasets of sepsis patients (n = 700). The authors described three transcriptomic subtypes based on their functional analysis: the inflammopathic, adaptive, and coagulopathic subtypes. The adaptive subtype was associated with a lower clinical severity and lower mortality rate than the other subtypes. The coagulopathic subtype was associated with higher mortality and occurrence of clinical coagulopathy than either the adaptative or inflammopathic subtypes. Septic shock was more frequent in the inflammopathic subtype. Wong *et al*[18,19] conducted a genome-wide expression profiling using whole blood-derived RNA from 98 children with septic shock, and identified three subclasses of patients, which they designated as A, B, and C. Patients in subclass A were characterized by repression of genes corresponding to adaptive immunity and glucocorticoid receptor signaling. The subclass A patients had higher illness severity and mortality rate than the patients in subclasses B and C.

In the future, transcriptomic studies should help us in the early identification of patients with evolutionary patterns associated with greater severity and mortality, allowing for more personalized treatment.

Metabolomics: Metabolomics is the study of the metabolome, a collection of small molecules produced by cells[20]. This technology has been increasingly used in various investigations, such as the identification of biomarkers, drug activities, or drug-induced toxicity and metabolism. Critical illnesses, such as sepsis, alter the metabolomic profile. Thus, metabolomic studies in sepsis have been aimed at discovering metabolites that discriminate between patients with sepsis and non-infectious systemic inflammatory response syndrome (SIRS), identifying prognostic factors, and recognizing changes in response to treatment[21].

Su *et al*[22] studied a total of 65 patients (35 with sepsis, 15 with SIRS, and 15 healthy subjects). Levels of dimethylisine, 2-phenylacetamide, glyceryl-phosphoryl-ethanolamine, and D-cysteine were associated with the severity of sepsis. In addition, four other metabolites (S-(3-methylbutanoyl)-dihydrolipoamide-E, glycerophosphocholine, and S-succinyl-glutathione) were elevated within 48 h prior to death, indicating their potential use in predicting mortality. Neugenbauer *et al*[23] demonstrated that high levels of putrescine, *lysoPCaC18:0*, and *SM C16: 1* are associated with higher mortality in community-acquired pneumonia and intra-abdominal infections. In a previous study, Mickiewicz *et al*[24] found 20 metabolites significant for discrimination between survivors and non-survivors. The pathways highlighted in this study were related to energy metabolism and branched-chain amino acid processes.

Metabolomic studies have characterized the fundamental role of lysophospholipids, especially lysophosphatidylcholine (LPC), in sepsis prognosis[25-27]. Ferrario *et al*[28] studied the changes in lipid homeostasis that occur during sepsis progression. Plasma samples from 20 patients with septic shock were studied on days 1 and 7 of septic evolution. The authors identified 137 metabolites, many of which were significantly different between survivors and non-survivors. LPC and phosphatidylcholine were found at lower levels in non-survivors than in survivors on day 1 and day 7. Using regression models, the lowest levels of LPC on day 7 were identified as the strongest predictors of mortality. Drobnik *et al*[26] observed that the LPC concentration was markedly reduced in patients with sepsis compared to controls, and a negative correlation between these levels and mortality was found. Instead, Cho *et al*[25] found no association between low LPC levels and severity of the disease in septic patients. They also observed no differences in LPC levels between survivors and non-survivors.

In sum, metabolomics is a tool that allows for predicting the severity and prognosis of sepsis patients. This technology also provides a higher level of biochemical detail and knowledge than other systems biology approaches.

Proteomics: Proteomics is the part of omics that is responsible for the study of the proteome. The proteome comprises the set of all proteins expressed by the genome of a cell, tissue, or organism at a given time and under certain conditions of time and environment[29]. This technology provides an analysis of the expression, location, function, and interaction of proteomes. Compared to other immunological tests, proteomics is a novel method that has the advantage of having high throughput, sensitivity, and specificity. The development of proteomics has provided a means to study cellular processes, such as cell signaling, identifying protein modifications, and the characterization of specific biological markers[30].

For more than a decade, the study of proteomics has been sought to find new biomarkers determining sepsis diagnosis and prognosis. Su *et al*[31] selected 192 proteins in patients with sepsis and septic shock for investigation. Of these, vimentin (a molecule that modulates lymphocyte apoptosis and inflammatory response) increased significantly in patients with sepsis and septic shock compared to controls. The non-survivors had higher vimentin levels in serum, and its expression was increased in lymphocytes in particular. As such, this molecule could be a marker for prognosis prediction in patients with sepsis. In a previous study of 16 critically ill patients, Punyadeera *et al*[32] found that a combination of various proteins [*e.g.*, IL-1α, interferon gamma-induced protein 10 (IP-10), soluble tumor necrosis factor receptor (sTNF-R)2 and soluble cell death receptor (sFAS)] could induce the progression of sepsis to septic shock. Furthermore, a combined measurement of matrix metalloproteinase (MMP)-3, IL-1α, IP-10, soluble IL-2 receptor (sIL-2R), sFas, sTNF-R1, soluble receptor for advanced glycation end products (*i.e.*, sRAGE), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1β, and eotaxin could differentiate survivors from non-survivors. Latour-Pérez *et al*[33] observed that increased levels of activator receptor 1 expressed in myeloid cells (*i.e.*, sTREM-1) throughout the first 3 d of evolution were associated with high mortality in critically ill patients with sepsis. The high initial severity of illness explained this finding. Gibot *et al*[34] found that the progressive decrease in plasma concentrations of sTREM-1 indicated a favorable clinical course during the recovery phase of sepsis and discriminated between survivors and non-survivors. Decoux *et al*[35] analyzed the serum proteome in a group of patients with early sepsis. To cope with the large dynamic range of serum protein samples, the authors performed N-glycosylation, a chemical enrichment of glycopeptides and subsequent differences were found in the serum proteome between survivors and non-survivors. For instance, some modified proteins and glycopeptides belong to common pathways, such as the coagulation cascade and the complement system. The authors also found decreased total neutrophil gelatinase-associated lipocalin (NGAL) and vascular cell adhesion molecule 1 (VCAM-1) levels in non-survivors, two molecules believed to be part of the inflammatory response. Thus, even though VCAM and NGAL increase in sepsis, their study suggested that these increases may be part of a beneficial response necessary for survival, and pointed to the complexity of the regulatory network that is already activated in these patients at an early stage.

Proteomics has also helped to understand the role of proteolysis in sepsis by studying circulating peptides. Bauzá-Martinez *et al*[36] described a higher number of circulating peptides in patients with septic shock than in sepsis patients or non-hospitalized healthy subjects. The peptide count and abundance in septic shock patients were higher in non-survivors than in survivors, suggesting an association between the magnitude of proteolysis and the outcome. The predominant role of serine proteases,

such as chymotrypsin and MMPs, in causing the observed proteolytic degradation was demonstrated.

Ultimately, proteomics helps increase our understanding of the pathophysiology of sepsis and identify new molecules that can predict patients' evolution. This technology also aids in the identification of significant prognostic factors in sepsis patients. Therefore, proteomic approaches are promising for clinical applications and biomarker studies of sepsis.

Bioinformatics

A major trend today in research is improving the accuracy of the diagnosis of sepsis. The definition of sepsis was updated in 2016 and advocated using the quick Sequential Organ Failure Assessment (qSOFA), which assesses blood pressure, respiratory rate, and mental status for sepsis diagnosis[8]. A major criticism by the medical community of this score lies in its low specificity[37]. For this reason, different research teams are trying to enhance this scale through the addition of bedside parameters (*e.g.*, biomarker data), which could improve these diagnostic criteria. Another critical aspect in clinical research is obtaining a set of baseline phenotypes and patient trajectories in the ICU through multivariate analysis techniques, such as principal component analysis, factor analysis, and probabilistic clustering. For instance, a previous study[38] defined the following four different phenotypes for sepsis through consensus k-means clustering: (1) Patients with low vasopressor titration; (2) Patients with chronic conditions and renal dysfunction; (3) Patients with high inflammation and pulmonary dysfunction; and (4) Patients with liver dysfunction and septic shock. Another study [39] defined the following phenotypes predicting ICU outcomes: (1) Patients requiring mechanical ventilation support; (2) Patients with severe organ dysfunction; (3) Patients with high severity scores; and (4) Patients with hepatic dysfunction.

Therefore, improved versions of the qSOFA scale are evaluated in the context of all available data at hospital admission through standard machine learning techniques, such as multivariate logistic regression, relevance vector machines, support vector machines, shallow neural networks or random forests, taking the diagnosis of sepsis confirmed through hemocultures as the main outcome. To predict organ dysfunction before its onset, phenotypes are now being improved by adding different clinical traits and biomarkers that become altered before organ dysfunction is detected at a systemic level. Current initiatives are intended to enhance these phenotypes by applying a generalization of the factor analysis method with Deep Autoencoders to assess the strength of associations between variables and their importance within each patient phenotype.

Deep Reinforcement Learning has also become an important research line for assessing the continuum of organ dysfunction in sepsis. For instance, Raghu *et al*[40] proposed a continuous state-space model for sepsis management in a twist beyond the more traditional development and use of discriminative classifiers.

Other studies have used Bayesian Networks and Random Forests[41] for assessing patient trajectories of septic and septic shock patients in the acute phase. A common trend between these initiatives is that they all pave the way to study patient trajectories in the ICU. Patient trajectory assessment includes studying the prevalence of each phenotype and their impact on other clinical outcomes, such as long-term survival (*e.g.*, 100-d survival rate), vasopressor resistance, and days on organ support [38,39,42].

An accurate assessment of the organ dysfunction continuum is possible with the inclusion of biomarker data (*e.g.*, complement cascade, platelet degranulation, acute inflammation response, negative regulation of endopeptidase activity, and blood coagulation), through the development of comprehensive, interpretable and mathematically rigorous models of knowledge representation through Deep Learning techniques such as Deep Reinforcement Learning and standard machine learning techniques based on graphical models[42]. These techniques will improve diagnosis, trajectory, and long-term survival prediction in sepsis and septic shock. Also, they could set the basis for the personalized treatment of organ dysfunction.

Available biomarkers at clinics

The reliability of clinical assessments in patients with sepsis is often limited, and there is a need to individualize decision-making processes based on objective data. The heterogeneity of patients with sepsis has led to the use of biomarkers for patient stratification according to prognosis and severity of illness, improving phenotyping, intensifying medical therapy in high-risk patients, guiding antimicrobial stewardship, and allocating hospital resources.

Procalcitonin (PCT) is the most widely studied biomarker and is helpful as an adjunctive clinical tool for predicting prognosis and supporting clinical decisions in sepsis[43]. In a previous study of patients with septic shock and high vasopressor requirements, patients who had PCT levels of > 2 ng/mL benefited from receiving adjuvant therapy with hydrocortisone, vitamin C, and thiamine to reduce the progression of organ dysfunction[44]. High initial levels of PCT (> 6 ng/mL) are helpful to predict progressive organ dysfunction and an increased risk of mortality [45]. Thus, this subgroup of patients may be considered for receiving personalized rescue therapies, as conventional treatment may be insufficient to improve prognosis. Interestingly, PCT non-clearance is a predictor of adverse outcomes and treatment failure[46-48]. In a large observational study, the inability to decrease PCT by more than 80% was a significant independent predictor of mortality[49]. This finding may aid in sepsis care, potential suitability of adjuvant treatments, and allocation of resources. Well-designed randomized controlled trials (RCTs) and meta-analyses have shown a mortality benefit when using PCT-guided algorithms for antimicrobial stewardship in sepsis[50-52].

Mid-region fragment of pro-adrenomedullin (MR-proADM) is a biomarker mainly produced by vascular endothelial cells. MR-pro-ADM directly reflects plasma levels of adrenomedullin, a potent vasodilator agent with metabolic and immune-modulating properties. MR-proADM levels increase in sepsis, and high plasma clearance at day 5 has been associated with better outcomes[53]. Furthermore, the role of this biomarker for the early identification of patients at higher risk of organ dysfunction has been recognized. In a recent study, the use of MR-proADM performed better in the prediction of mortality compared to lactate, PCT, C-reactive protein, and SOFA score [54]. Former studies have evaluated MR-proADM to predict ICU admission and the need for urgent treatment[55]. Thus, MR-pro-ADM is found beneficial to guide clinical decisions regarding the use of ICU and hospital resources.

The use of sepsis biomarkers is evolving as one of the most promising developments in precision medicine. Identifying additional reliable biomarkers in sepsis will significantly improve our understanding of this heterogeneous disease and help the medical community refine clinical assessments. Likewise, comprehensive clinical assessments should be the starting point for developing and studying clinically accurate biomarkers in sepsis[56,57].

Recent progress in several biomarker research areas, including the development of point-of-care testing technologies[58], will extend their application for diagnosis, risk stratification, molecular phenotyping, and monitoring therapeutic responses, leading to more personalized medicine at the bedside. Further clinical validation of current biomarkers should be sought in certain patients [*e.g.*, renal dysfunction, receiving continuous renal replacement therapy (*i.e.* CRRT), trauma]. Point-of-care sepsis biomarkers have the potential to be a game-changer as their implementation becomes widely available.

ENDOTYPES AND SPECIFIC POTENTIAL TREATMENTS

Immunoglobulins

The pathogenesis of sepsis is associated with dysregulation of the innate and adaptive immune systems. The adaptive immune system's underlying altered mechanism is the function of antibodies and immunoglobulins (Igs)[59]. Still, the SSC guidelines[4] make a weak recommendation for using Igs as a potential treatment in sepsis patients, given the low certainty of evidence derived from the main studies and a meta-analysis [60,61]. Although the previous studies have not assessed Igs' baseline status as an inclusion criterion, it is reasonable to think that patients with hypogammaglobulinemia could benefit from Ig treatment.

The underlying mechanisms causing decreased levels of Igs in sepsis are not entirely clear. Still, impaired Ig production, vascular leakage secondary to endothelial dysfunction, an imbalance between IgG production and its utilization by the complement system, excessive catabolism, or reduced plasma cell Ig secretion may be involved. Also, patients with sepsis frequently have lymphopenia and quantitative or functional abnormalities within T cell and B cell populations[62].

Several studies have shown higher mortality in sepsis patients with hypogammaglobulinemia. Although the definition of hypogammaglobulinemia is variable, low levels of gammaglobulins can be defined as IgG below 500 mg/dL in individuals older than 5 years or 2 standard deviations below reference values for age[63-67]. Low plasma levels of IgG (hypo-IgG) is the most common deficiency, with a prevalence as

high as 70%[68]. Hypo-IgG is associated with an increased risk of severe illness [higher acute physiology and chronic health evaluation II (*i.e.* APACHE II) score], a greater incidence of acute respiratory distress syndrome, and a longer duration of shock[69], especially on the day of diagnosis and the following 48 h[70]. Also, a synergistic role of IgG, IgM, and IgA in sepsis and septic shock has been described[66,71]. The combined presence of low levels of endogenous IgG, IgM, and IgA in plasma is associated with reduced survival in patients with sepsis or septic shock[72].

Some studies have reported that immunoglobulin formulations containing IgG did not improve mortality rates in patients with sepsis[60]. Conversely, Welte *et al*[73] demonstrated a clinically significant reduction of mortality risk in patients with pneumonia treated with intravenous Ig (IVIg). That study identified a population with a very high risk of mortality, namely patients with high levels of C-reactive protein and PCT, and hypo-IgM.

Polyvalent intravenous Igs represent a promising approach to modulate both the pro-and anti-inflammatory responses[74]. In adults, the use of IgM-enriched IVIg has shown favorable results[60,61,73-79]. IgM-IgA-enriched IVIg preparations are associated with a reduction in mortality[61,73,75,76]. A recent meta-analysis of 19 trials and > 1500 patients showed a significant reduction in mortality when using IgM- and IgA-enriched IVIg compared to human albumin solution or no treatment[80,81]. However, the eligibility criteria for receiving polyvalent IVIg and the best treatment strategy should be well defined[77]. The administration of a single dose of polyclonal gammaglobulin of 1 or 2 g/kg is widely accepted (level of evidence 2C)[82]. Other strategies propose IgM and IgA-enriched polyclonal IVIg dose of 250 mg/kg/d by a 10-h infusion, for 3 consecutive days[83], or an infusion of 42 mg/kg body weight of IgM-enriched polyclonal IVIg once daily for 5 consecutive days[73]. In a retrospective study, 129 adult patients benefited from receiving IgM-IgA enriched IVIg, when the administration was performed within the first 23 h from admission[78].

The routine administration of IVIg in sepsis patients is not recommended, as stated in the 2016 SSC. However, patients with hypogammaglobulinemia could benefit from this treatment. Further studies are needed to clinically validate the most appropriate dose and administration regimen of IVIg in sepsis patients with hypogammaglobulinemia.

Endotoxin hemoadsorption

Endotoxin is a lipopolysaccharide (LPS) present in the outer membrane of Gram-negative bacteria and is one of the best examples of pathogen-associated molecular patterns (*i.e.* PAMPs). Its presence, together with that damage-associated molecular patterns (*i.e.* DAMPs) released by host injured cells, results in the elevation of pro-inflammatory and anti-inflammatory cytokines[84], activating the anti-infectious innate immune response and mediating the clinical syndrome of sepsis. LPS elicits its actions through a transmembrane protein, the TLR4, a type of pattern recognizing receptor expressed on innate immune system cells, in a process in which many important molecules are involved. In this process, the LPS-binding protein (*i.e.* LBP) transports circulating endotoxin and facilitates its recognition by the cell through receptor CD14. CD14 directs the LPS-LBP complex to TLR4, and the accessory protein myeloid differentiation 2 (MD2) associated with TLR4 on the cell surface is involved in the LPS-TLR4 union. Recognition of the LPS-LBP complex by these receptors transduces the endotoxin signal to the cell nucleus, leading to the expression of a complex network of inflammatory mediators. The presence of endotoxin activates changes in the expression of more than 300 genes, leading to the activation of macrophages, endothelial cells, neutrophils, and the coagulation cascade. It also triggers the release of a complex cascade of host-derived inflammatory mediators[85,86].

Endotoxin activity has emerged as a valuable marker of disease severity. The lipid-A domain of endotoxin induces most of the toxicity associated with LPS, characterized by fever, diarrhea, hemodynamic instability, multiple organ failure, and, ultimately, death[87]. A previous study highlighted the clinical relevance of circulating levels of LPS, showing a significant correlation between endotoxin levels and severity of septic shock, organ dysfunction, and mortality[86]. The prevalence of endotoxemia in patients with septic shock was high, and up to 82% of patients showing intermediate or high endotoxin activity[88]. Patients with endotoxemia also presented significantly higher lactate concentration and inotropic score.

In human illness, the measurement of endotoxin is notoriously difficult. The chromogenic limulus amebocyte lysate assay was the first diagnostic test developed. It was based on endotoxin's ability to induce coagulation of proteins in the hemolymph of the horseshoe crab, *Limulus polyphemus*[89]. Since other microbial products,

especially from fungi, can activate the limulus reaction, the assay is not specific for endotoxin. Since 2004, the endotoxemia measurement in humans has been made through the Endotoxin Activity Assay (EAA), a chemiluminescent rapid (30-min) assay described by Romaschin in 1998[90]. That test is based on the ability of an antibody to form an antibody-antigen complex in whole blood. This antibody targets the highly conserved lipid A epitope of endotoxin. It has a very high binding affinity, leading to very high sensitivity. In addition, the antibody does not cross-react with Gram-positive or fungal components, allowing for very high specificity. The results are expressed in EAA units, where < 0.39 is considered low, 0.40-0.59 intermediate, and ≥ 0.60 high. As this assay uses patient's neutrophils as a readout system, it is impossible to store specimens for later assaying, and measurements must be performed within 3 h of obtaining the sample. The EAA is the only assay that is approved by the United States' Food and Drug Administration for measuring endotoxin activity in whole blood.

Endotoxin has been considered as one of the therapeutic targets for the treatment of sepsis and septic shock. The possibility of eliminating endotoxin through blood purification techniques and, specifically, by hemoadsorption has been raised. Adsorption with a fiber column immobilized with polymyxin B (PMX) (Toraymyxin®; Toray, Tokyo, Japan), is one of the best-known endotoxin elimination therapies. Another possibility is the oXiris® hemofilter (Baxter, Meyzieu, France).

Four clinical trials have evaluated the efficacy of endotoxin hemoadsorption in septic shock. In a multicenter, open-label, pilot, randomized, controlled study conducted in Europe, 36 postsurgical patients with severe sepsis or septic shock secondary to intraabdominal infection were randomized to receive PMX treatment over 2 h (n = 17) or standard therapy (n = 19)[91]. There were no statistically significant differences in endotoxin levels from baseline to 6, 8 or 24 h after treatment between the two groups. Five of the eighteen (28%) patients in the control group and five of the seventeen (29%) patients in the PMX group died during the study period. The survival analysis showed no statistical significance between the two groups. There was also no statistically significant difference in the mean duration of ICU stay nor the number of ICU-free days between the two groups. However, patients treated with PMX demonstrated substantial increases in cardiac index and oxygen delivery index, and the need for CRRT after study entry was reduced. PMX was well tolerated and showed no significant side effects. Thus, that study showed the PMX cartridge to be safe and to have the potential to improve cardiac and renal dysfunction due to sepsis or septic shock. The early use of polymyxin B hemoperfusion in abdominal septic shock (*i.e.* EUPHAS) trial[92] evaluated hemoperfusion with PMX in a small sample of 64 patients with intraabdominal infection-related severe sepsis and septic shock. The design was oriented to assess hemodynamic improvement. The recovery of mean arterial pressure allowed for the reduction of vasoactive drugs in the PMX group. SOFA scores improved in the PMX group. Furthermore, a significant reduction in 28-d mortality was observed in the intervention group (32%) compared to the conventional treatment group (53%). The ABDOMIX trial[93] studied 243 patients with septic shock within 12 h after emergency surgery for secondary peritonitis due to organ perforation. The PMX hemoperfusion (*i.e.* PMX-HP) group (n = 119) received conventional therapy plus two sessions of PMX-HP. There were no significant differences in the SOFA score nor the 28-d mortality rate between PMX-HP and control groups (27.7% *vs* 19.5%). The severity of the disease and mortality were moderate. Among the 220 sessions performed, a premature interruption was observed in 25 cases (11%), mainly during the first session and primarily due to circuit clotting. A total of two PMX-HP sessions were completed in only 81 of 119 patients (69.8%). Of note, plasma EAA levels were not measured in any RCTs previously discussed.

The Euphrates trial[94] is one of the RCTs with the largest sample of patients and features the highest scientific rigor. Among its main characteristics is the use of EAA as a predictive biomarker. This trial studied 450 critically ill patients with septic shock and an EAA level of 0.6 or higher. The intervention consisted of two PMX-HP treatments (90-120 min) plus standard therapy, completed within 24 h of enrollment (n = 224) or sham hemoperfusion plus standard therapy (n = 226). PMX-HP was not associated with a significant difference in 28-d mortality. However, Klein *et al*[95] performed a post-hoc analysis of 194 patients with EAA between 0.6-0.89. A survival benefit was observed in patients who received therapy with PMX hemofilters. Monti *et al*[96] published the first study describing the use of PMX-HP as rescue therapy, involving 52 patients with refractory septic shock unresponsive to conventional therapy. The SOFA score was 10 (8-14) points and serum lactate level was 5.89 ± 4.04 mmol/L. All patients were on mechanical ventilation, and 90% were treated with corticosteroids. Rapid and early reversal of circulatory dysfunction and other organ

failures were obtained. The overall 30-d mortality was lower (29%) than expected by the SAPS II score (47%).

Consequently, it seems reasonable that patients with refractory septic shock and severe multiorgan dysfunction, with adequate control of the focus and EAA 0.6-0.9 could be candidates for endotoxin hemoadsorption. The TIGRIS study[97] is ongoing, recruiting patients with SOFA score > 9 and EAA levels between 0.60 and 0.89. The results of that study will provide more information on the possible benefits of endotoxin hemoadsorption in patients with septic shock, high requirement for vasopressor support, and severe multiorgan dysfunction.

Cytokine hemoadsorption

Sepsis appears when the initially appropriate host response to infection becomes amplified and subsequently dysregulated, leading to an imbalance between pro-inflammatory and anti-inflammatory responses[98]. An excess of pro-inflammatory cytokines can lead to endothelial injury and SIRS. Severe cases can progress to disseminated intravascular coagulation and multiple organ failure that eventually leads to death[99].

A tightly regulated balance in the cytokine network is crucial for eliminating invading pathogens on the one hand and restricting excessive, tissue-damaging inflammation on the other. This network comprises pro-inflammatory cytokines [tumor necrosis factor-alpha (TNF-α), IL-1, IL-6, IL-12, interferon-gamma (IFN-γ) and macrophage migration inhibitory factor (MIF)], anti-inflammatory cytokines [IL-10, transforming growth factor-beta (TGF-β), and IL-4], and soluble inhibitors of pro-inflammatory cytokines[100], such as soluble TNF receptor (TNFR), IL-1 receptor antagonist (IL-1Ra), and IL-2 receptor antagonist (IL-1R2)[101,102]. In endothelial cells, TNF-α enhances the expression of adhesion molecules and increases integrin adhesiveness in neutrophils, promoting their extravasation into tissues[103,104]. TNF-α and IL-1 are the main mediators of inflammation-induced activation of coagulation [105]. In addition, TNF-α and IL-1 amplify inflammatory cascades in an autocrine and paracrine manner by activating macrophages to secrete other pro-inflammatory cytokines, lipid mediators, and reactive oxygen and nitrogen species, leading to sepsis-induced organ dysfunction[98,106]. A key function of IL-6 is the induction of fever [107] and the mediation of the acute phase response[108,109]. The high concentration of IL-6 binds to the soluble form of the IL-6 receptor. This complex combines with the signal-transducing component glycoprotein 130 on the cells, including endothelial cells, to elicit IL-6 signal activation. Despite its pro-inflammatory properties, IL-6 also has been shown to promote anti-inflammatory responses. IL-6 inhibits the release of TNF-α and IL-1[110] and enhances the circulation levels of anti-inflammatory mediators[111-113]. IL-10 and TGF-β suppress the production of pro-inflammatory mediators in immune cells and stimulate the production of IL-1Ra and sTNFRs[114, 115].

Several studies have suggested an association of IL-6 hypercytokinemia with organ dysfunction, response to treatment, and prognosis in sepsis. Kellum *et al*[116] found that 82% of patients with community-acquired pneumonia had a systemic elevation of cytokine levels. Furthermore, patients with higher levels of IL-6 and IL-10 had associated severe organ dysfunction[117,118] and higher mortality[116,118]. The association between high levels of IL-6 and IL-10 with organ dysfunction and mortality has been confirmed in other studies[117-120]. Patients who survive sepsis show a rapid decrease in IL-6 Levels, in contrast to the non-decreasing values or a slowly progressive decrease in non-survivors[119,120]. Thus, the reduction of IL-6 Levels is associated with a better prognosis[121], and IL-10 overproduction is the main predictor of severity and mortality[122,123].

Given the central role of increased systemic inflammation in the pathophysiology of sepsis-induced organ dysfunction, the development of therapies aimed at dampening the cytokine storm could help improve immune homeostasis. Extracorporeal blood purification therapies have been proposed as a strategy to improve the outcome of septic patients, attenuating the systemic expression of pro-inflammatory and anti-inflammatory mediators and restoring immune homeostasis[116]. These include different cytokine hemoadsorption techniques. Currently, we have several devices for assessing cytokine adsorption; these include Cytosorb® (CytoSorbents Corporation, Monmouth Junction, NJ, United States), oXyris (Baxter, Meyzieu, France), Alteco LPS Adsorber (Alteco Medical AB, Lund, Sweden), HA 330 and 380 (Jafron Biomedical Co., Zhuhai, GuangDong, China).

CytoSorb® is the most widely used cartridge, and our experience is greatest with it. It has been evaluated for various clinical conditions, such as SIRS after cardiopulmonary bypass, liver failure, and rhabdomyolysis-associated myoglobinemia[118-

120]. In it, cytokines are adsorbed by polymer beads within a perfused cartridge, through extracorporeal circulation[117]. Cytosorb® can attenuate both the pro-inflammatory and anti-inflammatory responses, achieving a recovery of balance much earlier.

Several observational studies have suggested the clinical benefits of using Cytosorb® in septic shock to reduce vasopressor support and even achieve a mortality reduction. Friesecke *et al*[124] studied 20 consecutive patients with refractory septic shock after 6 h of standard treatment and hypercytokinemia. Refractory septic shock was defined as a progressive shock despite full-standard therapy and lactate ≥ 2.9 mmol/L (or increased compared to baseline), and high noradrenaline requirements (> 0.3 mcg/kg/min). The mean IL-6 Levels were 25.523 ng/mL (range: 1052-491260 ng/mL). In that study, Cytosorb® application was found to be associated with a significant decrease in noradrenaline requirements and an increase in lactate clearance, which resulted in shock resolution in 13 patients. In another case series of 45 patients with septic shock treated with hemoadsorption, Paul *et al*[125] described a significant vasopressor dose reduction (*i.e.*, norepinephrine by 51.4%, epinephrine by 69.4%, and vasopressin by 13.9%). Besides, a reduction in IL-6 Levels (by 52.3%) and lactate levels (by 39.4%) was observed in the survivors. A survival rate of 75% was reported in patients who received treatment within 24 h of admission to the ICU. Patients who received treatment within 24-48 h after admission to the ICU had a survival rate of 68%. In a retrospective study conducted by Brouwer *et al*[126], Cytosorb® was associated with decreased 28-d all-cause mortality in patients with septic shock.

The scientific evidence on the clinical benefits of cytokine elimination derived from RCTs is scarce. Hawchar *et al*[127] performed a proof of concept, prospective, randomized pilot trial on the application of Cytosorb® in 20 patients with early-onset septic shock. A significant reduction in the need for vasopressor support was observed. In the control group, this change was not achieved with therapy. Rugg *et al*[128] compared patients with septic shock who received CytoSorb® in addition to CRRT (n = 42) *vs* matched controls (n = 42). Median catecholamine requirements approximately halved within 24 h after the initiation of Cytosorb®. In-hospital mortality was significantly lower in the CytoSorb® group (35.7% *vs* 61.9%; P = 0.015). Derived from our current knowledge, we can attribute the benefits of cytokine hemoadsorption only to the elimination of cytokines in the subgroup of patients with very high hypercytokinemia and associated refractory septic shock. Further studies are needed to define the influence of hemadsorption in the elimination of other substances.

Cytokine hemoadsorption may have a role as rescue therapy in a particular subgroup of patients with refractory septic shock, hyperlactatemia, multiorgan failure, and very high hypercytokinemia. As such, appropriate and well-designed RCTs should be performed in patients with this clinical profile, to validate its benefits.

Immunoparalysis

More than 20 years ago, it was hypothesized that the early hyperinflammatory phase in sepsis was followed by a compensatory anti-inflammatory response to limit tissue damage[129]. In recent years, the therapeutic advances incorporated in sepsis treatment have facilitated a reduction in sepsis mortality, especially in early mortality derived from septic shock and severe multiorgan dysfunction. Some of the patients surviving the first few days evolve to a situation of chronic multiorgan dysfunction, dependent on mechanical ventilation and vasopressor therapy. This stage, known as sepsis-associated immunoparalysis, resembles the normal aging process of the immune system (immunosenescence), characterized by a general dysregulation of innate and adaptive immune responses. Monocytes and macrophages play a critical role in critically ill patients with severe infections. These cells are the front-line of the innate cellular response that initiates and promotes the adaptive immune response.

The human leukocyte antigen (HLA)-DR isotype is a major histocompatibility complex class II cell surface receptor encoded by the HLA complex and constitutively expressed on antigen-presenting cells (*e.g.*, monocytes/macrophages, dendritic cells, and B lymphocytes). It is also inducible on T lymphocytes[130]. Decreased HLA-DR expression has been demonstrated in septic patients, at both the protein- and RNA-levels. There is also a relationship between circulating HLA-DR mRNA and HLA-DR expression *in vivo*[131]. Various studies *in vitro* have shown that constitutive and IFN-γ inducible HLA-DR expression is predominantly regulated at the transcriptional level. The observed loss of HLA-DR expression in monocytes of septic patients implies a transcriptional regulation *via* a decrease of its transactivator, specifically the class II transactivator (*i.e.*, CIITA)[130].

Although no association has been found between the kinetics of monocytic (m)HLA-DR expression and primary infection sites or causative pathogens, it has been associated with severity. Patients with high SOFA scores have an associated low expression of mHLA-DR. The prognosis of patients with low mHLA-DR expression is poor compared to patients with a rapid increase in mHLA-DR expression, primarily because of the higher incidence of secondary infections and mortality rate[132]. The most reliable marker for monitoring the immune alterations in critically ill patients is the decreased mHLA-DR expression, measured by flow cytometry[133].

Immunoparalysis can be identified by studying the expression of HLA-DR in monocytes. Multiple studies have linked the low expression of mHLA-DR with the presence of more significant adverse effects and higher short and long-term mortality rates (at 7 d and 28 d) in sepsis and septic shock[134,135]. Measures of mHLA-DR levels can not only be used as a marker of monocyte functionality and severity of the disease but also to guide innovative clinical therapies based on restoring the immune system[135,136].

In patients with immunoparalysis, several immuno-adjuvant agents are under investigation. GM-CSF, IFN-g, anti-programmed death-ligand 1 (*i.e.*, anti PDL-1), or IL-7 could have a role in treating sepsis-associated immunoparalysis. For instance, decreased mHLA-DR has been used to stratify patients for GM-CSF administration in a clinical trial, including a small sample of sepsis patients. This biomarker-guided GM-CSF therapy was found to be safe and effective in restoring monocyte immunocompetence, shortening mechanical ventilation duration, and reducing ICU/hospital stay [135]. Another clinical trial tested the hypothesis that GM-CSF improves neutrophil phagocytosis in critically ill patients. They previously measured the neutrophil phagocytic capacity and included the subgroup of patients in whom phagocytosis was known to be impaired (to < 50%). The study showed that GM-CSF did not improve mean neutrophil phagocytosis but was safe and appeared to increase the proportion of patients with adequate phagocytosis[137]. Novel therapies targeting the restoration of monocyte immunocompetence are promising for improving outcomes in later stages of sepsis.

CONCLUSION

The heterogeneity of sepsis is a complex and engaging feature of the disease that elicits novel strategies for improved patient classification. Thus, precision medicine creates an individualized approach on a case-by-case basis by identifying subgroups of sepsis patients with a high risk of adverse outcomes who may benefit from specific treatments or rescue therapies according to their particular characteristics (*e.g.*, genotypes or phenotypes). Of note, we urge the implementation of predictive-enrichment strategies for the design and development of future clinical trials to improve the certainty of scientific assessments.

Although some clinical tools are still being evaluated in the early stages of research, such as the omics technologies, precision medicine is becoming a reality that improves our clinical approaches when currently available tools are implemented in patients with sepsis, septic shock, and organic dysfunction. Further scientific contributions in this field will be essential to identify specific endotypes responding to targeted therapies and translate individualized treatments to the bedside.

REFERENCES

1 **Dellinger RP**, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM; Surviving Sepsis Campaign Management Guidelines Committee. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; **32**: 858-873 [PMID: 15090974 DOI: 10.1097/01.ccm.0000117317.18092.e4]

2 **Dellinger RP**, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine;

Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; **36**: 296-327 [PMID: 18158437 DOI: 10.1097/01.Ccm.0000298158.12101.41]

3 **Dellinger RP**, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; **39**: 165-228 [PMID: 23361625 DOI: 10.1007/s00134-012-2769-8]

4 **Evans L**, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Møller MH, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med* 2021; **47**: 1181-1247 [PMID: 34599691 DOI: 10.1007/s00134-021-06506-y]

5 **Levy MM**, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. *Intensive Care Med* 2018; **44**: 925-928 [PMID: 29675566 DOI: 10.1007/s00134-018-5085-0]

6 **Levy MM**, Rhodes A, Phillips GS, Townsend SR, Schorr CA, Beale R, Osborn T, Lemeshow S, Chiche JD, Artigas A, Dellinger RP. Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. *Crit Care Med* 2015; **43**: 3-12 [PMID: 25275252 DOI: 10.1097/CCM.0000000000000723]

7 **Yébenes JC**, Ruiz-Rodriguez JC, Ferrer R, Clèries M, Bosch A, Lorencio C, Rodriguez A, Nuvials X, Martin-Loeches I, Artigas A; SOCMIC (Catalonian Critical Care Society) Sepsis Working Group. Epidemiology of sepsis in Catalonia: analysis of incidence and outcomes in a European setting. *Ann Intensive Care* 2017; **7**: 19 [PMID: 28220453 DOI: 10.1186/s13613-017-0241-1]

8 **Singer M**, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 801-810 [PMID: 26903338 DOI: 10.1001/jama.2016.0287]

9 **Leligdowicz A**, Matthay MA. Heterogeneity in sepsis: new biological evidence with clinical applications. *Crit Care* 2019; **23**: 80 [PMID: 30850013 DOI: 10.1186/s13054-019-2372-2]

10 **Nakada TA**, Takahashi W, Nakada E, Shimada T, Russell JA, Walley KR. Genetic Polymorphisms in Sepsis and Cardiovascular Disease: Do Similar Risk Genes Suggest Similar Drug Targets? *Chest* 2019; **155**: 1260-1271 [PMID: 30660782 DOI: 10.1016/j.chest.2019.01.003]

11 **Lorente-Sorolla C**, Garcia-Gomez A, Català-Moll F, Toledano V, Ciudad L, Avendaño-Ortiz J, Maroun-Eid C, Martín-Quirós A, Martínez-Gallo M, Ruiz-Sanmartín A, Del Campo ÁG, Ferrer-Roca R, Ruiz-Rodriguez JC, Álvarez-Errico D, López-Collazo E, Ballestar E. Inflammatory cytokines and organ dysfunction associate with the aberrant DNA methylome of monocytes in sepsis. *Genome Med* 2019; **11**: 66 [PMID: 31665078 DOI: 10.1186/s13073-019-0674-2]

12 **Zheng Z**, Huang G, Gao T, Huang T, Zou M, Zou Y, Duan S. Epigenetic Changes Associated With Interleukin-10. *Front Immunol* 2020; **11**: 1105 [PMID: 32582189 DOI: 10.3389/fimmu.2020.01105]

13 **Tacke F**, Roderburg C, Benz F, Cardenas DV, Luedde M, Hippe HJ, Frey N, Vucur M, Gautheron J, Koch A, Trautwein C, Luedde T. Levels of circulating miR-133a are elevated in sepsis and predict mortality in critically ill patients. *Crit Care Med* 2014; **42**: 1096-1104 [PMID: 24413579 DOI: 10.1097/CCM.0000000000000131]

14 **Binnie A**, Walsh CJ, Hu P, Dwivedi DJ, Fox-Robichaud A, Liaw PC, Tsang JLY, Batt J, Carrasqueiro G, Gupta S, Marshall JC, Castelo-Branco P, Dos Santos CC; Epigenetic Profiling in Severe Sepsis (EPSIS) Study of the Canadian Critical Care Translational Biology Group (CCCTBG). Epigenetic Profiling in Severe Sepsis: A Pilot Study of DNA Methylation Profiles in Critical Illness. *Crit Care Med* 2020; **48**: 142-150 [PMID: 31939781 DOI: 10.1097/CCM.0000000000004097]

15 **Maslove DM**, Tang BM, McLean AS. Identification of sepsis subtypes in critically ill adults using gene expression profiling. *Crit Care* 2012; **16**: R183 [PMID: 23036193 DOI: 10.1186/cc11667]

16 **Davenport EE**, Burnham KL, Radhakrishnan J, Humburg P, Hutton P, Mills TC, Rautanen A, Gordon AC, Garrard C, Hill AV, Hinds CJ, Knight JC. Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. *Lancet Respir Med* 2016; **4**: 259-271 [PMID: 26917434 DOI: 10.1016/S2213-2600(16)00046-1]

17 **Sweeney TE**, Azad TD, Donato M, Haynes WA, Perumal TM, Henao R, Bermejo-Martin JF, Almansa R, Tamayo E, Howrylak JA, Choi A, Parnell GP, Tang B, Nichols M, Woods CW, Ginsburg GS, Kingsmore SF, Omberg L, Mangravite LM, Wong HR, Tsalik EL, Langley RJ, Khatri P. Unsupervised Analysis of Transcriptomics in Bacterial Sepsis Across Multiple Datasets Reveals Three Robust Clusters. *Crit Care Med* 2018; **46**: 915-925 [PMID: 29537985 DOI: 10.1097/CCM.0000000000003084]

18 **Wong HR**, Cvijanovich N, Lin R, Allen GL, Thomas NJ, Willson DF, Freishtat RJ, Anas N, Meyer K, Checchia PA, Monaco M, Odom K, Shanley TP. Identification of pediatric septic shock subclasses based on genome-wide expression profiling. *BMC Med* 2009; **7**: 34 [PMID: 19624809 DOI: 10.1186/1741-7015-7-34]

19 **Wong HR**, Cvijanovich NZ, Allen GL, Thomas NJ, Freishtat RJ, Anas N, Meyer K, Checchia PA, Lin R, Shanley TP, Bigham MT, Wheeler DS, Doughty LA, Tegtmeyer K, Poynter SE, Kaplan JM, Chima RS, Stalets E, Basu RK, Varisco BM, Barr FE. Validation of a gene expression-based subclassification strategy for pediatric septic shock. *Crit Care Med* 2011; **39**: 2511-2517 [PMID: 21705885 DOI: 10.1097/CCM.0b013e3182257675]

20 **Ludwig KR**, Hummon AB. Mass spectrometry for the discovery of biomarkers of sepsis. *Mol Biosyst* 2017; **13**: 648-664 [PMID: 28207922 DOI: 10.1039/c6mb00656f]

21 **Vincent JL**, Brealey D, Libert N, Abidi NE, O'Dwyer M, Zacharowski K, Mikaszewska-Sokolewicz M, Schrenzel J, Simon F, Wilks M, Picard-Maureau M, Chalfin DB, Ecker DJ, Sampath R, Singer M; Rapid Diagnosis of Infections in the Critically Ill Team. Rapid Diagnosis of Infection in the Critically Ill, a Multicenter Study of Molecular Detection in Bloodstream Infections, Pneumonia, and Sterile Site Infections. *Crit Care Med* 2015; **43**: 2283-2291 [PMID: 26327198 DOI: 10.1097/CCM.0000000000001249]

22 **Su L**, Huang Y, Zhu Y, Xia L, Wang R, Xiao K, Wang H, Yan P, Wen B, Cao L, Meng N, Luan H, Liu C, Li X, Xie L. Discrimination of sepsis stage metabolic profiles with an LC/MS-MS-based metabolomics approach. *BMJ Open Respir Res* 2014; **1**: e000056 [PMID: 25553245 DOI: 10.1136/bmjresp-2014-000056]

23 **Neugebauer S**, Giamarellos-Bourboulis EJ, Pelekanou A, Marioli A, Baziaka F, Tsangaris I, Bauer M, Kiehntopf M. Metabolite Profiles in Sepsis: Developing Prognostic Tools Based on the Type of Infection. *Crit Care Med* 2016; **44**: 1649-1662 [PMID: 27097292 DOI: 10.1097/CCM.0000000000001740]

24 **Mickiewicz B**, Duggan GE, Winston BW, Doig C, Kubes P, Vogel HJ; Alberta Sepsis Network. Metabolic profiling of serum samples by 1H nuclear magnetic resonance spectroscopy as a potential diagnostic approach for septic shock. *Crit Care Med* 2014; **42**: 1140-1149 [PMID: 24368342 DOI: 10.1097/CCM.0000000000000142]

25 **Cho WH**, Park T, Park YY, Huh JW, Lim CM, Koh Y, Song DK, Hong SB. Clinical significance of enzymatic lysophosphatidylcholine (LPC) assay data in patients with sepsis. *Eur J Clin Microbiol Infect Dis* 2012; **31**: 1805-1810 [PMID: 22167258 DOI: 10.1007/s10096-011-1505-6]

26 **Drobnik W**, Liebisch G, Audebert FX, Frohlich D, Gluck T, Vogel P, Rothe G, Schmitz G. Plasma ceramide and lysophosphatidylcholine inversely correlate with mortality in sepsis patients. *J Lipid Res* 2003; **44**: 754-761 [PMID: 12562829 DOI: 10.1194/jlr.M200401-JLR200]

27 **Lee SH**, Park MS, Park BH, Jung WJ, Lee IS, Kim SY, Kim EY, Jung JY, Kang YA, Kim YS, Kim SK, Chang J, Chung KS. Prognostic Implications of Serum Lipid Metabolism over Time during Sepsis. *Biomed Res Int* 2015; **2015**: 789298 [PMID: 26351639 DOI: 10.1155/2015/789298]

28 **Ferrario M**, Cambiaghi A, Brunelli L, Giordano S, Caironi P, Guatteri L, Raimondi F, Gattinoni L, Latini R, Masson S, Ristagno G, Pastorelli R. Mortality prediction in patients with severe septic shock: a pilot study using a target metabolomics approach. *Sci Rep* 2016; **6**: 20391 [PMID: 26847922 DOI: 10.1038/srep20391]

29 **Pitarch A**, Nombela C, Gil C. [Proteomics, a new challenge for clinical microbiology]. *Enferm Infecc Microbiol Clin* 2010; **28**: 489-491 [PMID: 20888998 DOI: 10.1016/j.eimc.2010.08.001]

30 **Siqueira-Batista R**, Mendonça EG, Gomes AP, Vitorino RR, Miyadahira R, Alvarez-Perez MC, Oliveira MG. Proteomic updates on sepsis. *Rev Assoc Med Bras (1992)* 2012; **58**: 376-382 [PMID: 22735232 DOI: 10.1590/S0104-42302012000300020]

31 **Su L**, Pan P, Yan P, Long Y, Zhou X, Wang X, Zhou R, Wen B, Xie L, Liu D. Role of vimentin in modulating immune cell apoptosis and inflammatory responses in sepsis. *Sci Rep* 2019; **9**: 5747 [PMID: 30952998 DOI: 10.1038/s41598-019-42287-7]

32 **Punyadeera C**, Schneider EM, Schaffer D, Hsu HY, Joos TO, Kriebel F, Weiss M, Verhaegh WF. A biomarker panel to discriminate between systemic inflammatory response syndrome and sepsis and sepsis severity. *J Emerg Trauma Shock* 2010; **3**: 26-35 [PMID: 20165718 DOI: 10.4103/0974-2700.58666]

33 **Latour-Pérez J**, Alcalá-López A, García-García MA, Sánchez-Hernández JF, Abad-Terrado C, Viedma-Contreras JA, Masiá-Canuto M, Broch-Porcar MJ, Arizo-León D, González-Tejera M, Bonilla-Rovira F, Gutiérrez F. [Prognostic value of the sTREM-1 plasma values in patients with sepsis: a cohort study]. *Med Intensiva* 2010; **34**: 231-236 [PMID: 20096962 DOI: 10.1016/j.medin.2009.11.009]

34 **Gibot S**, Cravoisy A, Kolopp-Sarda MN, Béné MC, Faure G, Bollaert PE, Levy B. Time-course of sTREM (soluble triggering receptor expressed on myeloid cells)-1, procalcitonin, and C-reactive protein plasma concentrations during sepsis. *Crit Care Med* 2005; **33**: 792-796 [PMID: 15818107 DOI: 10.1097/01.ccm.0000159089.16462.4a]

35 **DeCoux A**, Tian Y, DeLeon-Pennell KY, Nguyen NT, de Castro Brás LE, Flynn ER, Cannon PL, Griswold ME, Jin YF, Puskarich MA, Jones AE, Lindsey ML. Plasma Glycoproteomics Reveals Sepsis Outcomes Linked to Distinct Proteins in Common Pathways. *Crit Care Med* 2015; **43**: 2049-2058 [PMID: 26086942 DOI: 10.1097/CCM.0000000000001134]

36 **Bauzá-Martinez J**, Aletti F, Pinto BB, Ribas V, Odena MA, Díaz R, Romay E, Ferrer R, Kistler EB, Tedeschi G, Schmid-Schönbein GW, Herpain A, Bendjelid K, de Oliveira E. Proteolysis in

septic shock patients: plasma peptidomic patterns are associated with mortality. *Br J Anaesth* 2018; **121**: 1065-1074 [PMID: 30336851 DOI: 10.1016/j.bja.2018.05.072]

37 **Seymour CW**, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 762-774 [PMID: 26903335 DOI: 10.1001/jama.2016.0288]

38 **Seymour CW**, Kennedy JN, Wang S, Chang CH, Elliott CF, Xu Z, Berry S, Clermont G, Cooper G, Gomez H, Huang DT, Kellum JA, Mi Q, Opal SM, Talisa V, van der Poll T, Visweswaran S, Vodovotz Y, Weiss JC, Yealy DM, Yende S, Angus DC. Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis. *JAMA* 2019; **321**: 2003-2017 [PMID: 31104070 DOI: 10.1001/jama.2019.5791]

39 **Ribas V**, Vellido A, Ruiz-Rodríguez JC, Rello J. Severe sepsis mortality prediction with logistic regression over latent factors. *Expert Syst Appl* 2012; **1937** [DOI: 10.1016/j.eswa.2011.08.054]

40 **Raghu A**, Celi L, Szolovits P, Ghassemi M. Continuous state-space models for optimal sepsis treatment-a deep reinforcement learning approach. arXiv preprint arXiv:170508422. Cited 23 May 2017

41 **Aushev A**, Ripoll VR, Vellido A, Aletti F, Pinto BB, Herpain A, Post EH, Medina ER, Ferrer R, Baselli G, Bendjelid K. Feature selection for the accurate prediction of septic and cardiogenic shock ICU mortality in the acute phase. *PLoS One* 2018; **13**: e0199089 [PMID: 30457997 DOI: 10.1371/journal.pone.0199089]

42 **Ribas Ripoll VJ**, Vellido A, Romero E, Ruiz-Rodríguez JC. Sepsis mortality prediction with the Quotient Basis Kernel. *Artif Intell Med* 2014; **61**: 45-52 [PMID: 24726036 DOI: 10.1016/j.artmed.2014.03.004]

43 **Plata-Menchaca EP**, Ferrer R. Procalcitonin Is Useful for Antibiotic Deescalation in Sepsis. *Crit Care Med* 2021; **49**: 693-696 [PMID: 33315698 DOI: 10.1097/CCM.0000000000004776]

44 **Marik PE**, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. *Chest* 2017; **151**: 1229-1238 [PMID: 27940189 DOI: 10.1016/j.chest.2016.11.036]

45 **Clec'h C**, Ferriere F, Karoubi P, Fosse JP, Cupa M, Hoang P, Cohen Y. Diagnostic and prognostic value of procalcitonin in patients with septic shock. *Crit Care Med* 2004; **32**: 1166-1169 [PMID: 15190968 DOI: 10.1097/01.ccm.0000126263.00551.06]

46 **Patnaik R**, Azim A, Mishra P. Should serial monitoring of procalcitonin be done routinely in critically ill patients of ICU: A systematic review and metaanalysis. *J Anaesthesiol Clin Pharmacol* 2020; **36**: 458-464 [PMID: 33840923 DOI: 10.4103/joacp.JOACP_388_19]

47 **Ruiz-Rodríguez JC**, Caballero J, Ruiz-Sanmartin A, Ribas VJ, Pérez M, Bóveda JL, Rello J. Usefulness of procalcitonin clearance as a prognostic biomarker in septic shock. A prospective pilot study. *Med Intensiva* 2012; **36**: 475-480 [PMID: 22257436 DOI: 10.1016/j.medin.2011.11.024]

48 **Ruiz-Rodríguez J**, Rello J. Predicting treatment failure in severe sepsis and septic shock: looking for the Holy Grail. *Crit Care* 2013; **17**: 180 [PMID: 24004571 DOI: 10.1186/cc12877]

49 **Schuetz P**, Birkhahn R, Sherwin R, Jones AE, Singer A, Kline JA, Runyon MS, Self WH, Courtney DM, Nowak RM, Gaieski DF, Ebmeyer S, Johannes S, Wiemer JC, Schwabe A, Shapiro NI. Serial Procalcitonin Predicts Mortality in Severe Sepsis Patients: Results From the Multicenter Procalcitonin MOnitoring SEpsis (MOSES) Study. *Crit Care Med* 2017; **45**: 781-789 [PMID: 28257335 DOI: 10.1097/CCM.0000000000002321]

50 **Lam SW**, Bauer SR, Fowler R, Duggal A. Systematic Review and Meta-Analysis of Procalcitonin-Guidance Versus Usual Care for Antimicrobial Management in Critically Ill Patients: Focus on Subgroups Based on Antibiotic Initiation, Cessation, or Mixed Strategies. *Crit Care Med* 2018; **46**: 684-690 [PMID: 29293146 DOI: 10.1097/CCM.0000000000002953]

51 **Wirz Y**, Meier MA, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, Schroeder S, Nobre V, Annane D, Reinhart K, Damas P, Nijsten M, Shajiei A, deLange DW, Deliberato RO, Oliveira CF, Shehabi Y, van Oers JAH, Beishuizen A, Girbes ARJ, de Jong E, Mueller B, Schuetz P. Effect of procalcitonin-guided antibiotic treatment on clinical outcomes in intensive care unit patients with infection and sepsis patients: a patient-level meta-analysis of randomized trials. *Crit Care* 2018; **22**: 191 [PMID: 30111341 DOI: 10.1186/s13054-018-2125-7]

52 **Schuetz P**, Beishuizen A, Broyles M, Ferrer R, Gavazzi G, Gluck EH, González Del Castillo J, Jensen JU, Kanizsai PL, Kwa ALH, Krueger S, Luyt CE, Oppert M, Plebani M, Shlyapnikov SA, Toccafondi G, Townsend J, Welte T, Saeed K. Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use. *Clin Chem Lab Med* 2019; **57**: 1308-1318 [PMID: 30721141 DOI: 10.1515/cclm-2018-1181]

53 **Önal U**, Valenzuela-Sánchez F, Vandana KE, Rello J. Mid-Regional Pro-Adrenomedullin (MR-proADM) as a Biomarker for Sepsis and Septic Shock: Narrative Review. *Healthcare (Basel)* 2018; **6** [PMID: 30177659 DOI: 10.3390/healthcare6030110]

54 **Baldirà J**, Ruiz-Rodríguez JC, Wilson DC, Ruiz-Sanmartin A, Cortes A, Chiscano L, Ferrer-Costa R, Comas I, Larrosa N, Fàbrega A, González-López JJ, Ferrer R. Biomarkers and clinical scores to aid the identification of disease severity and intensive care requirement following activation of an in-hospital sepsis code. *Ann Intensive Care* 2020; **10**: 7 [PMID: 31940096 DOI: 10.1186/s13613-020-0625-5]

55 **Schuetz P**, Hausfater P, Amin D, Amin A, Haubitz S, Faessler L, Kutz A, Conca A, Reutlinger B, Canavaggio P, Sauvin G, Bernard M, Huber A, Mueller B; TRIAGE Study group. Biomarkers from

distinct biological pathways improve early risk stratification in medical emergency patients: the multinational, prospective, observational TRIAGE study. *Crit Care* 2015; **19**: 377 [PMID: 26511878 DOI: 10.1186/s13054-015-1098-z]

56 **Gibot S**, Béné MC, Noel R, Massin F, Guy J, Cravoisy A, Barraud D, De Carvalho Bittencourt M, Quenot JP, Bollaert PE, Faure G, Charles PE. Combination biomarkers to diagnose sepsis in the critically ill patient. *Am J Respir Crit Care Med* 2012; **186**: 65-71 [PMID: 22538802 DOI: 10.1164/rccm.201201-0037OC]

57 **Angeletti S**, Ciccozzi M, Fogolari M, Spoto S, Lo Presti A, Costantino S, Dicuonzo G. Procalcitonin and MR-proAdrenomedullin combined score in the diagnosis and prognosis of systemic and localized bacterial infections. *J Infect* 2016; **72**: 395-398 [PMID: 26723912 DOI: 10.1016/j.jinf.2015.12.006]

58 **Belushkin A**, Yesilkoy F, González-López JJ, Ruiz-Rodríguez JC, Ferrer R, Fàbrega A, Altug H. Rapid and Digital Detection of Inflammatory Biomarkers Enabled by a Novel Portable Nanoplasmonic Imager. *Small* 2020; **16**: e1906108 [PMID: 31830370 DOI: 10.1002/smll.201906108]

59 **Angus DC**, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013; **369**: 840-851 [PMID: 23984731 DOI: 10.1056/NEJMra1208623]

60 **Werdan K**, Pilz G, Bujdoso O, Fraunberger P, Neeser G, Schmieder RE, Viell B, Marget W, Seewald M, Walger P, Stuttmann R, Speichermann N, Peckelsen C, Kurowski V, Osterhues HH, Verner L, Neumann R, Müller-Werdan U; Score-Based Immunoglobulin Therapy of Sepsis (SBITS) Study Group. Score-based immunoglobulin G therapy of patients with sepsis: the SBITS study. *Crit Care Med* 2007; **35**: 2693-2701 [PMID: 18074471 DOI: 10.1097/01.ccm.0000295426.37471.79]

61 **Alejandria MM**, Lansang MA, Dans LF, Mantaring JB 3rd. Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock. *Cochrane Database Syst Rev* 2013; CD001090 [PMID: 24043371 DOI: 10.1002/14651858.CD001090.pub2]

62 **Bermejo-Martin JF**, Andaluz-Ojeda D, Almansa R, Gandía F, Gómez-Herreras JI, Gomez-Sanchez E, Heredia-Rodríguez M, Eiros JM, Kelvin DJ, Tamayo E. Defining immunological dysfunction in sepsis: A requisite tool for precision medicine. *J Infect* 2016; **72**: 525-536 [PMID: 26850357 DOI: 10.1016/j.jinf.2016.01.010]

63 **Orange JS**, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, Buckley R, Chinen J, El-Gamal Y, Mazer BD, Nelson RP Jr, Patel DD, Secord E, Sorensen RU, Wasserman RL, Cunningham-Rundles C; Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2006; **117**: S525-S553 [PMID: 16580469 DOI: 10.1016/j.jaci.2006.01.015]

64 **Bonilla FA**, Khan DA, Ballas ZK, Chinen J, Frank MM, Hsu JT, Keller M, Kobrynski LJ, Komarow HD, Mazer B, Nelson RP Jr, Orange JS, Routes JM, Shearer WT, Sorensen RU, Verbsky JW, Bernstein DI, Blessing-Moore J, Lang D, Nicklas RA, Oppenheimer J, Portnoy JM, Randolph CR, Schuller D, Spector SL, Tilles S, Wallace D; Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the Joint Council of Allergy, Asthma & Immunology. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol* 2015; **136**: 1186-205.e1 [PMID: 26371839 DOI: 10.1016/j.jaci.2015.04.049]

65 **Picard C**, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, Cunningham-Rundles C, Etzioni A, Holland SM, Klein C, Nonoyama S, Ochs HD, Oksenhendler E, Puck JM, Sullivan KE, Tang ML, Franco JL, Gaspar HB. Primary Immunodeficiency Diseases: an Update on the Classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015. *J Clin Immunol* 2015; **35**: 696-726 [PMID: 26482257 DOI: 10.1007/s10875-015-0201-1]

66 **Bermejo-Martín JF**, Rodriguez-Fernandez A, Herrán-Monge R, Andaluz-Ojeda D, Muriel-Bombín A, Merino P, García-García MM, Citores R, Gandía F, Almansa R, Blanco J; GRECIA Group (Grupo de Estudios y Análisis en Cuidados Intensivos). Immunoglobulins IgG1, IgM and IgA: a synergistic team influencing survival in sepsis. *J Intern Med* 2014; **276**: 404-412 [PMID: 24815605 DOI: 10.1111/joim.12265]

67 **Venet F**, Gebeile R, Bancel J, Guignant C, Poitevin-Later F, Malcus C, Lepape A, Monneret G. Assessment of plasmatic immunoglobulin G, A and M levels in septic shock patients. *Int Immunopharmacol* 2011; **11**: 2086-2090 [PMID: 21924385 DOI: 10.1016/j.intimp.2011.08.024]

68 **Shankar-Hari M**, Culshaw N, Post B, Tamayo E, Andaluz-Ojeda D, Bermejo-Martín JF, Dietz S, Werdan K, Beale R, Spencer J, Singer M. Endogenous IgG hypogammaglobulinaemia in critically ill adults with sepsis: systematic review and meta-analysis. *Intensive Care Med* 2015; **41**: 1393-1401 [PMID: 25971390 DOI: 10.1007/s00134-015-3845-7]

69 **Taccone FS**, Stordeur P, De Backer D, Creteur J, Vincent JL. Gamma-globulin levels in patients with community-acquired septic shock. *Shock* 2009; **32**: 379-385 [PMID: 19295479 DOI: 10.1097/SHK.0b013e3181a2c0b2]

70 **Andaluz-Ojeda D**, Iglesias V, Bobillo F, Almansa R, Rico L, Gandía F, Loma AM, Nieto C, Diego R, Ramos E, Nocito M, Resino S, Eiros JM, Tamayo E, de Lejarazu RO, Bermejo-Martin JF. Early natural killer cell counts in blood predict mortality in severe sepsis. *Crit Care* 2011; **15**: R243 [PMID: 22018048 DOI: 10.1186/cc10501]

71 **Tian L**, Zhu J, Jin J, Tong C, Zeng W, Deng S, Zou S. Prognostic value of circulating lymphocyte B and plasma immunoglobulin M on septic shock and sepsis: a systematic review and meta-analysis. *Am J Transl Res* 2019; **11**: 7223-7232 [PMID: 31934274]

72 **Krautz C**, Maier SL, Brunner M, Langheinrich M, Giamarellos-Bourboulis EJ, Gogos C, Armaganidis A, Kunath F, Grützmann R, Weber GF. Reduced circulating B cells and plasma IgM levels are associated with decreased survival in sepsis - A meta-analysis. *J Crit Care* 2018; **45**: 71-75 [PMID: 29413726 DOI: 10.1016/j.jcrc.2018.01.013]

73 **Welte T**, Dellinger RP, Ebelt H, Ferrer M, Opal SM, Singer M, Vincent JL, Werdan K, Martin-Loeches I, Almirall J, Artigas A, Ignacio Ayestarán J, Nuding S, Ferrer R, Sirgo Rodríguez G, Shankar-Hari M, Álvarez-Lerma F, Riessen R, Sirvent JM, Kluge S, Zacharowski K, Bonastre Mora J, Lapp H, Wöbker G, Achtzehn U, Brealey D, Kempa A, Sánchez García M, Brederlau J, Kochanek M, Reschreiter HP, Wise MP, Belohradsky BH, Bobenhausen I, Dälken B, Dubovy P, Langohr P, Mayer M, Schüttrumpf J, Wartenberg-Demand A, Wippermann U, Wolf D, Torres A. Efficacy and safety of trimodulin, a novel polyclonal antibody preparation, in patients with severe community-acquired pneumonia: a randomized, placebo-controlled, double-blind, multicenter, phase II trial (CIGMA study). *Intensive Care Med* 2018; **44**: 438-448 [PMID: 29632995 DOI: 10.1007/s00134-018-5143-7]

74 **Busani S**, Damiani E, Cavazzuti I, Donati A, Girardis M. Intravenous immunoglobulin in septic shock: review of the mechanisms of action and meta-analysis of the clinical effectiveness. *Minerva Anestesiol* 2016; **82**: 559-572 [PMID: 26474267]

75 **Kreymann KG**, de Heer G, Nierhaus A, Kluge S. Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock. *Crit Care Med* 2007; **35**: 2677-2685 [PMID: 18074464 DOI: 10.1097/01.CCM.0000295263.12774.97]

76 **Rodríguez A**, Rello J, Neira J, Maskin B, Ceraso D, Vasta L, Palizas F. Effects of high-dose of intravenous immunoglobulin and antibiotics on survival for severe sepsis undergoing surgery. *Shock* 2005; **23**: 298-304 [PMID: 15803051 DOI: 10.1097/01.shk.0000157302.69125.f8]

77 **Nierhaus A**, Berlot G, Kindgen-Milles D, Müller E, Girardis M. Best-practice IgM- and IgA-enriched immunoglobulin use in patients with sepsis. *Ann Intensive Care* 2020; **10**: 132 [PMID: 33026597 DOI: 10.1186/s13613-020-00740-1]

78 **Berlot G**, Vassallo MC, Busetto N, Bianchi M, Zornada F, Rosato I, Tartamella F, Prisco L, Bigotto F, Bigolin T, Ferluga M, Batticci I, Michelone E, Borelli M, Viviani M, Tomasini A. Relationship between the timing of administration of IgM and IgA enriched immunoglobulins in patients with severe sepsis and septic shock and the outcome: a retrospective analysis. *J Crit Care* 2012; **27**: 167-171 [PMID: 21737236 DOI: 10.1016/j.jcrc.2011.05.012]

79 **Pildal J**, Gøtzsche PC. Polyclonal immunoglobulin for treatment of bacterial sepsis: a systematic review. *Clin Infect Dis* 2004; **39**: 38-46 [PMID: 15206051 DOI: 10.1086/421089]

80 **Cui J**, Wei X, Lv H, Li Y, Li P, Chen Z, Liu G. The clinical efficacy of intravenous IgM-enriched immunoglobulin (pentaglobin) in sepsis or septic shock: a meta-analysis with trial sequential analysis. *Ann Intensive Care* 2019; **9**: 27 [PMID: 30725235 DOI: 10.1186/s13613-019-0501-3]

81 **Cavazzuti I**, Serafini G, Busani S, Rinaldi L, Biagioni E, Buoncristiano M, Girardis M. Early therapy with IgM-enriched polyclonal immunoglobulin in patients with septic shock. *Intensive Care Med* 2014; **40**: 1888-1896 [PMID: 25217146 DOI: 10.1007/s00134-014-3474-6]

82 **Olivares MM**, Olmos CE, Álvarez MI, Fajardo AM, Zea-Vera AF, Ortega MC, Medina D, Pérez PM, Beltrán DG, Duque B, Álvarez CA, Lenis G, Solano JM, Gómez D, Franco JL, Díaz MC, Orrego JC, Velásquez MM, Chaparro M, Pinto JL, Izquierdo Á, Ramírez SF. [Colombian Guidelines of clinical practice for the use of immunoglobulins in the treatment of replacement and immunomodulation]. *Rev Alerg Mex* 2017; **64** Suppl 2: s5-s65 [PMID: 28863425 DOI: 10.29262/ram.v64i0.300]

83 **Berlot G**, Vassallo MC, Busetto N, Nieto Yabar M, Istrati T, Baronio S, Quarantotto G, Bixio M, Barbati G, Dattola R, Longo I, Chillemi A, Scamperle A, Iscra F, Tomasini A. Effects of the timing of administration of IgM- and IgA-enriched intravenous polyclonal immunoglobulins on the outcome of septic shock patients. *Ann Intensive Care* 2018; **8**: 122 [PMID: 30535962 DOI: 10.1186/s13613-018-0466-7]

84 **Ankawi G**, Neri M, Zhang J, Breglia A, Ricci Z, Ronco C. Extracorporeal techniques for the treatment of critically ill patients with sepsis beyond conventional blood purification therapy: the promises and the pitfalls. *Crit Care* 2018; **22**: 262 [PMID: 30360755 DOI: 10.1186/s13054-018-2181-z]

85 **Lakshmikanth CL**, Jacob SP, Chaithra VH, de Castro-Faria-Neto HC, Marathe GK. Sepsis: in search of cure. *Inflamm Res* 2016; **65**: 587-602 [PMID: 26995266 DOI: 10.1007/s00011-016-0937-y]

86 **Marshall JC**, Foster D, Vincent JL, Cook DJ, Cohen J, Dellinger RP, Opal S, Abraham E, Brett SJ, Smith T, Mehta S, Derzko A, Romaschin A; MEDIC study. Diagnostic and prognostic implications of endotoxemia in critical illness: results of the MEDIC study. *J Infect Dis* 2004; **190**: 527-534 [PMID: 15243928 DOI: 10.1086/422254]

87 **Ronco C**. Endotoxin removal: history of a mission. *Blood Purif* 2014; **37** Suppl 1: 5-8 [PMID: 24457488 DOI: 10.1159/000356831]

88 **Bottiroli M**, Monti G, Pinciroli R, Vecchi I, Terzi V, Ortisi G, Casella G, Fumagalli R. Prevalence and clinical significance of early high Endotoxin Activity in septic shock: An observational study. *J Crit Care* 2017; **41**: 124-129 [PMID: 28525777 DOI: 10.1016/j.jcrc.2017.04.030]

89 **Levin J**, Bang FB. Clottable protein in Limulus; its localization and kinetics of its coagulation by endotoxin. *Thromb Diath Haemorrh* 1968; **19**: 186-197 [PMID: 5690028 DOI: 10.1055/s-0038-1651195]

90 **Romaschin AD**, Harris DM, Ribeiro MB, Paice J, Foster DM, Walker PM, Marshall JC. A rapid assay of endotoxin in whole blood using autologous neutrophil dependent chemiluminescence. *J Immunol Methods* 1998; **212**: 169-185 [PMID: 9672205 DOI: 10.1016/s0022-1759(98)00003-9]

91 **Vincent JL**, Laterre PF, Cohen J, Burchardi H, Bruining H, Lerma FA, Wittebole X, De Backer D, Brett S, Marzo D, Nakamura H, John S. A pilot-controlled study of a polymyxin B-immobilized hemoperfusion cartridge in patients with severe sepsis secondary to intra-abdominal infection. *Shock* 2005; **23**: 400-405 [PMID: 15834304 DOI: 10.1097/01.shk.0000159930.87737.8a]

92 **Cruz DN**, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A, Malcangi V, Petrini F, Volta G, Bobbio Pallavicini FM, Rottoli F, Giunta F, Ronco C. Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. *JAMA* 2009; **301**: 2445-2452 [PMID: 19531784 DOI: 10.1001/jama.2009.856]

93 **Payen DM**, Guilhot J, Launey Y, Lukaszewicz AC, Kaaki M, Veber B, Pottecher J, Joannes-Boyau O, Martin-Lefevre L, Jabaudon M, Mimoz O, Coudroy R, Ferrandière M, Kipnis E, Vela C, Chevallier S, Mallat J, Robert R; ABDOMIX Group. Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial. *Intensive Care Med* 2015; **41**: 975-984 [PMID: 25862039 DOI: 10.1007/s00134-015-3751-z]

94 **Dellinger RP**, Bagshaw SM, Antonelli M, Foster DM, Klein DJ, Marshall JC, Palevsky PM, Weisberg LS, Schorr CA, Trzeciak S, Walker PM; EUPHRATES Trial Investigators. Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level: The EUPHRATES Randomized Clinical Trial. *JAMA* 2018; **320**: 1455-1463 [PMID: 30304428 DOI: 10.1001/jama.2018.14618]

95 **Klein DJ**, Foster D, Walker PM, Bagshaw SM, Mekonnen H, Antonelli M. Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial. *Intensive Care Med* 2018; **44**: 2205-2212 [PMID: 30470853 DOI: 10.1007/s00134-018-5463-7]

96 **Monti G**, Terzi V, Calini A, Di Marco F, Cruz D, Pulici M, Brioschi P, Vesconi S, Fumagalli R, Casella G. Rescue therapy with polymyxin B hemoperfusion in high-dose vasopressor therapy refractory septic shock. *Minerva Anestesiol* 2015; **81**: 516-525 [PMID: 25319136]

97 **Iba T**, Klein DJ. The wind changed direction and the big river still flows: from EUPHRATES to TIGRIS. *J Intensive Care* 2019; **7**: 31 [PMID: 31131109 DOI: 10.1186/s40560-019-0386-0]

98 **Cohen J**. The immunopathogenesis of sepsis. *Nature* 2002; **420**: 885-891 [PMID: 12490963 DOI: 10.1038/nature01326]

99 **Levi M**, van der Poll T. Coagulation and sepsis. *Thromb Res* 2017; **149**: 38-44 [PMID: 27886531 DOI: 10.1016/j.thromres.2016.11.007]

100 **Matsumoto H**, Ogura H, Shimizu K, Ikeda M, Hirose T, Matsuura H, Kang S, Takahashi K, Tanaka T, Shimazu T. The clinical importance of a cytokine network in the acute phase of sepsis. *Sci Rep* 2018; **8**: 13995 [PMID: 30228372 DOI: 10.1038/s41598-018-32275-8]

101 **Hack CE**, Aarden LA, Thijs LG. Role of cytokines in sepsis. *Adv Immunol* 1997; **66**: 101-195 [PMID: 9328641 DOI: 10.1016/s0065-2776(08)60597-0]

102 **van der Poll T**, van Deventer SJ. Cytokines and anticytokines in the pathogenesis of sepsis. *Infect Dis Clin North Am* 1999; **13**: 413-426, ix [PMID: 10340175 DOI: 10.1016/s0891-5520(05)70083-0]

103 **Nakae H**, Endo S, Inada K, Takakuwa T, Kasai T. Changes in adhesion molecule levels in sepsis. *Res Commun Mol Pathol Pharmacol* 1996; **91**: 329-338 [PMID: 8829772]

104 **Shimaoka M**, Park EJ. Advances in understanding sepsis. *Eur J Anaesthesiol Suppl* 2008; **42**: 146-153 [PMID: 18289433 DOI: 10.1017/S0265021507003389]

105 **Schouten M**, Wiersinga WJ, Levi M, van der Poll T. Inflammation, endothelium, and coagulation in sepsis. *J Leukoc Biol* 2008; **83**: 536-545 [PMID: 18032692 DOI: 10.1189/jlb.0607373]

106 **Fong Y**, Tracey KJ, Moldawer LL, Hesse DG, Manogue KB, Kenney JS, Lee AT, Kuo GC, Allison AC, Lowry SF. Antibodies to cachectin/tumor necrosis factor reduce interleukin 1 beta and interleukin 6 appearance during lethal bacteremia. *J Exp Med* 1989; **170**: 1627-1633 [PMID: 2809510 DOI: 10.1084/jem.170.5.1627]

107 **Chai Z**, Gatti S, Toniatti C, Poli V, Bartfai T. Interleukin (IL)-6 gene expression in the central nervous system is necessary for fever response to lipopolysaccharide or IL-1 beta: a study on IL-6-deficient mice. *J Exp Med* 1996; **183**: 311-316 [PMID: 8551238 DOI: 10.1084/jem.183.1.311]

108 **Kopf M**, Baumann H, Freer G, Freudenberg M, Lamers M, Kishimoto T, Zinkernagel R, Bluethmann H, Köhler G. Impaired immune and acute-phase responses in interleukin-6-deficient mice. *Nature* 1994; **368**: 339-342 [PMID: 8127368 DOI: 10.1038/368339a0]

109 **Tilg H**, Dinarello CA, Mier JW. IL-6 and APPs: anti-inflammatory and immunosuppressive mediators. *Immunol Today* 1997; **18**: 428-432 [PMID: 9293158 DOI: 10.1016/s0167-5699(97)01103-1]

110 **Schindler R**, Mancilla J, Endres S, Ghorbani R, Clark SC, Dinarello CA. Correlations and interactions in the production of interleukin-6 (IL-6), IL-1, and tumor necrosis factor (TNF) in human blood mononuclear cells: IL-6 suppresses IL-1 and TNF. *Blood* 1990; **75**: 40-47 [PMID: 2294996 DOI: 10.1182/blood.V75.1.40.bloodjournal75140]

111 **Steensberg A**, Fischer CP, Keller C, Møller K, Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *Am J Physiol Endocrinol Metab* 2003; **285**: E433-E437 [PMID: 12857678

DOI: 10.1152/ajpendo.00074.2003]
112 **Tilg H**, Trehu E, Atkins MB, Dinarello CA, Mier JW. Interleukin-6 (IL-6) as an anti-inflammatory cytokine: induction of circulating IL-1 receptor antagonist and soluble tumor necrosis factor receptor p55. *Blood* 1994; **83**: 113-118 [PMID: 8274730 DOI: 10.1182/blood.V83.1.113.bloodjournal831113]
113 **Zhang XL**, Topley N, Ito T, Phillips A. Interleukin-6 regulation of transforming growth factor (TGF)-beta receptor compartmentalization and turnover enhances TGF-beta1 signaling. *J Biol Chem* 2005; **280**: 12239-12245 [PMID: 15661740 DOI: 10.1074/jbc.M413284200]
114 **de Waal Malefyt R**, Abrams J, Bennett B, Figdor CG, de Vries JE. Interleukin 10(IL-10) inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes. *J Exp Med* 1991; **174**: 1209-1220 [PMID: 1940799 DOI: 10.1084/jem.174.5.1209]
115 **Fiorentino DF**, Zlotnik A, Mosmann TR, Howard M, O'Garra A. IL-10 inhibits cytokine production by activated macrophages. *J Immunol* 1991; **147**: 3815-3822 [PMID: 1940369]
116 **Kellum JA**, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, Fine J, Krichevsky A, Delude RL, Angus DC; GenIMS Investigators. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. *Arch Intern Med* 2007; **167**: 1655-1663 [PMID: 17698689 DOI: 10.1001/archinte.167.15.1655]
117 **Oda S**, Hirasawa H, Shiga H, Nakanishi K, Matsuda K, Nakamua M. Sequential measurement of IL-6 blood levels in patients with systemic inflammatory response syndrome (SIRS)/sepsis. *Cytokine* 2005; **29**: 169-175 [PMID: 15652449 DOI: 10.1016/j.cyto.2004.10.010]
118 **Bozza FA**, Salluh JI, Japiassu AM, Soares M, Assis EF, Gomes RN, Bozza MT, Castro-Faria-Neto HC, Bozza PT. Cytokine profiles as markers of disease severity in sepsis: a multiplex analysis. *Crit Care* 2007; **11**: R49 [PMID: 17448250 DOI: 10.1186/cc5783]
119 **Tschaikowsky K**, Hedwig-Geissing M, Braun GG, Radespiel-Troeger M. Predictive value of procalcitonin, interleukin-6, and C-reactive protein for survival in postoperative patients with severe sepsis. *J Crit Care* 2011; **26**: 54-64 [PMID: 20646905 DOI: 10.1016/j.jcrc.2010.04.011]
120 **Jekarl DW**, Lee SY, Lee J, Park YJ, Kim Y, Park JH, Wee JH, Choi SP. Procalcitonin as a diagnostic marker and IL-6 as a prognostic marker for sepsis. *Diagn Microbiol Infect Dis* 2013; **75**: 342-347 [PMID: 23391607 DOI: 10.1016/j.diagmicrobio.2012.12.011]
121 **Kumar AT**, Sudhir U, Punith K, Kumar R, Ravi Kumar VN, Rao MY. Cytokine profile in elderly patients with sepsis. *Indian J Crit Care Med* 2009; **13**: 74-78 [PMID: 19881187 DOI: 10.4103/0972-5229.56052]
122 **Gogos CA**, Drosou E, Bassaris HP, Skoutelis A. Pro- *vs* anti-inflammatory cytokine profile in patients with severe sepsis: a marker for prognosis and future therapeutic options. *J Infect Dis* 2000; **181**: 176-180 [PMID: 10608764 DOI: 10.1086/315214]
123 **Chaudhry H**, Zhou J, Zhong Y, Ali MM, McGuire F, Nagarkatti PS, Nagarkatti M. Role of cytokines as a double-edged sword in sepsis. *In Vivo* 2013; **27**: 669-684 [PMID: 24292568]
124 **Friesecke S**, Stecher SS, Gross S, Felix SB, Nierhaus A. Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study. *J Artif Organs* 2017; **20**: 252-259 [PMID: 28589286 DOI: 10.1007/s10047-017-0967-4]
125 **Paul R**, Sathe P, Kumar S, Prasad S, Aleem M, Sakhalvalkar P. Multicentered prospective investigator initiated study to evaluate the clinical outcomes with extracorporeal cytokine adsorption device (CytoSorb®) in patients with sepsis and septic shock. *World J Crit Care Med* 2021; **10**: 22-34 [PMID: 33505870 DOI: 10.5492/wjccm.v10.i1.22]
126 **Brouwer WP**, Duran S, Kuijper M, Ince C. Hemoadsorption with CytoSorb shows a decreased observed *vs* expected 28-day all-cause mortality in ICU patients with septic shock: a propensity-score-weighted retrospective study. *Crit Care* 2019; **23**: 317 [PMID: 31533846 DOI: 10.1186/s13054-019-2588-1]
127 **Hawchar F**, László I, Öveges N, Trásy D, Ondrik Z, Molnar Z. Extracorporeal cytokine adsorption in septic shock: A proof of concept randomized, controlled pilot study. *J Crit Care* 2019; **49**: 172-178 [PMID: 30448517 DOI: 10.1016/j.jcrc.2018.11.003]
128 **Rugg C**, Klose R, Hornung R, Innerhofer N, Bachler M, Schmid S, Fries D, Ströhle M. Hemoadsorption with CytoSorb in Septic Shock Reduces Catecholamine Requirements and In-Hospital Mortality: A Single-Center Retrospective 'Genetic' Matched Analysis. *Biomedicines* 2020; **8** [PMID: 33255912 DOI: 10.3390/biomedicines8120539]
129 **Bone RC**. Sir Isaac Newton, sepsis, SIRS, and CARS. *Crit Care Med* 1996; **24**: 1125-1128 [PMID: 8674323 DOI: 10.1097/00003246-199607000-00010]
130 **Le Tulzo Y**, Pangault C, Amiot L, Guilloux V, Tribut O, Arvieux C, Camus C, Fauchet R, Thomas R, Drénou B. Monocyte human leukocyte antigen-DR transcriptional downregulation by cortisol during septic shock. *Am J Respir Crit Care Med* 2004; **169**: 1144-1151 [PMID: 15028560 DOI: 10.1164/rccm.200309-1329OC]
131 **Leijte GP**, Rimmelé T, Kox M, Bruse N, Monard C, Gossez M, Monneret G, Pickkers P, Venet F. Monocytic HLA-DR expression kinetics in septic shock patients with different pathogens, sites of infection and adverse outcomes. *Crit Care* 2020; **24**: 110 [PMID: 32192532 DOI: 10.1186/s13054-020-2830-x]
132 **Cajander S**, Bäckman A, Tina E, Strålin K, Söderquist B, Källman J. Preliminary results in quantitation of HLA-DRA by real-time PCR: a promising approach to identify immunosuppression in sepsis. *Crit Care* 2013; **17**: R223 [PMID: 24093602 DOI: 10.1186/cc13046]
133 **Monneret G**, Venet F. Monocyte HLA-DR in sepsis: shall we stop following the flow? *Crit Care*

2014; **18**: 102 [PMID: 24393356 DOI: 10.1186/cc13179]

134 **Cazalis MA**, Friggeri A, Cavé L, Demaret J, Barbalat V, Cerrato E, Lepape A, Pachot A, Monneret G, Venet F. Decreased HLA-DR antigen-associated invariant chain (CD74) mRNA expression predicts mortality after septic shock. *Crit Care* 2013; **17**: R287 [PMID: 24321376 DOI: 10.1186/cc13150]

135 **Meisel C**, Schefold JC, Pschowski R, Baumann T, Hetzger K, Gregor J, Weber-Carstens S, Hasper D, Keh D, Zuckermann H, Reinke P, Volk HD. Granulocyte-macrophage colony-stimulating factor to reverse sepsis-associated immunosuppression: a double-blind, randomized, placebo-controlled multicenter trial. *Am J Respir Crit Care Med* 2009; **180**: 640-648 [PMID: 19590022 DOI: 10.1164/rccm.200903-0363OC]

136 **Spinetti T**, Hirzel C, Fux M, Walti LN, Schober P, Stueber F, Luedi MM, Schefold JC. Reduced Monocytic Human Leukocyte Antigen-DR Expression Indicates Immunosuppression in Critically Ill COVID-19 Patients. *Anesth Analg* 2020; **131**: 993-999 [PMID: 32925314 DOI: 10.1213/ANE.0000000000005044]

137 **Pinder EM**, Rostron AJ, Hellyer TP, Ruchaud-Sparagano MH, Scott J, Macfarlane JG, Wiscombe S, Widdrington JD, Roy AI, Linnett VC, Baudouin SV, Wright SE, Chadwick T, Fouweather T, Juss JK, Chilvers ER, Bowett SA, Parker J, McAuley DF, Conway Morris A, Simpson AJ. Randomised controlled trial of GM-CSF in critically ill patients with impaired neutrophil phagocytosis. *Thorax* 2018; **73**: 918-925 [PMID: 30064991 DOI: 10.1136/thoraxjnl-2017-211323]

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MINIREVIEWS

Acute exacerbation of interstitial lung disease in the intensive care unit

Antonios Charokopos, Teng Moua, Jay H Ryu, Nathan J Smischney

ORCID number: Antonios Charokopos 0000-0002-8895-687X; Teng Moua 0000-0003-3329-5717; Jay H Ryu 0000-0002-9576-2272; Nathan J Smischney 0000-0003-1051-098X.

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Antonios Charokopos, Teng Moua, Jay H Ryu, Department of Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN 55905, United States

Nathan J Smischney, Department of Anesthesiology and Perioperative Medicine, Division of Critical Care Medicine, Mayo Clinic, Rochester, MN 55905, United States

Corresponding author: Nathan J Smischney, MD, MSc, Assistant Professor, Department of Anesthesiology and Perioperative Medicine, Division of Critical Care Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905, United States. smischney.nathan@mayo.edu

Abstract

Acute exacerbations of interstitial lung disease (AE-ILD) represent an acute, frequent and often highly morbid event in the disease course of ILD patients. Admission in the intensive care unit (ICU) is very common and the need for mechanical ventilation arises early. While non-invasive ventilation has shown promise in staving off intubation in selected patients, it is unclear whether mechanical ventilation can alter the exacerbation course unless it is a bridge to lung transplantation. Risk stratification using clinical and radiographic findings, and early palliative care involvement, are important in ICU care. In this review, we discuss many of the pathophysiological aspects of AE-ILD and raise the hypothesis that ventilation strategies used in acute respiratory distress syndrome might be implemented in AE-ILD. We present possible decision-making and management algorithms that can be used by the intensivist when caring for these patients.

Key Words: Interstitial lung diseases; Disease exacerbation; Mechanical ventilation; Intensive care unit; Pathophysiological aspect

Core Tip: During the acute and morbid event of acute exacerbation of interstitial lung disease, an intensivist needs to understand the pathophysiology and reversible causes of acute exacerbations, the diagnostics and treatments that are usually recommended, and the experimental therapies on the horizon. More importantly, the intensivist needs to be able to risk stratify the patients, selectively pursue mechanical ventilation,

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minimize ventilator induced lung injury, and involve palliative care early in non-lung transplant candidates.

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INTRODUCTION

Definitions and epidemiology

Acute exacerbations in interstitial lung diseases (AE-ILD) represent an acute, and frequently morbid, deterioration of the patients' respiratory function, often leading to hospital admission. Intensivists are at the forefront of care for these patients, and often need to make critical decisions about treatment and whether mechanical ventilation will be beneficial. While originally and most thoroughly described in idiopathic pulmonary fibrosis (IPF), acute exacerbations are increasingly recognized in other types of fibrotic interstitial lung disease (ILD) such as fibrotic (chronic) hypersensitivity pneumonitis[1,2] and connective-tissue disease related ILD[3-5]. To distinguish between the two entities, we will refer to i) acute exacerbations of IPF (AE-IPF) and ii) acute exacerbations of non-IPF interstitial lung disease (AE-nonIPF), grouped together as AE-ILD.

The definition of AE-IPF has shifted between 2007 (Idiopathic Pulmonary Fibrosis network, IPFnet)[6] and 2016 (revised criteria by international working group)[7]. The definition currently includes: (1) Known diagnosis of IPF; (2) Worsening dyspnea within the last 30 d; and (3) New bilateral ground glass opacities and/or consolidation upon a background of usual interstitial pneumonia (UIP); the previous requirement for exclusion of concurrent pulmonary embolism (PE) and identifiable infection has been eliminated[7].

The incidence rate of AE-IPF has been estimated to be 41 cases per 1000 person-years[8] with approximately 10% of IPF patients experiencing an acute exacerbation in the two years following their diagnosis[9]. AE-IPF tends to be more prevalent in those with more advanced disease, as measured by worse pulmonary function (especially forced vital capacity, and diffusing capacity for carbon monoxide), shorter 6 min walking distance, and lower baseline oxygenation[10-14].

Pathophysiology and triggers of acute exacerbations of ILD

An acute exacerbation occurring in patients with IPF and other fibrotic ILDs is often unpredictable, but specific intrinsic and extrinsic factors have been hypothesized to trigger the event. Intrinsic factors, such as epithelial homeostatic imbalance affecting fibrocyte differentiation, macrophage immune polarization, and possibly autoimmunity emergence against heat-shock proteins and phospholipid-binding proteins[15-18], have been identified in patients with AE-IPF. Several other factors, such as air pollution[19] and micro-aspiration[20,21], have also been identified. Interestingly, in a retrospective analysis of three well-known IPF placebo controlled clinical trials, none of the patients who developed AE-IPF were on anti-acid treatment[22,23]. A higher eosinophil percentage in bronchoalveolar lavage (BAL) has been associated with the onset of AE-IPF[24].

When an identifiable extrinsic trigger for AE-ILD is lacking, then the AE-ILD is considered idiopathic. On the contrary, infection, aspiration and drug toxicity are common extrinsic triggers of AE-ILD. Infection has been identified in 10% to 30% of patients with AE-ILD[25-27]. Furthermore, post-procedural AE-ILD has also been reported, including video-assisted thoracoscopic procedures and bronchoscopy with lavage[28-30]. The underlying mechanism is thought to be due to possible ventilator-induced injury (including hyperoxia or barotrauma), perioperative mechanical stretch, or fluid balance[7,31]. In a large study of acute exacerbations in all types of ILD, 52% of admissions for acute respiratory worsening were considered idiopathic, 20% due to infection, 15% due to subacute progression or end-stage disease, 6% due to heart failure or severe pulmonary hypertension, 4% due to venous thromboembolic disease, and 2% from diffuse alveolar hemorrhage or peri-procedural exacerbation[25].

Both AE-ILD and acute respiratory distress syndrome (ARDS) have bilateral ground glass opacities and/or consolidations on imaging and often refractory hypoxemia. Similar to ARDS, the most frequent histopathologic finding on lung biopsy seen in AE-ILD is diffuse alveolar damage[3,32], which involves an acute exudative phase followed by an organizing-proliferative phase[33]. It is likely that both patients with AE-ILD and ARDS have an aberrant and defective healing response to lung injury, that involves a pro-fibrotic positive-feedback loop[34-36].

Diagnostic evaluation indicated on hospital or intensive care unit admission

When a patient with ILD, or specifically IPF, is admitted for acute respiratory worsening, it is up to the inpatient physician, or more often the intensivist, to distinguish between idiopathic acute exacerbation *vs* acute exacerbation secondary to a specific "treatable" trigger such as infection. In-hospital survival is worse in those with idiopathic AE-ILD compared to those stemming from a known-trigger[25], possibly due to lack of targeted treatment.

Interestingly, acute exacerbation may be the first presentation of previously undiagnosed ILD, with such patients comprising 29% of one large academic cohort [25]. Radiologic findings of fibrotic disease including reticulation and traction bronchiectasis, in a patient without known pulmonary disease suggests undiagnosed ILD. Surgical lung biopsy is often avoided during AE-IPF as its results often do not alter the course of acute exacerbation[32], and have increased peri/post-operative morbidity[37].

If the patient has previously undiagnosed ILD as noted above, then autoimmune serologies, including evaluation for pulmonary vasculitis with antineutrophil cytoplasmic antibodies, would be indicated to further clarify any potential autoimmunity that would suggest a related connective-tissue disease or interstitial pneumonia with autoimmune features (IPAF). This may potentially affect management, as patients with autoimmune disease-related ILDs are more likely to be treated with immunosuppression, unlike in IPF patients[38].

Infection can be evaluated by various sources, including laboratory findings (white cell count, urine *Legionella* or *Streptococcus pneumoniae* antigens, procalcitonin[39], nasal or sputum viral polymerase chain reaction [PCR] tests), vital signs, and of course blood or respiratory cultures[40]. The yield of bronchoscopy has been found to be relatively low; only 13% of bronchoscopies in AE-ILD yielded abnormal results according to a major study[27], with 25% of patients having bronchoscopy on the general floor necessitating post-procedural ICU transfer. When bronchoscopy is performed, BAL specimens should be sent for bacterial, fungal and mycobacterial cultures, including viral PCR tests. Since AE-non-IPF patients are often immunocompromised, an intensivist should consider pneumocystis jirovecii and herpesvirus infections, which represented 25% and 18% of positive bronchoscopies in one study, respectively[27].

High-resolution computed tomography (CT) is critical in clarifying the extent of underlying fibrotic interstitial disease and suspected new or superimposed ground glass or consolidative abnormalities. The extent and pattern of superimposed infiltrates on high-resolution CT have been found to be predictive of survival in AE-IPF[41,42]. The separation of the Kaplan-Meier survival curves depending on 3 different types of CT findings (peripheral, multifocal, or diffuse pattern) was found to be quite striking[41]. A protocol assessing for pulmonary embolism - or a ventilation-perfusion and lower extremity doppler scan in patients with renal impairment - may be reasonable to exclude thromboembolic disease. However, a PE protocol study was performed in only 43% of admissions for acute respiratory worsening in ILD patients [25]. Interestingly, a link between a profibrotic and a prothrombotic state has been found[43], with studies reporting higher risk of venous thromboembolism (VTE) in IPF patients[44,45]. Physical examination, serum brain natriuretic peptide concentrations, and echocardiography are used to evaluate for any component of heart failure and pulmonary hypertension[7].

TO INTUBATE OR NOT TO INTUBATE?

When an intensivist encounters a deteriorating patient with AE-ILD, the decision for invasive mechanical ventilation (IMV) must be balanced with the prognosis and reversibility of the patient's condition. Multiple studies have shown poor outcomes in this population, including studies that analyzed admissions before[46-48] and after[25, 49] changes in lung protective ventilation following the publication of the ARDSnet

trial in 2000. In-hospital mortality may reach 50% with 1-year mortality at 70%. In the years before lung protective ventilation strategies, studies identified that 85% mechanically ventilated patients with AE-IPF died while ventilated, and proposed that ICU admission and intubation may be futile[46]. Nevertheless, both due to: (1) the acceptance of lower tidal volumes in ICUs; and (2) Changes in the definition of AE-IPF to include potentially reversible causes, the outcomes of ventilated patients with AE-IPF have improved, but still remain poor. In a nationwide cohort from 2006-2012, in-hospital mortality of AE-IPF patients who received mechanical ventilation was 51.6% (although improved from 58.4% in 2006 to 49.3% in 2012) and of patients who received non-invasive ventilation (NIV) was 30.9%[49]. In another study of patients in French ICUs from 2002 to 2009, only 30% of those mechanically ventilated were successfully weaned[50]. As expected, in-hospital mortality varies according to ventilation type, being higher in patients requiring IMV compared to patients requiring NIV or no ventilation support in a large multicenter ICU database study[51]. NIV is a reasonable therapeutic option which may allow certain patients to avoid the morbidity of IMV[51, 52].

In general, mortality is affected by disease type, with IPF for example having worse outcomes compared to other fibrotic ILD associated with autoimmune disorders or hypersensitivity pneumonitis. In a landmark study that explored admissions for acute respiratory worsening in patients with chronic fibrotic lung disease, in-hospital mortality was the same between IPF and patients without IPF (55% *vs* 45%, $P > 0.05$) [25], although other studies found nonspecific interstitial pneumonia to be associated with a relatively good discharge rate and long-term prognosis[4]. In a different study, 90-day mortality was found to be significantly higher in AE-IPF than AE-non-IPF (69% *vs* 34%)[53]. One-year mortality after hospitalization for acute exacerbation was worse in IPF than non-IPF (87% *vs* 71%), yet still very high in both groups[25]. Furthermore, while infection accounted for a third of AE-ILD cases in another United States cohort, outcomes did not differ between those with infection and those without[26]. However, post-operative exacerbation and respiratory failure in ILD patients is associated with a better prognosis[54]. Specific findings on high-resolution CT at admission in AE-IPF patients have been correlated with prognosis[41,42]. Artificial intelligence software is increasingly showing application and promise in the analysis of CT scans in ILD patients, and may potentially be used for prognostication[55].

In the authors' opinion, risk stratification and goals of care discussion need to take place early on when a patient with AE-ILD is admitted to the ICU. Studies have shown that a subset of patients can be weaned from mechanical ventilation and discharged, suggesting that IMV should not be systematically denied to these patients but considered individually[50]. Risk stratification certainly depends on clinical judgement, but can also be assisted by other published insights, including the aforementioned CT characteristics[41,42]. On admission to the hospital for respiratory worsening, only 20% of patients with fibrotic lung disease have a "do not resuscitate, do not intubate" code status[25]. Palliative care should be consulted early in the patients' admission, and eligibility (or pre-existing enrollment with previous work-up completion) of patients for lung transplant should play important roles in the management decision tree (Figure 1). While the poor outcomes of mechanical ventilation place it in the role of "bridge therapy", lung transplant is a potential "destination therapy" even for patients with severe acute exacerbations and deteriorating oxygenation. In non-transplant candidates who are deemed high risk for poor outcome, hospice should be brought up early in family discussions and goals of patient comfort and wishes for end-of-life strongly taken into consideration.

USUAL TREATMENTS IN ACUTE EXCERBATIONS

While the outcomes of AE-ILD patients have been well described, well-designed prospective clinical research in the management of these patients is lacking. It is unclear if the high morbidity and mortality of acute exacerbations creates a fertile environment for research as accepted by distressed patients and their families. International guidelines for AE-IPF make a weak recommendation for the use of corticosteroids, namely that corticosteroids should be used in the majority of patients with acute exacerbation of IPF, but not using may be reasonable in a minority[56]. This weak recommendation is based on expert opinion and retrospective reports[41,46,53]. No particular corticosteroid formulation has been found preferrable over another in AE-ILD, despite good outcomes with dexamethasone in ARDS and Coronavirus disease 2019 (Covid-19) associated lung injury[57,58]. Doses ranging from 1mg/kg of

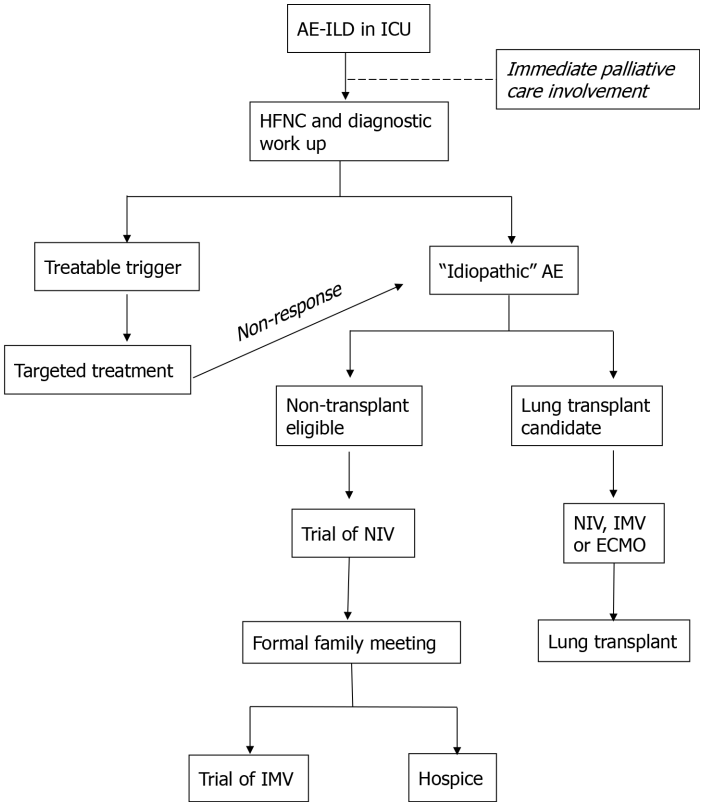

Figure 1 Suggested decision-making tree and management approach of patients admitted to the intensive care unit with acute exacerbation of interstitial lung disease. AE-ILD: Acute exacerbation of interstitial lung disease; ICU: Intensive care unit; HFNC: High flow nasal cannula; AE: Acute exacerbation; NIV: Non-invasive ventilation; IMV: Invasive mechanical ventilation; ECMO: Extracorporeal membrane oxygenation.

prednisone to pulse steroids (methylprednisolone 1 g daily for 3 d) have been used, depending on institutional preference and severity of presentation. In studies comparing corticosteroid treatment in acute exacerbations in idiopathic interstitial pneumonias *vs* connective tissue disease-associated ILD, both groups were observed to be treated with corticosteroids[53]. While others have argued for a steroid-free approach in AE-IPF[59,60], the frequent misdiagnosis of fibrotic hypersensitivity pneumonitis as IPF may be confounding[61]. The uncertainty but routine use of corticosteroids in AE-ILD supports a need for a prospective clinical trial.

Antibiotics are routinely used in AE-ILD, accompanied by appropriate work up to evaluate underlying infection. Both broad spectrum and coverage for atypical pathogens should be considered. Azithromycin, which has been reported to improve outcomes in acute lung injury[62], has also shown particular promise in AE-ILD[63]. This is thought to a result of azithromycin's anti-inflammatory and immune-modulating effects rather than antimicrobial activity, as it has been compared to fluoroquinolones which also cover atypical bacteria[63]. If no underlying infection is found, a routine 7 to 10 day course is reasonable. In a randomized trial, use of procalcitonin to guide antibiotic therapy in patients with AE-IPF resulted in reduced exposure to antibiotics without adversely affecting patient outcomes[39]. Since AE-non-IPF patients are often immunocompromised prior to admission, search for opportunistic pathogens and targeted treatment is prudent (Figure 2).

Key treatments that have been shown to partially prevent AE-IPF or AE-ILD in the outpatient setting - such as antacid therapy[22] and nintentanib[64] - have not been evaluated clinically during acute exacerbation. From the authors' point of view, it is reasonable to continue inpatient use of both antacids and antifibrotics in patients previously treated with them. While there is no peer-reviewed evidence for benefit in initiating antifibrotics in the acute setting except rare case reports[65], antacid therapy should be easily and already instituted in AE-ILD patients treated with corticosteroids and/or mechanical ventilation.

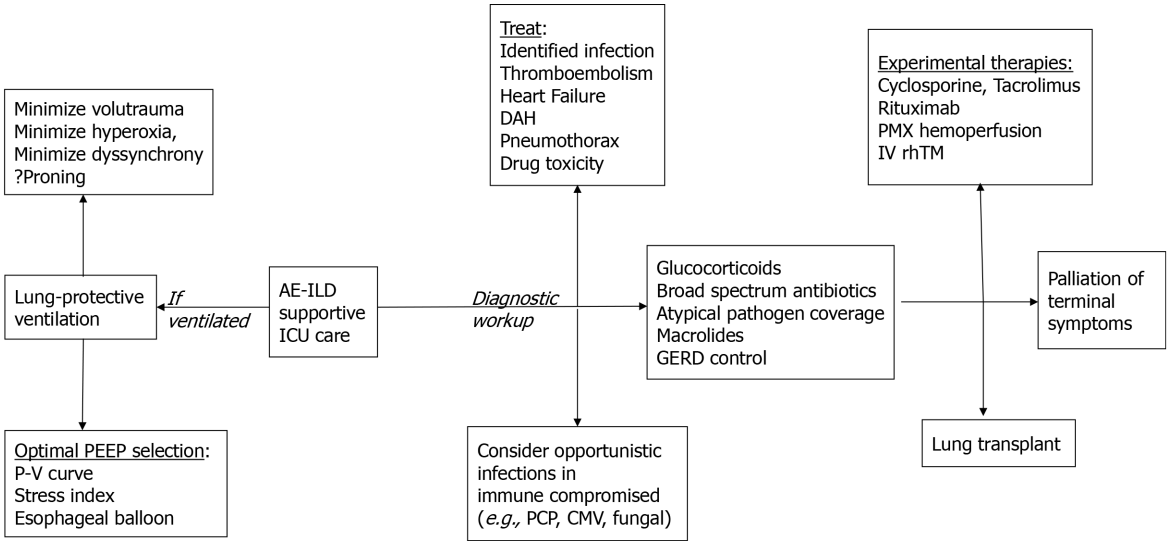

Figure 2 Treatment approaches for acute exacerbation interstitial lung disease. AE-ILD: Acute exacerbation interstitial lung disease; ICU: Intensive care unit; PEEP: Positive end-expiratory pressure; P-V curve: Pressure-volume curve; PCP: Pneumocystis jirovecii pneumonia; CMV: Cytomegalovirus; DAH: Diffuse alveolar hemorrhage; GERD: Gastro-esophageal reflux disease; PMX: Polymyxin-B immobilized fiber column hemoperfusion; IV rhTM: Intravenous recombinant human thrombomodulin.

OPTIMIZATION OF MECHANICAL VENTILATION

AE-ILD has some parallels with ARDS both from a clinical (ground glass infiltrates and severe hypoxemia) and histological (diffuse alveolar damage on pathology) perspective. Similar to ARDS, patients with AE-ILD are prone to ventilator induced injury. Thus, mechanical ventilation strategies used in ARDS should be reasonably utilized in patients with AE-ILD[66]. Avoidance of ventilator-patient dyssynchrony (causing stacked inspired tidal volumes) and prevention of ventilator induced lung injury are of particular importance. Notably 42% of AE-ILD patients required paralytics in a large cohort, although paralytic use was associated with higher mortality in unadjusted analysis and possibly reflective of underlying disease severity [67]. Optimization of positive end-expiratory pressure (PEEP) and lung recruitment using pressure-volume hysteresis curves, stress index, or calculation of transpulmonary pressure with esophageal balloons present an opportunity to at least prevent iatrogenic contribution to a patient's already difficult prognosis. While prone positioning of ventilated patients is strongly supported in ARDS[68], patients with pulmonary fibrosis may be less responsive to proning[69] in the presence of end-stage fibrosis and absence of significant non-hydrostatic pulmonary edema.

Only two studies have examined the effect of ventilator parameters on mortality in patients with AE-ILD[54,67]. The largest study examined 114 admissions for AE-ILD, of which 34% were AE-IPF and 66% were AE-nonIPF[67]. Only 50% of patients in this study achieved a low tidal volume strategy (plateau pressure ≤ 30 cm H_2O) within 3 h of intubation. A variety of modifiable and nonmodifiable parameters - including increased time to intubation, higher initial fraction of inspired oxygen or PEEP, higher mean airway pressures, vasopressor use and right ventricular systolic pressure - were associated with in-hospital mortality. In the second retrospective study, step changes in positive end-expiratory pressure > 10 cm of water were found to have been attempted in 20 patients and resulted in increased airway pressures and decrease in respiratory system compliance suggestive of overdistension[54].

The importance of fluid management - with a goal of net-neutral or net-negative fluid balance - has been increasingly recognized[70], similarly to the management of ARDS. A retrospective study of postoperative AE-IPF patients surgically treated for lung cancer, a common finding in the IPF population[71], showed that more intraoperative fluid administration was associated with higher probability of AE-IPF[31]. Total net fluid status was also an important adjusted risk predictor for mortality in a large study of mechanical ventilation in AE-ILD[67].

EXPERIMENTAL TREATMENTS

In light of currently limited therapeutic options and the high mortality of patients with AE-ILD, experimental therapies have been tested in only a few small studies. Based on the premise of immune dysregulation being a primary driver of AE-IPF and/or AE-nonIPF[72], studies have focused on alternative immunosuppressants or cytokine filtration removal, often in conjunction with corticosteroids (Figure 2). Cyclophosphamide has not been studied using matched controls, but in one single-institution study administration of 1 g daily of methylprednisolone for 3 d followed by monthly cyclophosphamide administration for up to 6 doses showed a favorable overall survival at 3 mo (73%), 6 mo (63%) and 12 mo (55%) compared to the general literature [73]. Calcineurin inhibitors, such as tacrolimus and cyclosporine, have shown some benefit but have only been evaluated in small retrospective studies of 15-45 patients [74-76]. Due to possible autoantibodies in AE-IPF[18], rituximab and plasma exchange were studied in 11 patients with AE-IPF and compared to 20 controls, showing 82% of treated patients improved in terms of oxygenation with some sustaining a relapse-free response[77]. Polymyxin-B immobilized fiber (PMX) hemoperfusion is an alternative approach mostly studied in removing bacterial toxins, but has also been postulated for removing proinflammatory cytokines[78,79] and promoting antifibrotic cytokines[80]. Retrospective studies have shown notable survival benefit from PMX treatment in AE-IPF (12-month survival 41.7% in the PMX group *vs* 9.8% in the non-PMX group)[81, 82], although this has not been confirmed in randomized trials. Disordered hypercoagulation has also been implicated in AE-IPF pathophysiology. Recombinant human thrombomodulin (rhTM), a cofactor for thrombin and anti-coagulant molecule, was recently evaluated as add-on therapy to routine corticosteroid-treated AE-IPF patients decreasing 3 mo mortality to 30%-40 from control levels of 65%-70%[83-85].

CONCLUSION

Despite the relatively common occurrence of AE-IPF and AE-ILD in general[8,9], randomized clinical trials of interventions in acute exacerbations are lacking. As noted in a recent International Working Group report, the optimal management of AE-IPF represents an area of major unmet medical need[7]. Robust prospective clinical studies and randomized trials of therapeutics and maybe ventilation strategies are critical to advance the field and improve the grim prognosis of these patients.

REFERENCES

1 **Miyazaki Y**, Tateishi T, Akashi T, Ohtani Y, Inase N, Yoshizawa Y. Clinical predictors and histologic appearance of acute exacerbations in chronic hypersensitivity pneumonitis. *Chest* 2008; **134**: 1265-1270 [PMID: 18689595 DOI: 10.1378/chest.08-0866]

2 **Olson AL**, Huie TJ, Groshong SD, Cosgrove GP, Janssen WJ, Schwarz MI, Brown KK, Frankel SK. Acute exacerbations of fibrotic hypersensitivity pneumonitis: a case series. *Chest* 2008; **134**: 844-850 [PMID: 18842917 DOI: 10.1378/chest.08-0428]

3 **Rice AJ**, Wells AU, Bouros D, du Bois RM, Hansell DM, Polychronopoulos V, Vassilakis D, Kerr JR, Evans TW, Nicholson AG. Terminal diffuse alveolar damage in relation to interstitial pneumonias. An autopsy study. *Am J Clin Pathol* 2003; **119**: 709-714 [PMID: 12760290 DOI: 10.1309/UVAR-MDY8-FE9F-JDKU]

4 **Park IN**, Kim DS, Shim TS, Lim CM, Lee SD, Koh Y, Kim WS, Kim WD, Jang SJ, Colby TV. Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. *Chest* 2007; **132**: 214-220 [PMID: 17400667 DOI: 10.1378/chest.07-0323]

5 **Suda T**, Kaida Y, Nakamura Y, Enomoto N, Fujisawa T, Imokawa S, Hashizume H, Naito T, Hashimoto D, Takehara Y, Inui N, Nakamura H, Colby TV, Chida K. Acute exacerbation of interstitial pneumonia associated with collagen vascular diseases. *Respir Med* 2009; **103**: 846-853 [PMID: 19181509 DOI: 10.1016/j.rmed.2008.12.019]

6 **Collard HR**, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE Jr, Lasky JA, Loyd JE, Noth I, Olman MA, Raghu G, Roman J, Ryu JH, Zisman DA, Hunninghake GW, Colby TV, Egan JJ, Hansell DM, Johkoh T, Kaminski N, Kim DS, Kondoh Y, Lynch DA, Müller-Quernheim J, Myers JL, Nicholson AG, Selman M, Toews GB, Wells AU, Martinez FJ; Idiopathic Pulmonary Fibrosis Clinical Research Network Investigators. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007; **176**: 636-643 [PMID: 17585107 DOI: 10.1164/rccm.200703-463PP]

7 **Collard HR**, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, Lee JS, Maher TM, Wells AU, Antoniou KM, Behr J, Brown KK, Cottin V, Flaherty KR, Fukuoka J, Hansell DM, Johkoh T, Kaminski N, Kim DS, Kolb M, Lynch DA, Myers JL, Raghu G, Richeldi L, Taniguchi H, Martinez

FJ. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. *Am J Respir Crit Care Med* 2016; **194**: 265-275 [PMID: 27299520 DOI: 10.1164/rccm.201604-0801CI]

8 **Atkins CP**, Loke YK, Wilson AM. Outcomes in idiopathic pulmonary fibrosis: a meta-analysis from placebo controlled trials. *Respir Med* 2014; **108**: 376-387 [PMID: 24440032 DOI: 10.1016/j.rmed.2013.11.007]

9 **Kim DS**, Park JH, Park BK, Lee JS, Nicholson AG, Colby T. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. *Eur Respir J* 2006; **27**: 143-150 [PMID: 16387947 DOI: 10.1183/09031936.06.00114004]

10 **Collard HR**, Yow E, Richeldi L, Anstrom KJ, Glazer C; IPFnet investigators. Suspected acute exacerbation of idiopathic pulmonary fibrosis as an outcome measure in clinical trials. *Respir Res* 2013; **14**: 73 [PMID: 23848435 DOI: 10.1186/1465-9921-14-73]

11 **Song JW**, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *Eur Respir J* 2011; **37**: 356-363 [PMID: 20595144 DOI: 10.1183/09031936.00159709]

12 **Kondoh Y**, Taniguchi H, Ebina M, Azuma A, Ogura T, Taguchi Y, Suga M, Takahashi H, Nakata K, Sugiyama Y, Kudoh S, Nukiwa T. Risk factors for acute exacerbation of idiopathic pulmonary fibrosis--Extended analysis of pirfenidone trial in Japan. *Respir Investig* 2015; **53**: 271-278 [PMID: 26521104 DOI: 10.1016/j.resinv.2015.04.005]

13 **Kondoh Y**, Taniguchi H, Katsuta T, Kataoka K, Kimura T, Nishiyama O, Sakamoto K, Johkoh T, Nishimura M, Ono K, Kitaichi M. Risk factors of acute exacerbation of idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis Off J WASOG* 2010; **27**: 103-110

14 **Simon-Blancal V**, Freynet O, Nunes H, Bouvry D, Naggara N, Brillet PY, Denis D, Cohen Y, Vincent F, Valeyre D, Naccache JM. Acute exacerbation of idiopathic pulmonary fibrosis: outcome and prognostic factors. *Respiration* 2012; **83**: 28-35 [PMID: 21860222 DOI: 10.1159/000329891]

15 **Moeller A**, Gilpin SE, Ask K, Cox G, Cook D, Gauldie J, Margetts PJ, Farkas L, Dobranowski J, Boylan C, O'Byrne PM, Strieter RM, Kolb M. Circulating fibrocytes are an indicator of poor prognosis in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009; **179**: 588-594 [PMID: 19151190 DOI: 10.1164/rccm.200810-1534OC]

16 **Schupp JC**, Binder H, Jäger B, Cillis G, Zissel G, Müller-Quernheim J, Prasse A. Macrophage activation in acute exacerbation of idiopathic pulmonary fibrosis. *PLoS One* 2015; **10**: e0116775 [PMID: 25590613 DOI: 10.1371/journal.pone.0116775]

17 **Kahloon RA**, Xue J, Bhargava A, Csizmadia E, Otterbein L, Kass DJ, Bon J, Soejima M, Levesque MC, Lindell KO, Gibson KF, Kaminski N, Banga G, Oddis CV, Pilewski JM, Sciurba FC, Donahoe M, Zhang Y, Duncan SR. Patients with idiopathic pulmonary fibrosis with antibodies to heat shock protein 70 have poor prognoses. *Am J Respir Crit Care Med* 2013; **187**: 768-775 [PMID: 23262513 DOI: 10.1164/rccm.201203-0506OC]

18 **Kurosu K**, Takiguchi Y, Okada O, Yumoto N, Sakao S, Tada Y, Kasahara Y, Tanabe N, Tatsumi K, Weiden M, Rom WN, Kuriyama T. Identification of annexin 1 as a novel autoantigen in acute exacerbation of idiopathic pulmonary fibrosis. *J Immunol* 2008; **181**: 756-767 [PMID: 18566442 DOI: 10.4049/jimmunol.181.1.756]

19 **Johannson KA**, Vittinghoff E, Lee K, Balmes JR, Ji W, Kaplan GG, Kim DS, Collard HR. Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. *Eur Respir J* 2014; **43**: 1124-1131 [PMID: 24176998 DOI: 10.1183/09031936.00122213]

20 **Lee JS**, Ryu JH, Elicker BM, Lydell CP, Jones KD, Wolters PJ, King TE Jr, Collard HR. Gastroesophageal reflux therapy is associated with longer survival in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; **184**: 1390-1394 [PMID: 21700909 DOI: 10.1164/rccm.201101-0138OC]

21 **Lee AS**, Lee JS, He Z, Ryu JH. Reflux-Aspiration in Chronic Lung Disease. *Ann Am Thorac Soc* 2020; **17**: 155-164 [PMID: 31697575 DOI: 10.1513/AnnalsATS.201906-427CME]

22 **Lee JS**, Collard HR, Anstrom KJ, Martinez FJ, Noth I, Roberts RS, Yow E, Raghu G; IPFnet Investigators. Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials. *Lancet Respir Med* 2013; **1**: 369-376 [PMID: 24429201 DOI: 10.1016/S2213-2600(13)70105-X]

23 **Leuschner G**, Behr J. Acute Exacerbation in Interstitial Lung Disease. *Front Med (Lausanne)* 2017; **4**: 176 [PMID: 29109947 DOI: 10.3389/fmed.2017.00176]

24 **Kakugawa T**, Sakamoto N, Sato S, Yura H, Harada T, Nakashima S, Hara A, Oda K, Ishimoto H, Yatera K, Ishimatsu Y, Obase Y, Kohno S, Mukae H. Risk factors for an acute exacerbation of idiopathic pulmonary fibrosis. *Respir Res* 2016; **17**: 79 [PMID: 27401332 DOI: 10.1186/s12931-016-0400-1]

25 **Moua T**, Westerly BD, Dulohery MM, Daniels CE, Ryu JH, Lim KG. Patients With Fibrotic Interstitial Lung Disease Hospitalized for Acute Respiratory Worsening: A Large Cohort Analysis. *Chest* 2016; **149**: 1205-1214 [PMID: 26836940 DOI: 10.1016/j.chest.2015.12.026]

26 **Huie TJ**, Olson AL, Cosgrove GP, Janssen WJ, Lara AR, Lynch DA, Groshong SD, Moss M, Schwarz MI, Brown KK, Frankel SK. A detailed evaluation of acute respiratory decline in patients with fibrotic lung disease: aetiology and outcomes. *Respirology* 2010; **15**: 909-917 [PMID: 20546190 DOI: 10.1111/j.1440-1843.2010.01774.x]

27 **Arcadu A**, Moua T. Bronchoscopy assessment of acute respiratory failure in interstitial lung disease. *Respirology* 2017; **22**: 352-359 [PMID: 27712021 DOI: 10.1111/resp.12909]

28 **Bando M**, Ohno S, Hosono T, Yanase K, Sato Y, Sohara Y, Hironaka M, Sugiyama Y. Risk of Acute Exacerbation After Video-assisted Thoracoscopic Lung Biopsy for Interstitial Lung Disease. *J Bronchology Interv Pulmonol* 2009; **16**: 229-235 [PMID: 23168584 DOI: 10.1097/LBR.0b013e3181b767cc]

29 **Sakamoto K**, Taniguchi H, Kondoh Y, Wakai K, Kimura T, Kataoka K, Hashimoto N, Nishiyama O, Hasegawa Y. Acute exacerbation of IPF following diagnostic bronchoalveolar lavage procedures. *Respir Med* 2012; **106**: 436-442 [PMID: 22138357 DOI: 10.1016/j.rmed.2011.11.006]

30 **Suzuki H**, Sekine Y, Yoshida S, Suzuki M, Shibuya K, Yonemori Y, Hiroshima K, Nakatani Y, Mizuno S, Takiguchi Y, Yoshino I. Risk of acute exacerbation of interstitial pneumonia after pulmonary resection for lung cancer in patients with idiopathic pulmonary fibrosis based on preoperative high-resolution computed tomography. *Surg Today* 2011; **41**: 914-921 [PMID: 21748606 DOI: 10.1007/s00595-010-4384-z]

31 **Mizuno Y**, Iwata H, Shirahashi K, Takamochi K, Oh S, Suzuki K, Takemura H. The importance of intraoperative fluid balance for the prevention of postoperative acute exacerbation of idiopathic pulmonary fibrosis after pulmonary resection for primary lung cancer. *Eur J Cardiothorac Surg* 2012; **41**: e161-e165 [PMID: 22504895 DOI: 10.1093/ejcts/ezs147]

32 **Parambil JG**, Myers JL, Ryu JH. Histopathologic features and outcome of patients with acute exacerbation of idiopathic pulmonary fibrosis undergoing surgical lung biopsy. *Chest* 2005; **128**: 3310-3315 [PMID: 16304277 DOI: 10.1378/chest.128.5.3310]

33 **Faverio P**, De Giacomi F, Sardella L, Fiorentino G, Carone M, Salerno F, Ora J, Rogliani P, Pellegrino G, Sferrazza Papa GF, Bini F, Bodini BD, Messinesi G, Pesci A, Esquinas A. Management of acute respiratory failure in interstitial lung diseases: overview and clinical insights. *BMC Pulm Med* 2018; **18**: 70 [PMID: 29764401 DOI: 10.1186/s12890-018-0643-3]

34 **Parker MW**, Rossi D, Peterson M, Smith K, Sikström K, White ES, Connett JE, Henke CA, Larsson O, Bitterman PB. Fibrotic extracellular matrix activates a profibrotic positive feedback loop. *J Clin Invest* 2014; **124**: 1622-1635 [PMID: 24590289 DOI: 10.1172/JCI71386]

35 **Marshall RP**, Bellingan G, Webb S, Puddicombe A, Goldsack N, McAnulty RJ, Laurent GJ. Fibroproliferation occurs early in the acute respiratory distress syndrome and impacts on outcome. *Am J Respir Crit Care Med* 2000; **162**: 1783-1788 [PMID: 11069813 DOI: 10.1164/ajrccm.162.5.2001061]

36 **Rocco PRM**, Dos Santos C, Pelosi P. Lung parenchyma remodeling in acute respiratory distress syndrome. *Minerva Anestesiol* 2009; **75**: 730-740

37 **Hutchinson JP**, Fogarty AW, McKeever TM, Hubbard RB. In-Hospital Mortality after Surgical Lung Biopsy for Interstitial Lung Disease in the United States. 2000 to 2011. *Am J Respir Crit Care Med* 2016; **193**: 1161-1167 [PMID: 26646481 DOI: 10.1164/rccm.201508-1632OC]

38 **Idiopathic Pulmonary Fibrosis Clinical Research Network**. , Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012; **366**: 1968-1977 [PMID: 22607134 DOI: 10.1056/NEJMoa1113354]

39 **Ding J**, Chen Z, Feng K. Procalcitonin-guided antibiotic use in acute exacerbations of idiopathic pulmonary fibrosis. *Int J Med Sci* 2013; **10**: 903-907 [PMID: 23781136 DOI: 10.7150/ijms.4972]

40 **Azadeh N**, Limper AH, Carmona EM, Ryu JH. The Role of Infection in Interstitial Lung Diseases: A Review. *Chest* 2017; **152**: 842-852 [PMID: 28400116 DOI: 10.1016/j.chest.2017.03.033]

41 **Akira M**, Kozuka T, Yamamoto S, Sakatani M. Computed tomography findings in acute exacerbation of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008; **178**: 372-378 [PMID: 18451320 DOI: 10.1164/rccm.200709-1365OC]

42 **Fujimoto K**, Taniguchi H, Johkoh T, Kondoh Y, Ichikado K, Sumikawa H, Ogura T, Kataoka K, Endo T, Kawaguchi A, Müller NL. Acute exacerbation of idiopathic pulmonary fibrosis: high-resolution CT scores predict mortality. *Eur Radiol* 2012; **22**: 83-92 [PMID: 21822949 DOI: 10.1007/s00330-011-2211-6]

43 **Sprunger DB**, Olson AL, Huie TJ, Fernandez-Perez ER, Fischer A, Solomon JJ, Brown KK, Swigris JJ. Pulmonary fibrosis is associated with an elevated risk of thromboembolic disease. *Eur Respir J* 2012; **39**: 125-132 [PMID: 21737559 DOI: 10.1183/09031936.00041411]

44 **Hubbard RB**, Smith C, Le Jeune I, Gribbin J, Fogarty AW. The association between idiopathic pulmonary fibrosis and vascular disease: a population-based study. *Am J Respir Crit Care Med* 2008; **178**: 1257-1261 [PMID: 18755924 DOI: 10.1164/rccm.200805-725OC]

45 **Sode BF**, Dahl M, Nielsen SF, Nordestgaard BG. Venous thromboembolism and risk of idiopathic interstitial pneumonia: a nationwide study. *Am J Respir Crit Care Med* 2010; **181**: 1085-1092 [PMID: 20167844 DOI: 10.1164/rccm.200912-1951OC]

46 **Al-Hameed FM**, Sharma S. Outcome of patients admitted to the intensive care unit for acute exacerbation of idiopathic pulmonary fibrosis. *Can Respir J* 2004; **11**: 117-122 [PMID: 15045042 DOI: 10.1155/2004/379723]

47 **Rangappa P**, Moran JL. Outcomes of patients admitted to the intensive care unit with idiopathic pulmonary fibrosis. *Crit Care Resusc J Australas Acad Crit Care Med* 2009; **11**: 102-109

48 **Saydain G**, Islam A, Afessa B, Ryu JH, Scott JP, Peters SG. Outcome of patients with idiopathic pulmonary fibrosis admitted to the intensive care unit. *Am J Respir Crit Care Med* 2002; **166**: 839-842 [PMID: 12231494 DOI: 10.1164/rccm.2104038]

49 **Rush B**, Wiskar K, Berger L, Griesdale D. The use of mechanical ventilation in patients with idiopathic pulmonary fibrosis in the United States: A nationwide retrospective cohort analysis. *Respir Med* 2016; **111**: 72-76 [PMID: 26733227 DOI: 10.1016/j.rmed.2015.12.005]

50 **Gaudry S**, Vincent F, Rabbat A, Nunes H, Crestani B, Naccache JM, Wolff M, Thabut G, Valeyre D, Cohen Y, Mal H. Invasive mechanical ventilation in patients with fibrosing interstitial pneumonia. *J Thorac Cardiovasc Surg* 2014; **147**: 47-53 [PMID: 23968871 DOI: 10.1016/j.jtcvs.2013.06.039]

51 **Schrader M**, Sathananthan M, Jeganathan N. Patients With Idiopathic Pulmonary Fibrosis Admitted to the ICU With Acute Respiratory Failure-A Reevaluation of the Risk Factors and Outcomes. *J Intensive Care Med* 2021; 885066621989244 [PMID: 33511890 DOI: 10.1177/0885066621989244]

52 **Yokoyama T**, Kondoh Y, Taniguchi H, Kataoka K, Kato K, Nishiyama O, Kimura T, Hasegawa R, Kubo K. Noninvasive ventilation in acute exacerbation of idiopathic pulmonary fibrosis. *Intern Med* 2010; **49**: 1509-1514 [PMID: 20686281 DOI: 10.2169/internalmedicine.49.3222]

53 **Tachikawa R**, Tomii K, Ueda H, Nagata K, Nanjo S, Sakurai A, Otsuka K, Kaji R, Hayashi M, Katakami N, Imai Y. Clinical features and outcome of acute exacerbation of interstitial pneumonia: collagen vascular diseases-related *vs* idiopathic. *Respiration* 2012; **83**: 20-27 [PMID: 21912082 DOI: 10.1159/000329893]

54 **Fernández-Pérez ER**, Yilmaz M, Jenad H, Daniels CE, Ryu JH, Hubmayr RD, Gajic O. Ventilator settings and outcome of respiratory failure in chronic interstitial lung disease. *Chest* 2008; **133**: 1113-1119 [PMID: 17989156 DOI: 10.1378/chest.07-1481]

55 **Jacob J**, Bartholmai BJ, Rajagopalan S, Kokosi M, Nair A, Karwoski R, Walsh SL, Wells AU, Hansell DM. Mortality prediction in idiopathic pulmonary fibrosis: evaluation of computer-based CT analysis with conventional severity measures. *Eur Respir J* 2017; **49** [PMID: 27811068 DOI: 10.1183/13993003.01011-2016]

56 **Raghu G**, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE Jr, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schünemann HJ; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; **183**: 788-824 [PMID: 21471066 DOI: 10.1164/rccm.2009-040GL]

57 **Villar J**, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA, Aguilar G, Alba F, González-Higueras E, Conesa LA, Martín-Rodríguez C, Díaz-Domínguez FJ, Serna-Grande P, Rivas R, Ferreres J, Belda J, Capilla L, Tallet A, Añón JM, Fernández RL, González-Martín JM; dexamethasone in ARDS network. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med* 2020; **8**: 267-276 [PMID: 32043986 DOI: 10.1016/S2213-2600(19)30417-5]

58 **RECOVERY Collaborative Group**, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med* (e-pub ahead of print 17 July 2020) [DOI: 10.1056/NEJMoa2021436]

59 **Papiris SA**, Kagouridis K, Kolilekas L, Papaioannou AI, Roussou A, Triantafillidou C, Baou K, Malagari K, Argentos S, Kotanidou A, Karakatsani A, Manali ED. Survival in Idiopathic pulmonary fibrosis acute exacerbations: the non-steroid approach. *BMC Pulm Med* 2015; **15**: 162 [PMID: 26666385 DOI: 10.1186/s12890-015-0146-4]

60 **Farrand E**, Vittinghoff E, Ley B, Butte AJ, Collard HR. Corticosteroid use is not associated with improved outcomes in acute exacerbation of IPF. *Respirology* 2020; **25**: 629-635 [PMID: 31846126 DOI: 10.1111/resp.13753]

61 **Morell F**, Villar A, Montero MÁ, Muñoz X, Colby TV, Pipvath S, Cruz MJ, Raghu G. Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. *Lancet Respir Med* 2013; **1**: 685-694 [PMID: 24429272 DOI: 10.1016/S2213-2600(13)70191-7]

62 **Walkey AJ**, Wiener RS. Macrolide antibiotics and survival in patients with acute lung injury. *Chest* 2012; **141**: 1153-1159 [PMID: 22116799 DOI: 10.1378/chest.11-1908]

63 **Kawamura K**, Ichikado K, Suga M, Yoshioka M. Efficacy of azithromycin for treatment of acute exacerbation of chronic fibrosing interstitial pneumonia: a prospective, open-label study with historical controls. *Respiration* 2014; **87**: 478-484 [PMID: 24802885 DOI: 10.1159/000358443]

64 **Richeldi L**, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, Brown KK, Flaherty KR, Noble PW, Raghu G, Brun M, Gupta A, Juhel N, Klüglich M, du Bois RM. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med* 2011; **365**: 1079-1087 [PMID: 21992121 DOI: 10.1056/NEJMoa1103690]

65 **Briones Claudett KH**, Briones Claudett MH, Vargas Domenica E, Rodriguez Garcia S, Benites Solis J, Andrade Cabrera C, Grunauer Andrade M. Volume-assured pressure support mode plus pirfenidone as resuscitation therapy in patients with exacerbation of idiopathic pulmonary fibrosis. *Adv Respir Med* 2020; **88**: 147-152 [PMID: 32383467 DOI: 10.5603/ARM.2020.0077]

66 **Marchioni A**, Tonelli R, Ball L, Fantini R, Castaniere I, Cerri S, Luppi F, Malerba M, Pelosi P, Clini E. Acute exacerbation of idiopathic pulmonary fibrosis: lessons learned from acute respiratory distress syndrome? *Crit Care* 2018; **22**: 80 [PMID: 29566734 DOI: 10.1186/s13054-018-2002-4]

67 **Martin MJ**, Moua T. Mechanical Ventilation and Predictors of In-Hospital Mortality in Fibrotic Interstitial Lung Disease With Acute Respiratory Failure: A Cohort Analysis Through the Paradigm

of Acute Respiratory Distress Syndrome. *Crit Care Med* 2020; **48**: 993-1000 [PMID: 32355133 DOI: 10.1097/CCM.0000000000004366]

68 **Guérin C**, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M, Hilbert G, Bengler C, Richecoeur J, Gainnier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; **368**: 2159-2168 [PMID: 23688302 DOI: 10.1056/NEJMoa1214103]

69 **Nakos G**, Tsangaris I, Kostanti E, Nathanail C, Lachana A, Koulouras V, Kastani D. Effect of the prone position on patients with hydrostatic pulmonary edema compared with patients with acute respiratory distress syndrome and pulmonary fibrosis. *Am J Respir Crit Care Med* 2000; **161**: 360-368 [PMID: 10673172 DOI: 10.1164/ajrccm.161.2.9810037]

70 **Azadeh N**, Moua T, Baqir M, Ryu JH. Treatment of acute exacerbations of interstitial lung disease. *Expert Rev Respir Med* 2018; **12**: 309-313 [PMID: 29486130 DOI: 10.1080/17476348.2018.1446831]

71 **Hubbard R**, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. *Am J Respir Crit Care Med* 2000; **161**: 5-8 [PMID: 10619790 DOI: 10.1164/ajrccm.161.1.9906062]

72 **Shenderov K**, Collins SL, Powell JD, Horton MR. Immune dysregulation as a driver of idiopathic pulmonary fibrosis. *J Clin Invest* 2021; **131** [PMID: 33463535 DOI: 10.1172/JCI143226]

73 **Novelli L**, Ruggiero R, De Giacomi F, Biffi A, Faverio P, Bilucaglia L, Gamberini S, Messinesi G, Pesci A. Corticosteroid and cyclophosphamide in acute exacerbation of idiopathic pulmonary fibrosis: a single center experience and literature review. *Sarcoidosis Vasc Diffuse Lung Dis Off J WASOG* 2016; **33**: 385-391

74 **Horita N**, Akahane M, Okada Y, Kobayashi Y, Arai T, Amano I, Takezawa T, To M, To Y. Tacrolimus and steroid treatment for acute exacerbation of idiopathic pulmonary fibrosis. *Intern Med* 2011; **50**: 189-195 [PMID: 21297319 DOI: 10.2169/internalmedicine.50.4327]

75 **Homma S**, Sakamoto S, Kawabata M, Kishi K, Tsuboi E, Motoi N, Yoshimura K. Cyclosporin treatment in steroid-resistant and acutely exacerbated interstitial pneumonia. *Intern Med* 2005; **44**: 1144-1150 [PMID: 16357451 DOI: 10.2169/internalmedicine.44.1144]

76 **Inase N**, Sawada M, Ohtani Y, Miyake S, Isogai S, Sakashita H, Miyazaki Y, Yoshizawa Y. Cyclosporin A followed by the treatment of acute exacerbation of idiopathic pulmonary fibrosis with corticosteroid. *Intern Med* 2003; **42**: 565-570 [PMID: 12879947 DOI: 10.2169/internalmedicine.42.565]

77 **Donahoe M**, Valentine VG, Chien N, Gibson KF, Raval JS, Saul M, Xue J, Zhang Y, Duncan SR. Autoantibody-Targeted Treatments for Acute Exacerbations of Idiopathic Pulmonary Fibrosis. *PLoS One* 2015; **10**: e0127771 [PMID: 26083430 DOI: 10.1371/journal.pone.0127771]

78 **Abe S**, Hayashi H, Seo Y, Matsuda K, Kamio K, Saito Y, Usuki J, Azuma A, Kudo S, Gemma A. Reduction in serum high mobility group box-1 Level by polymyxin B-immobilized fiber column in patients with idiopathic pulmonary fibrosis with acute exacerbation. *Blood Purif* 2011; **32**: 310-316 [PMID: 21893977 DOI: 10.1159/000330325]

79 **Oishi K**, Mimura-Kimura Y, Miyasho T, Aoe K, Ogata Y, Katayama H, Murata Y, Ueoka H, Matsumoto T, Mimura Y. Association between cytokine removal by polymyxin B hemoperfusion and improved pulmonary oxygenation in patients with acute exacerbation of idiopathic pulmonary fibrosis. *Cytokine* 2013; **61**: 84-89 [PMID: 23021430 DOI: 10.1016/j.cyto.2012.08.032]

80 **Tachibana K**, Inoue Y, Nishiyama A, Sugimoto C, Matsumuro A, Hirose M, Kitaichi M, Akira M, Arai T, Hayashi S. Polymyxin-B hemoperfusion for acute exacerbation of idiopathic pulmonary fibrosis: serum IL-7 as a prognostic marker. *Sarcoidosis Vasc Diffuse Lung Dis Off J WASOG* 2011; **28**: 113-122

81 **Oishi K**, Aoe K, Mimura Y, Murata Y, Sakamoto K, Koutoku W, Matsumoto T, Ueoka H, Yano M. Survival from an Acute Exacerbation of Idiopathic Pulmonary Fibrosis with or without Direct Hemoperfusion with a Polymyxin B-immobilized Fiber Column: A Retrospective Analysis. *Intern Med* 2016; **55**: 3551-3559 [PMID: 27980253 DOI: 10.2169/internalmedicine.55.6056]

82 **Abe S**, Azuma A, Mukae H, Ogura T, Taniguchi H, Bando M, Sugiyama Y. Polymyxin B-immobilized fiber column (PMX) treatment for idiopathic pulmonary fibrosis with acute exacerbation: a multicenter retrospective analysis. *Intern Med* 2012; **51**: 1487-1491 [PMID: 22728479 DOI: 10.2169/internalmedicine.51.6965]

83 **Isshiki T**, Sakamoto S, Kinoshita A, Sugino K, Kurosaki A, Homma S. Recombinant human soluble thrombomodulin treatment for acute exacerbation of idiopathic pulmonary fibrosis: a retrospective study. *Respiration* 2015; **89**: 201-207 [PMID: 25659984 DOI: 10.1159/000369828]

84 **Kataoka K**, Taniguchi H, Kondoh Y, Nishiyama O, Kimura T, Matsuda T, Yokoyama T, Sakamoto K, Ando M. Recombinant Human Thrombomodulin in Acute Exacerbation of Idiopathic Pulmonary Fibrosis. *Chest* 2015; **148**: 436-443 [PMID: 25811735 DOI: 10.1378/chest.14-2746]

85 **Tsushima K**, Yamaguchi K, Kono Y, Yokoyama T, Kubo K, Matsumura T, Ichimura Y, Abe M, Terada J, Tatsumi K. Thrombomodulin for acute exacerbations of idiopathic pulmonary fibrosis: a proof of concept study. *Pulm Pharmacol Ther* 2014; **29**: 233-240 [PMID: 24836398 DOI: 10.1016/j.pupt.2014.04.008]

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MINIREVIEWS

Endotracheal intubation sedation in the intensive care unit

Pritee Tarwade, Nathan J Smischney

ORCID number: Pritee Tarwade 0000-0001-5960-267X; Nathan J Smischney 0000-0003-1051-098X.

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Pritee Tarwade, Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN 55905, United States

Nathan J Smischney, Anesthesiology and Perioperative Medicine, Division of Critical Care Medicine, Mayo Clinic, Rochester, MN 55905, United States

Corresponding author: Nathan J Smischney, MD, MSc, Associate Professor, Anesthesiology and Perioperative Medicine, Division of Critical Care Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905, United States. smischney.nathan@mayo.edu

Abstract

Endotracheal intubation is one of the most common, yet most dangerous procedure performed in the intensive care unit (ICU). Complications of ICU intubations include severe hypotension, hypoxemia, and cardiac arrest. Multiple observational studies have evaluated risk factors associated with these complications. Among the risk factors identified, the choice of sedative agents administered, a modifiable risk factor, has been reported to affect these complications (hypotension). Propofol, etomidate, and ketamine or in combination with benzodiazepines and opioids are commonly used sedative agents administered for endotracheal intubation. Propofol demonstrates rapid onset and offset, however, has drawbacks of profound vasodilation and associated cardiac depression. Etomidate is commonly used in the critically ill population. However, it is known to cause reversible inhibition of 11 β-hydroxylase which suppresses the adrenal production of cortisol for at least 24 h. This added organ impairment with the use of etomidate has been a potential contributing factor for the associated increased morbidity and mortality observed with its use. Ketamine is known to provide analgesia with sedation and has minimal respiratory and cardiovascular effects. However, its use can lead to tachycardia and hypertension which may be deleterious in a patient with heart disease or cause unpleasant hallucinations. Moreover, unlike propofol or etomidate, ketamine requires organ dependent elimination by the liver and kidney which may be problematic in the critically ill. Lately, a combination of ketamine and propofol, "Ketofol", has been increasingly used as it provides a balancing effect on hemodynamics without any of the side effects known to be associated with the parent drugs. Furthermore, the doses of both drugs are reduced. In situations where a difficult airway is anticipated, awake intubation with the help of a fiberoptic scope or video laryngoscope is considered. Dexmedetomidine is a commonly used sedative agent for these procedures.

Key Words: Critically ill; Endotracheal intubation; Etomidate; Hypotension; Intensive care

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Core Tip: Intensive care unit endotracheal intubations are associated with a higher risk of complications such as hypotension, hypoxemia, and cardiac arrest when compared to non-intensive care unit endotracheal intubations. A necessity of endotracheal intubations, sedation, is a modifiable risk factor in the pathway to cardiovascular instability. The goal of this review is to present the pros and cons of each sedative agent used for endotracheal intubation while comparing the outcomes. This will help the reader to make an informed decision when choosing a sedative agent for endotracheal intubation in the intensive care unit.

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INTRODUCTION

Endotracheal intubations are one of the most common, yet most dangerous procedures performed in the intensive care unit (ICU). Complications from ICU endotracheal intubations are seen in approximately 40%-45% of patients and include severe hypotension (10%-43%), severe hypoxemia (9%-25%), and cardiac arrest(2%-3%)[1]. Severe cardiovascular collapse is one of the most common complications after ICU endotracheal intubation[2]. Understandably, identification of risk factors for cardiovascular collapse surrounding endotracheal intubation becomes extremely imperative to mitigate or avoid this devastating complication. In a multicenter observational study, Perbet *et al*[2] identified patient risk factors for cardiovascular collapse which included advanced patient age, higher sequential organ failure assessment score, acute respiratory failure, brain injury, trauma, and chronic obstructive pulmonary disease. Procedural risk factors included multiple intubations, use of propofol for induction, and desaturation during intubation[2]. Recently, a multicenter observational prospective study derived and validated a hypotension prediction score for patients undergoing endotracheal intubation in the ICU. The investigators identified 11 variables (increasing illness severity; increasing age; sepsis diagnosis; endotracheal intubation in the setting of cardiac arrest, mean arterial pressure < 65 mmHg, and acute respiratory failure; diuretic use 24 h preceding endotracheal intubation; decreasing systolic blood pressure from 130 mmHg; catecholamine or phenylephrine use immediately prior to endotracheal intubation; and use of etomidate during endotracheal intubation) that were independently associated with peri-intubation hypotension with a C-statistic of 0.75 [95% confidence interval (CI): 0.72-0.78]. Of the 11 variables, the use of etomidate was found to protect against peri-intubation hypotension[3].

Incidence of adverse events like death or hypoxic brain damage are higher with intubations done in ICUs compared to those performed in the operating rooms[4]. In contrast to the ICU, endotracheal intubations in the operating room are frequently performed in a controlled fashion under non-emergent conditions. Although patients may have numerous comorbidities, personnel are specifically trained in airway management, and due to the elective nature of surgical procedures, preparations can be made for difficulties encountered[5,6].

Thus, based on the above evidence, preparation and planning for endotracheal intubations is paramount in critically ill patients to avoid life-threatening complications. An element of endotracheal intubation that is modifiable is the choice of sedative agents administered, which as the evidence suggests, may alter ICU complications, in particular, severe hypotension.

ICU SEDATION AGENTS

Propofol

Propofol is currently the most common anesthetic induction agent used worldwide. Its rapid onset and short duration of action is ideally suited to settings such as the ICU. Propofol's sedative effects are mediated through gamma aminobutyric acid receptors with some activity on N-methyl-D-aspartate receptors. Termination of action of propofol is by redistribution and is independent of organ elimination, thereby making it very useful in ICU patients who may have organ impairment. Standard induction doses of propofol in a healthy adult are 2-2.5mg/kg[7]. However, dosing in the ICU is dramatically different due to the nature of the patent population with patients usually requiring endotracheal intubation for acute respiratory failure or cardiovascular collapse as illustrated recently[1]. In fact, propofol has been shown to have increased potency in shock states indicating less is more[8]. This finding demonstrates the profound vasodilatory effects and associated cardiac depression of propofol[7]. For the healthy patient, this is well tolerated but in patients who are in septic or cardiogenic shock, this attribute can have a detrimental effect on patient hemodynamics. Hence, caution is warranted when using propofol in the critically ill population. A recent study evaluating intubation practices in critically ill patients from 29 countries showed that propofol is the most used sedative and was significantly associated with hemodynamic instability in 63.7% of patients who exhibited precarious hemodynamics, as compared to etomidate with only 49.5% of patients developing hemodynamic instability[1]. Another study performed at the Long Island Jewish Medical center looked at safety of propofol in urgent endotracheal intubations in the medical ICU[9]. Propofol was the sole sedative agent used in 87% of the patients, in 4% it was combined with other agents like benzodiazepines and in the remaining 9%, other sedative agents were used. Interestingly, only 4% of the patients in which propofol was used developed hypotension. This may be explained by the observation that patients were pre-emptively administered vasoactive agents along with propofol to maintain a targeted perfusion pressure. Despite the hemodynamic decompensation known to be associated with propofol, it remains an ideal induction agent in the ICU because of its rapid onset, short duration of action, minimal drug interactions, and organ independent elimination likely explaining its frequent use in the critically ill.

Ketamine

Ketamine is an anesthetic agent which causes complete anesthesia while providing analgesia at the same time. In addition, its causes less respiratory depression and has hemodynamic effects that are opposite that of propofol[7]. This property makes it a desired drug in multiple settings. It is a phencyclidine derivative which acts on the N-methyl-D-aspartate receptor[10,11]. The standard induction dose of ketamine is 1-2 mg/kg. Ketamine's hemodynamic effects are mediated through central nervous system stimulation and inhibition of catecholamine reuptake. However, it is also a known direct myocardial depressant. Thus, in severely ill patients such as the patient in septic shock who is depleted of catecholamines, the direct myocardial depressant effects can be unmasked[7,12]. In addition, ketamine may cause increased intracranial pressure through increased cerebral perfusion thereby limiting its use in trauma patients[13]. Lastly, ketamine is known to induce salivation which can be problematic in airway management in the setting of difficult airways where visualization of the airway is paramount[7]. Although medications such as atropine or glycopyrrolate can be administered to help reduce this effect, these medications may alter the patient's hemodynamics which may not be desirable. When compared to etomidate in the setting of rapid sequence intubation for trauma patients, no significant difference was observed for peri-intubation outcomes such as first pass intubation success, need for rescue surgical airway, and peri-intubation cardiac arrest. However, ketamine was associated with lower odds of hospital acquired sepsis [adjusted odds ratio [OR] 0.72, 95%CI: 0.52-0.99] but higher number of days on vasopressor therapy (adjusted OR 0.74 95%CI: 0.58-0.95)[14]. Another trial which compared these two agents was the Ketased trial which failed to show any difference in immediate post-intubation complications, catecholamine free days at day 28, or 28-d mortality[15].

Etomidate

Etomidate is an anesthetic induction agent commonly used because of its ability to maintain stable hemodynamics. Etomidate causes sedation by its agonistic action on gamma aminobutyric acid receptors and it is thought to maintain hemodynamics through simultaneous stimulation of α-2b adrenoreceptors[16]. In addition to this,

etomidate also reversibly inhibits 11β-hydroxylase and therefore suppresses the adrenal production of cortisol for at least 24 h after a single induction dose[17]. This specific adverse effect is a major reason that causes many intensivists to shy away from using etomidate in the critically ill. Furthermore, the use of etomidate for endotracheal intubation in septic patients has been associated with increased mortality and poor outcomes[18-20]. Moreover, this trend has been seen in surgical patients[21]. For example, a study at Cleveland Clinic in non-cardiac surgery patients showed that patients who received etomidate had a 2.5 (98%CI: 1.9–3.4) higher odds of dying than those who received propofol anesthesia. In addition, patients who received etomidate had a prolonged hospital stay without a significant difference in intraoperative vasopressor requirements[21]. A recent metanalysis that included 29 trials totaling 8584 patients comparing etomidate with other induction agents demonstrated that etomidate was associated with adrenal insufficiency [risk ratio (RR) = 1.54, 95%CI: 1.42, 1.67, $P < 0.001$] and increased overall relative mortality rates (RR = 1.09, 95%CI: 1.04, 1.16, $P = 0.001$). However, on meta-regression, the increased mortality was associated with increasing severity of disease[22]. Hence, the association between etomidate and increased mortality should be interpreted with caution. It is likely that etomidate does lead to additional organ dysfunction, through adrenal suppression, in the critically ill resulting in possibly increased morbidity and mortality.

In the past, high doses of benzodiazepines and opioids were used for sedation during endotracheal intubation. However, with the association of benzodiazepines and increased delirium combined with the awareness to maintain lighter sedation levels, these practices have decreased[23,24].

Ketamine-Propofol Admixture ("Ketofol")

Lately, a combination of two sedatives, namely ketamine and propofol ("Ketofol"), has demonstrated efficacy in terms of hemodynamic preservation when sedating for airway management. This is supported by two randomized controlled trials in which "Ketofol" was compared to propofol only and to half-dose etomidate. In addition to the hemodynamic stability offered by "Ketofol", both trials also suggested that "Ketofol" reduced opioid requirements as compared to the competitor[25,26]. In one trial, "Ketofol" was associated with reduced transfusion requirements as compared to etomidate due to cortisol's role in maintaining vascular homoeostasis (inhibited by etomidate)[26]. Other systemic reviews and meta-analyses have suggested that "Ketofol" is associated with less respiratory events than propofol alone[27,28]. Thus, this unique drug combination has the ability to cause less hemodynamic alterations than either parent compound while providing non-opioid pain control, which may translate into improved metrics such as reduction in post-intubation hypotension and therefore, morbidity and mortality.

Clinical implications of "Ketofol"

An ideal anesthetic is one that has a balanced effect on the cardiopulmonary system while providing hypnosis and analgesia[7]. The "Ketofol" admixture possesses these qualities and as such, its use is applicable to a variety of patient care settings. The rationale behind the drug combination is to provide an admixture that when used together, attenuates blood pressure swings and provides a smooth blood pressure profile during endotracheal intubation and beyond (Figure 1). Although this depends on dosing used for both individual medications, most of the evidence points to a stabilizing effect on blood pressure. This stabilization has the potential to translate into direct and indirect benefits to patients across multiple hospital settings (*e.g.*, emergency room, ICU, operating room, procedural suites) throughout the world. For example, the admixture may offer neuroprotection *via* maintenance of cerebral perfusion through mean arterial pressure, which may reduce post-ICU psychological phenomena (*e.g.*, cognitive dysfunction, depression, *etc.*) in long-term critical care survivors as well as delirium in surgical patients through reduction of benzodiazepines. Moreover, maintenance of hemodynamics in these settings has the potential to translate into reduced rates of adverse cardiac events, acute kidney injury, and mortality. This is of major significance as propofol is the most common anesthetic in use today[29]. Equally important is the ability to limit opioid medications with this admixture due to the properties of ketamine[7]. Every day, more than 130 people in the United States die after overdosing on opioids resulting in an economic burden of 78.5 billion dollar/year[30]. Thus, the admixture may result in reduced exposure to opioid medications by providing a non-opioid alternative to patients needing sedation in multiple locations (e.g., pre-hospital, emergency room, ICU, operating room). This initiative aligns with the United States Health Human Services' opioid crisis strategy [30]. Thus, the "Ketofol" admixture offers the advantage of stable hemodynamics that

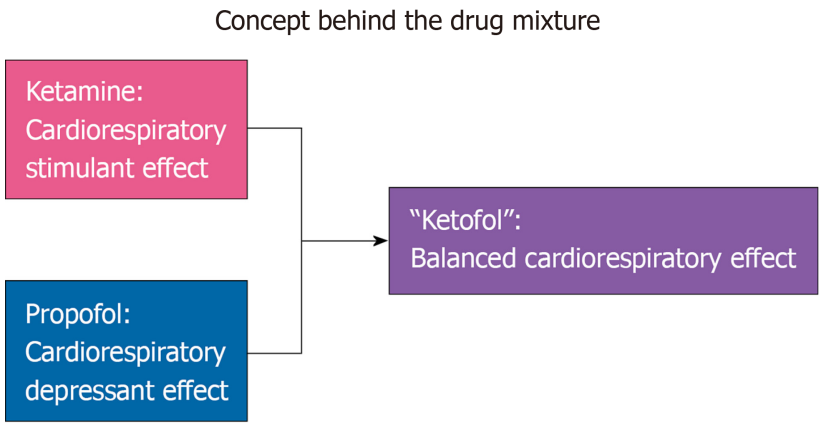

Figure 1 Ketofol concept. In addition, this drug mixture provides hypnosis and analgesia (closest to an ideal anesthetic agent).

is similar to etomidate with non-opioid pain control and minimal, if any, ill effects on patients over ketamine, propofol, or etomidate.

Muscle relaxants

Use of muscle relaxants also varies for endotracheal intubations in the ICU. An observational study comparing outcomes of intubation with or without the use of muscle relaxants failed to show any significant difference in post intubation complications, however, it did show that excellent intubation conditions were achieved in patients in which muscle relaxants were used[31]. Another observational study showed higher first attempt success rate when neuromuscular blockers were used (80.9% *vs* 69.6%, $P = 0.003$)[32].

Special occasions

There are many unique occasions which affect the choice of sedatives in the ICU other than those mentioned above. Cardiac arrest is one such occasion. Typically, no drugs are administered during the intubation. For difficult airways, sedatives may be chosen that provide quick onset and offset or have specific reversal agents associated with their use. Burns, angioedema, and superior vena cava syndrome are some examples when awake fiberoptic intubation might be preferred over routine intubation. In addition, another setting in which sedatives are altered from the usual intubation practice include awake video laryngoscopy, which has been increasingly used to avoid a lost airway or spontaneous respirations[33]. Dexmedetomidine has been used during these situations, along with topical anesthesia, due to its anxiolytic effect with minimal adverse effects on spontaneous respirations[34].

CONCLUSION

Endotracheal intubation is a common procedure, yet can be associated with devastating complications, namely hypoxemia and cardiovascular collapse, that increase when conducted outside a controlled setting such as the operating room. Sedation is frequently administered to facilitate this procedure. However, sedation can sometimes exacerbate these complications, especially relevant when endotracheal intubation is carried out in an urgent/emergent context (*e.g.*, ICU, emergency department, *etc.*). Several sedatives are available to facilitate airway management. Each has its own drawbacks as discussed above which the clinician needs to take into consideration when performing this procedure. As an alternative to the individual sedatives, a combination of sedatives may be needed to achieve the desired outcome such as "Ketofol" in which available evidence suggests a hemodynamic sparring effect with reduced opioid requirements.

REFERENCES

1 **Russotto V**, Myatra SN, Laffey JG, Tassistro E, Antolini L, Bauer P, Lascarrou JB, Szuldrzynski K, Camporota L, Pelosi P, Sorbello M, Higgs A, Greif R, Putensen C, Agvald-Öhman C, Chalkias A,

Bokums K, Brewster D, Rossi E, Fumagalli R, Pesenti A, Foti G, Bellani G; INTUBE Study Investigators. Intubation Practices and Adverse Peri-intubation Events in Critically Ill Patients From 29 Countries. *JAMA* 2021; **325**: 1164-1172 [PMID: 33755076 DOI: 10.1001/jama.2021.1727]

2 **Perbet S**, De Jong A, Delmas J, Futier E, Pereira B, Jaber S, Constantin JM. Incidence of and risk factors for severe cardiovascular collapse after endotracheal intubation in the ICU: a multicenter observational study. *Crit Care* 2015; **19**: 257 [PMID: 26084896 DOI: 10.1186/s13054-015-0975-9]

3 **Smischney NJ**, Kashyap R, Khanna AK, Brauer E, Morrow LE, Seisa MO, Schroeder DR, Diedrich DA, Montgomery A, Franco PM, Ofoma UR, Kaufman DA, Sen A, Callahan C, Venkata C, Demiralp G, Tedja R, Lee S, Geube M, Kumar SI, Morris P, Bansal V, Surani S; SCCM Discovery (Critical Care Research Network of Critical Care Medicine) HEMAIR Investigators Consortium. Risk factors for and prediction of post-intubation hypotension in critically ill adults: A multicenter prospective cohort study. *PLoS One* 2020; **15**: e0233852 [PMID: 32866219 DOI: 10.1371/journal.pone.0233852]

4 **Cook TM**, Woodall N, Frerk C; Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 1: anaesthesia. *Br J Anaesth* 2011; **106**: 617-631 [PMID: 21447488 DOI: 10.1093/bja/aer058]

5 **Divatia JV**, Khan PU, Myatra SN. Tracheal intubation in the ICU: Life saving or life threatening? *Indian J Anaesth* 2011; **55**: 470-475 [PMID: 22174463 DOI: 10.4103/0019-5049.89872]

6 **Taboada M**, Doldan P, Calvo A, Almeida X, Ferreiroa E, Baluja A, Cariñena A, Otero P, Caruezo V, Naveira A, Alvarez J. Comparison of Tracheal Intubation Conditions in Operating Room and Intensive Care Unit: A Prospective, Observational Study. *Anesthesiology* 2018; **129**: 321-328 [PMID: 29787386 DOI: 10.1097/ALN.0000000000002269]

7 **Miller RD**, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Cohen NH, Young WL. Miller's anesthesia e-book. Elsevier Health Sciences, 2014

8 **Johnson KB**, Egan TD, Kern SE, McJames SW, Cluff ML, Pace NL. Influence of hemorrhagic shock followed by crystalloid resuscitation on propofol: a pharmacokinetic and pharmacodynamic analysis. *Anesthesiology* 2004; **101**: 647-659 [PMID: 15329589 DOI: 10.1097/00000542-200409000-00013]

9 **Koenig SJ**, Lakticova V, Narasimhan M, Doelken P, Mayo PH. Safety of Propofol as an Induction Agent for Urgent Endotracheal Intubation in the Medical Intensive Care Unit. *J Intensive Care Med* 2015; **30**: 499-504 [PMID: 24536033 DOI: 10.1177/0885066614523100]

10 **Flood P**, Rathmell JP, Shafer S. Stoelting's pharmacology and physiology in anesthetic practice. 5th ed. LWW, 2015

11 **Zuin M**, Rigatelli G, Dell'Avvocata F, Faggian G, Conte L, Giatti S, Michielan F, Roncon L. Ketamine and midazolam differently impact post-intubation hemodynamic profile when used as induction agents during emergency airway management in hemodynamically stable patients with ST elevation myocardial infarction. *Heart Vessels* 2018; **33**: 213-225 [PMID: 28889210 DOI: 10.1007/s00380-017-1049-5]

12 **Dewhirst E**, Frazier WJ, Leder M, Fraser DD, Tobias JD. Cardiac arrest following ketamine administration for rapid sequence intubation. *J Intensive Care Med* 2013; **28**: 375-379 [PMID: 22644454 DOI: 10.1177/0885066612448732]

13 **Filanovsky Y**, Miller P, Kao J. Myth: Ketamine should not be used as an induction agent for intubation in patients with head injury. *CJEM* 2010; **12**: 154-157 [PMID: 20219164 DOI: 10.1017/s1481803500012197]

14 **Upchurch CP**, Grijalva CG, Russ S, Collins SP, Semler MW, Rice TW, Liu D, Ehrenfeld JM, High K, Barrett TW, McNaughton CD, Self WH. Comparison of Etomidate and Ketamine for Induction During Rapid Sequence Intubation of Adult Trauma Patients. *Ann Emerg Med* 2017; **69**: 24-33.e2 [PMID: 27993308 DOI: 10.1016/j.annemergmed.2016.08.009]

15 **Jabre P**, Combes X, Lapostolle F, Dhaouadi M, Ricard-Hibon A, Vivien B, Bertrand L, Beltramini A, Gamand P, Albizzati S, Perdrizet D, Lebail G, Chollet-Xemard C, Maxime V, Brun-Buisson C, Lefrant JY, Bollaert PE, Megarbane B, Ricard JD, Anguel N, Vicaut E, Adnet F; KETASED Collaborative Study Group. Etomidate *vs* ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. *Lancet* 2009; **374**: 293-300 [PMID: 19573904 DOI: 10.1016/S0140-6736(09)60949-1]

16 **Paris A**, Philipp M, Tonner PH, Steinfath M, Lohse M, Scholz J, Hein L. Activation of alpha 2B-adrenoceptors mediates the cardiovascular effects of etomidate. *Anesthesiology* 2003; **99**: 889-895 [PMID: 14508322 DOI: 10.1097/00000542-200310000-00022]

17 **Jung B**, Clavieras N, Nougaret S, Molinari N, Roquilly A, Cisse M, Carr J, Chanques G, Asehnoune K, Jaber S. Effects of etomidate on complications related to intubation and on mortality in septic shock patients treated with hydrocortisone: a propensity score analysis. *Crit Care* 2012; **16**: R224 [PMID: 23171852 DOI: 10.1186/cc11871]

18 **Sunshine JE**, Deem S, Weiss NS, Yanez ND, Daniel S, Keech K, Brown M, Treggiari MM. Etomidate, adrenal function, and mortality in critically ill patients. *Respir Care* 2013; **58**: 639-646 [PMID: 22906838 DOI: 10.4187/respcare.01956]

19 **Chan CM**, Mitchell AL, Shorr AF. Etomidate is associated with mortality and adrenal insufficiency in sepsis: a meta-analysis*. *Crit Care Med* 2012; **40**: 2945-2953 [PMID: 22971586 DOI: 10.1097/CCM.0b013e31825fec26]

20 **Albert SG**, Ariyan S, Rather A. The effect of etomidate on adrenal function in critical illness: a systematic review. *Intensive Care Med* 2011; **37**: 901-910 [PMID: 21373823 DOI: 10.1007/s00134-011-2160-1]

21 **Komatsu R**, You J, Mascha EJ, Sessler DI, Kasuya Y, Turan A. Anesthetic induction with etomidate, rather than propofol, is associated with increased 30-day mortality and cardiovascular morbidity after noncardiac surgery. *Anesth Analg* 2013; **117**: 1329-1337 [PMID: 24257383 DOI: 10.1213/ANE.0b013e318299a516]

22 **Albert SG**, Sitaula S. Etomidate, Adrenal Insufficiency and Mortality Associated With Severity of Illness: A Meta-Analysis. *J Intensive Care Med* 2020; 885066620957596 [PMID: 32912050 DOI: 10.1177/0885066620957596]

23 **Pisani MA**, Murphy TE, Araujo KL, Slattum P, Van Ness PH, Inouye SK. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. *Crit Care Med* 2009; **37**: 177-183 [PMID: 19050611 DOI: 10.1097/CCM.0b013e318192fcf9]

24 **Hughes CG**, McGrane S, Pandharipande PP. Sedation in the intensive care setting. *Clin Pharmacol* 2012; **4**: 53-63 [PMID: 23204873 DOI: 10.2147/CPAA.S26582]

25 **Smischney NJ**, Beach ML, Loftus RW, Dodds TM, Koff MD. Ketamine/propofol admixture (ketofol) is associated with improved hemodynamics as an induction agent: a randomized, controlled trial. *J Trauma Acute Care Surg* 2012; **73**: 94-101 [PMID: 22743378 DOI: 10.1097/TA.0b013e318250cdb8]

26 **Smischney NJ**, Nicholson WT, Brown DR, Gallo De Moraes A, Hoskote SS, Pickering B, Oeckler RA, Iyer VN, Gajic O, Schroeder DR, Bauer PR. Ketamine/propofol admixture *vs* etomidate for intubation in the critically ill: KEEP PACE Randomized clinical trial. *J Trauma Acute Care Surg* 2019; **87**: 883-891 [PMID: 31335755 DOI: 10.1097/TA.0000000000002448]

27 **Ghojazadeh M**, Sanaie S, Paknezhad SP, Faghih SS, Soleimanpour H. Using Ketamine and Propofol for Procedural Sedation of Adults in the Emergency Department: A Systematic Review and Meta-Analysis. *Adv Pharm Bull* 2019; **9**: 5-11 [PMID: 31011553 DOI: 10.15171/apb.2019.002]

28 **Yan JW**, McLeod SL, Iansavitchene A. Ketamine-Propofol Versus Propofol Alone for Procedural Sedation in the Emergency Department: A Systematic Review and Meta-analysis. *Acad Emerg Med* 2015; **22**: 1003-1013 [PMID: 26292077 DOI: 10.1111/acem.12737]

29 **CDC/NCHS National Hospital Discharge Survey**. Number of all-listed procedures for discharges from short-stay hospitals, by procedure category and age: United States, 2010. [cited 10 February 2021]. Available from: https://www.cdc.gov/nchs/data/nhds/4procedures/2010pro4_numberprocedureage.pdf

30 **United States Department of Health and Human Services**. About the epidemic 2019. [cited 10 February 2021]. Available from: https://www.hhs.gov/opioids/about-the-epidemic/index.html

31 **Baillard C**, Adnet F, Borron SW, Racine SX, Ait Kaci F, Fournier JL, Larmignat P, Cupa M, Samama CM. Tracheal intubation in routine practice with and without muscular relaxation: an observational study. *Eur J Anaesthesiol* 2005; **22**: 672-677 [PMID: 16163913 DOI: 10.1017/s0265021505001110]

32 **Mosier JM**, Sakles JC, Stolz U, Hypes CD, Chopra H, Malo J, Bloom JW. Neuromuscular blockade improves first-attempt success for intubation in the intensive care unit. A propensity matched analysis. *Ann Am Thorac Soc* 2015; **12**: 734-741 [PMID: 25719512 DOI: 10.1513/AnnalsATS.201411-517OC]

33 **Alhomary M**, Ramadan E, Curran E, Walsh SR. Videolaryngoscopy vs. fibreoptic bronchoscopy for awake tracheal intubation: a systematic review and meta-analysis. *Anaesthesia* 2018; **73**: 1151-1161 [PMID: 29687891 DOI: 10.1111/anae.14299]

34 **Tang ZH**, Chen Q, Wang X, Su N, Xia Z, Wang Y, Ma WH. A systematic review and meta-analysis of the safety and efficacy of remifentanil and dexmedetomidine for awake fiberoptic endoscope intubation. *Medicine (Baltimore)* 2021; **100**: e25324 [PMID: 33832107 DOI: 10.1097/MD.0000000000025324]

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ORIGINAL ARTICLE

Retrospective Study

Medico-legal risks associated to hand and wrist trauma

Dionysia Vasdeki, Sokratis E Varitimidis, Charalambos Chryssanthakis, Nikolaos Stefanou, Zoe H Dailiana

ORCID number: Dionysia Vasdeki 0000-0003-4214-7046; Sokratis E Varitimidis 0000-0003-3193-9566; Charalambos Chryssanthakis 0000-0002-3271-7001; Nikolaos Stefanou 0000-0002-6784-6022; Zoe H Dailiana 0000-0003-3890-0832.

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Dionysia Vasdeki, Nikolaos Stefanou, Zoe H Dailiana, Department of Orthopaedic Surgery, Faculty of Medicine, University of Thessaly, Larissa 41500, Greece

Sokratis E Varitimidis, Department of Orthopaedics, University of Thessalia, Larissa 41110, Greece

Charalambos Chryssanthakis, Department of Administrative Science and Public Administration, National and Kapodistrian University of Athens, Athens 10678, Greece

Zoe H Dailiana, Department of Hand, Upper Extremity and Microsurgery, Iaso Thessalias, Nikaia, Larissa 41500, Greece

Corresponding author: Zoe H Dailiana, MD, PhD, Professor, Surgeon, Department of Orthopaedic Surgery, Faculty of Medicine, University of Thessaly, 3 Panepistimiou Street, Biopolis, Larissa 41500, Greece. dailiana@med.uth.gr

Abstract

BACKGROUND

Acute hand and wrist injuries are common and may lead to long-term disability if not managed adequately. Claims for negligence have been increasing in medical practice over the past few decades, with hand and wrist injuries and their treatment representing a significant percentage of orthopedic surgery lawsuits. There is no available literature regarding medical malpractice claims in hand and wrist injuries and surgery in Greece.

AIM

To identify claims related to hand and wrist trauma and surgery and to define the reasons of successful litigations.

METHODS

We performed a retrospective study of all legal claims of negligence for hand and upper extremity surgery that went to a trial, attributed to all surgical specialties, in Greece for a 20-year period. Data was further analyzed to identify claims related to hand and wrist trauma and surgery.

RESULTS

There were six malpractice claims related to hand and wrist trauma that ended in a trial. A missed diagnosis, which resulted in failure of initial management of the injury, was the main reason for a claim. Three of the six cases resulted in complete or partial loss of a finger. Two cases are still open, requiring an expert witness's report, two cases were closed in favor of the defendant, and two cases were closed

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in favor of the plaintiff with a mean compensation of €2000 (€1000-€3000).

CONCLUSION
Missed diagnosis was the main reason for a malpractice claim. Better understanding of factors leading to successful claims will help surgeons improve their practice to minimize legal implications and litigation.

Key Words: Hand trauma; Wrist trauma; Litigation; Claim; Negligence

Core Tip: This is the first report related to hand and wrist trauma malpractice claims in Greece. Hand and wrist injuries, although non-fatal, can lead to long-term disability if a delay in diagnosis or treatment occurs. Additionally, missed diagnosis and inadequate management of these injuries can be the leading cause for medical malpractice claims, which appear to have an upward trend over the last decades. We present six malpractice claims related to hand and wrist trauma that resulted in a trial over a 20-year period in Greece and their outcomes, aiming to determine the reasons that lead to successful litigations.

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INTRODUCTION

Hand and wrist injuries are common and account for approximately 10%-30% of all presentations to emergency departments (EDs), affecting mainly young and economically productive people[1,2]. Although not commonly life threatening, delayed diagnosis or mismanagement of these injuries can result in prolonged recovery and likely long-term disability, having a negative impact on patient's quality of life, income, social activities and occasionally mental health[3,4].

Claims for negligence have been increasing in medical practice over the past few decades, with hand and wrist injuries and their treatment representing a significant percentage of orthopedic surgery lawsuits[5,6]. There are a few articles addressing the issue of malpractice in hand and wrist surgery, with most studies being performed in Europe[6]. However, there are no reports related to medical malpractice claims in hand and wrist injuries and surgery in Greece.

The purpose of this study was to seek the available data about medical malpractice in hand and wrist trauma and surgery in Greece, to define the reasons and to evaluate the burden of successful litigations in Greece and to compare this data with the international malpractice data.

MATERIALS AND METHODS

Data on all legal claims of negligence for hand and upper extremity surgery attributed to all surgical specialties that ended in a trial during the period of 2000-2019 was obtained after permission from the archives of the Council of State in Greece. We further analyzed the data to determine the number of claims related to hand and wrist trauma, the reasons that a claim was filed, the outcome of each claim and the financial size of the plaintiff's compensation in the case of a successful claim.

Our study was approved by our institutional research ethics board. All data was anonymized as indicated by the General Data Protection Regulation.

RESULTS

Among the malpractice claims related to hand and upper extremity surgery that went to a trial in the period between 2000 and 2019, six cases were correlated to hand and wrist trauma. Missed diagnosis, which resulted in failure of management and in one case in delayed referral to a specialized unit, was the main reason for a claim. Substandard surgery was an additional reason for claim in one case.

The mean time between injury and definite treatment was 9.1 (1-25) d. In all but one case adult patients were involved. The majority of cases (5) concerned the soft tissues, while one case was related to a wrist bone (scaphoid fracture). Three of six cases resulted in complete or partial loss of a finger.

Two of six cases are still open, requiring an expert witness's report, two cases were closed in favor of the defendant, and the remaining two cases were closed in favor of the plaintiff, with a mean compensation of €2000 (€1000-€3000). A brief summary of each case follows.

Case 1

A 51-year-old man presented to the ED of a district hospital on a Greek island, reporting high pressure injury of the proximal phalanx of his left index finger while cleaning a painting machinery. He was initially reviewed by a general surgery resident who under the guidance of a general surgeon cleaned the wound. On a follow-up visit 3 d after the injury, the wound was found to be necrotic. Due to lack of an orthopedic surgeon in the hospital, he was advised to visit the hospital of a nearby island, where this specialty was available. Following assessment by an orthopedic surgeon there, the patient was finally referred to a plastic surgery unit in Athens. Six days after the injury, the patient underwent an amputation of his left index finger at the level of the metacarpophalangeal joint.

A claim was filed by the patient stating that the amputation was the result of missed diagnosis and delayed referral to a specialized hand trauma unit. The case is still open, and an expert witness's report is required before a final decision is made.

Case 2

A fireman presented to the ED of a general hospital with a deep laceration of his left thumb following an injury by a satellite dish. The patient was reviewed by an orthopedic surgeon, and the wound was closed. On follow-up visit 15 d later, the patient complained of persistent pain and inability to move his thumb. Despite his complaints, no further action was taken. Due to persistence of symptoms 25 d after his injury, the patient was examined by a hand surgeon, and laceration of the flexor pollicis longus and the digital nerve was diagnosed. Reconstruction of the structures followed.

The patient filed a claim for initial missed diagnosis of his injury with subsequent late reconstruction and delay in his recovery. Compensation of €1000 was set for the patient. The case closed 8 years after the claim was filed.

Case 3

A 40-year-old woman presented to the ED of a general hospital with pain and swelling of her index finger and her thumb following an injury with a knife 4 d before. She was examined by a plastic surgery resident, who prescribed oral antibiotics and suggested reassessment in 2 d. The following day the patient was examined in a different hospital, where infection of her right hand and ischemic changes of the index finger were reported, necessitating surgical debridement. Four days later, in a specialized hand and microsurgery unit of a private hospital, the patient underwent amputation of the distal phalanx, further debridement of the index finger and reconstruction with a cross-finger flap. The patient filed a claim reporting missed diagnosis and improper management of her injury. The case was closed in favor of the defendant 10 years after the claim was filed.

Case 4

A woman presented to the ED of a general hospital following an injury to her left wrist with a glass. She was reviewed by both an orthopedic and a general surgeon. The wound was closed, and oral antibiotics were prescribed. On reassessment 12 d later, laceration of her ulnar nerve was diagnosed. Therefore, she was referred to a specialized unit and had her ulnar nerve repaired. Despite management in a specialized center, the patient was not able to fully use her left hand postoperatively. The patient filed a claim reporting missed diagnosis of her injury. The case was closed

in favor of the plaintiff and compensation of €3000 was set. The case closed 7 years after the claim was filed.

Case 5

A man presented to the ED of a general hospital following a fall from 2.5 m height and injury of his left wrist. He was assessed by an Orthopedic Surgery resident, and a radiograph was performed the same day. His wrist was splinted, and a follow-up visit was scheduled in 8 d. The follow-up radiograph depicted a fracture of the scaphoid bone, and 2 d later the patient was treated surgically. The fracture was fixed with Kirschner wires. Intraoperatively, one of the wires broke, and the remnant of the wire was left in the bone. The patient complained of reduced range of motion of his left wrist postoperatively. The patient filed a claim reporting missed diagnosis and substandard surgery. The case is still open, and an expert witness's report is required before a final decision is made.

Case 6

A 9-year-old boy was brought to the ED of an urban general hospital by his parents following a crush injury to his left index, middle and ring fingers. He was there assessed by a general surgery resident who sutured the lacerations. Three days later the boy was brought back to the ED due to ischemic changes to his middle finger. Despite admission in the hospital, the parents' wish was to visit a pediatric surgeon in another hospital. A degloving injury of the boy's middle finger was diagnosed, and amputation of the finger was performed (the level of the amputation was not mentioned in the claim). The family filed a claim reporting missed diagnosis of the boy's injury and subsequent mismanagement. The case was finally closed in favor of the defendant 7 years later.

Verdicts

In our study two cases were closed in favor of the plaintiff and two cases were closed in favor of the defendant. The reasonings behind the court's final decisions varied. Documentation, rarity of injury, functional outcome and delay in recovery have been the main reasons for the verdicts.

The two cases which were closed in favor of the plaintiff involved delay in the diagnosis of ulnar nerve laceration and of flexor pollicis longus and digital nerve laceration. In the first case, compensation was set because there was no full recovery of the nerve, even though the reconstruction was performed within the allowed time-period for nerve reconstruction. According to the decision, nerve reconstruction within the first days of the injury would have higher chances for full recovery. In the second case there was full recovery of both the nerve and the tendon despite the delay in diagnosis. However, due to the delay in diagnosis the plaintiff experienced pain and inability to use his hand for 25 d until the reconstruction of the structures and that was the reasoning for a verdict in favor of the plaintiff.

The two cases that were closed in favor of the defendant involved a degloving injury of a finger and an infection of a finger. The first case concerned a rare injury of the finger, the degloving injury, which a junior resident of an allied specialty (general surgery) was unlikely to know and have experience on its management. The degloving injury of the finger would be approached by every non-experienced doctor in the way the involved doctor did. The verdict of the second case was based on the clear documentation the involved doctor presented regarding the findings on the day of examination. The different and contradictory clinical presentation that the plaintiff contended could not be supported by any documentation or image to prove any inaccuracy in the doctor's documentation.

DISCUSSION

Acute hand and wrist injuries represent a common cause of visit to the ED. Hand injuries occur with a significant rate, constituting a considerable proportion of non-fatal injuries requiring medical attention[3]. Missed diagnosis and subsequent inadequate initial management of these injuries may lead to a prolonged period of disability and absence from work and social activities, further procedures and potentially a suboptimal outcome. The hand has complex anatomical and functional features and may be affected by a wide range of trauma, ranging from simple lacerations to injuries that require multiple reconstructive procedures. Adequate knowledge of the different mechanisms of injury and their association with certain

patterns of injury is essential to help the surgeon decide on the diagnostic and therapeutic process[4].

In Greece, hand and wrist injuries that present to the ED are initially assessed by orthopedic, plastic or general surgery residents, who usually review the cases with a consultant. The residents examine the patient, request laboratory and imaging evaluations and decide treatment in "simple" cases, while complex cases that cannot be managed in the hospital are referred to specialized hand surgery units. In district hospitals, initial assessment and management is performed by an orthopedic or a general surgeon. However, management of hand injuries by non-specialists (residents or consultants) carries the risk of poor outcome with subsequent increase in the cost for the patient, employer and society as stated by Kenesi and Masmejean in 2004[7].

Claims for negligence is a global problem with an upward trend[5]. According to the Greek Penal Code (article 28) "whoever due to lack of attention - that he should and could have paid according to the circumstances - didn't foresee the punishable result which his action caused or had foreseen it as possible but didn't believe it would actually happen, is acting in the content of negligence". Gidwani *et al*[8] reported substandard surgery and delay in diagnosis or treatment having been the most frequent reasons for litigation[8-10]. Similarly, in a study of all claims related to hand injuries against EDs in England during the period 2004-2014, failure or delay in the diagnosis and in the treatment of the injury were the two most common reasons for litigation[10].

Despite best efforts, hand and wrist injuries may be missed, and therefore proper management can be delayed. Morrison *et al*[11] studied 500 acute hand injuries that were referred to the Regional Plastic Surgery Unit in Northern Ireland. There were 16 (3.2%) missed injuries, and these were more common in patients examined by junior medical staff and in patients with trauma caused by glass. In minor lacerations the extent of the underlying injury can sometimes be underestimated. Previous studies reported that perioperative clinical findings of upper limb injuries may have an 8%-14% error rate when compared to intraoperative findings. Miranda *et al*[12] compared the clinical and intraoperative findings of 1526 hand injuries that were referred to a Hand Trauma Unit. Flexor tendon injuries were associated with a poor diagnostic concordance, while lacerative injuries were most likely to be associated with additional injuries. Mahdavian Delavary *et al*[7] studied all the claims related to hand and wrist injury for a period of 15 years in the Netherlands. A significant number of claims were related to the management of wrist fractures, while the commonest cause for a claim was inadequate management (34.8%), followed by missed diagnosis (33.8%). In the same study, 102 cases involved a missed nerve or tendon injury after a cut, and in 74.5% of these misdiagnosed cases, initial diagnosis was made by a resident. Finally, it was concluded that general surgeons, who occasionally treat hand conditions, were more likely to be involved in litigation[7].

In an ED setting the assessment of hand injuries can be challenging. Distracting injuries may also be present, patient's compliance may be poor due to alcohol or substance use, complexity of hand anatomy and the involvement of junior doctors or general surgeons, with limited experience in hand surgery can all contribute to errors [10].

In general, management of fractures has been associated with a high risk of claims. It has been reported that approximately 49% of the upper extremity claims are related to fracture management. The higher risk is associated with the patient's expectation to return to their pre-injury condition and with treatment by the on-call doctor, who may have a different area of expertise[14].

Scaphoid fractures are common wrist injuries, accounting for 82%-89% of carpal injuries. However, radiographs are often false-negative, and thus their contribution in diagnosing this injury is poor[13]. Litigation in wrist trauma is common with 48% of the claims related to hand and wrist surgery being for wrist fractures according to a study of Khan and Giddins[9]. Ring *et al*[13] studied all orthopedic claims registered in the National Health Service Litigation Authority between 1995 and 2012. Of all registered orthopedic claims, 36.3% were related to wrist and scaphoid fractures, with an average settlement per case of £45500 for wrist fractures and £51500 for scaphoid fractures[13]. The main reasons for successful claims was delayed, incorrect or missed diagnosis (43.5%), followed by alleged mismanagement (29.5%), poor patient care (10.1%) and alleged incompetent surgery[13].

Soft tissue injuries of the hand represent up to 82% of all hand injuries assessed in EDs. They can range from simple lacerations to more complex injuries requiring structural repair, with the high-pressure injection injuries being the "most urgent of all emergencies of the hand". High-pressure injection injuries, although not very frequent with an estimated incidence of 1 in 600 injuries, can be catastrophic for the patient if

Table 1 Learning points from the present study

First report of medical negligence claims related to hand and wrist trauma and surgery in Greece
Missed diagnosis was the main reason for filling a claim in hand and wrist trauma surgery
Missed diagnosis and subsequent inadequate management resulted in partial or complete loss of a finger in half of the cases
Junior doctors and doctors from allied specialties (other than orthopedic or plastic surgery) were involved in most of the claims
The main reasoning of the verdicts included accurate documentation, rarity of injury, functional outcome and delay in recovery

not referred to a hand unit promptly and not managed adequately. They have been associated with a high risk of amputation of the affected finger, ranging from 16% to 48% as well with the risk of systemic intoxication, if missed and not treated appropriately[15]. On the contrary, tendon injuries are common with an incidence of approximately 33.2 injuries per 100000 person-years and accompany most penetrating injuries of the hand. A concomitant tendon injury may be present in 54.8% of small lacerations and 92.5% of deep injuries through a small laceration[16].

Claims for negligence have been increasing in medical practice over the past few decades. In a retrospective study by Ajwani *et al*[5] of 325 successful claims related to hand and wrist injuries and surgery in England from the period 2002-2012, payouts for hand injuries were reported to range from £1000 to £374077 while for wrist injuries from £200 to £669471. In the same study, poor outcome, nerve damage, unnecessary pain due to delayed diagnosis or management, additional procedures and fracture were identified as the commonest reasons for successful litigation[5].

In our study, all claims were for missed diagnosis that resulted in delay of proper treatment. The amounts of plaintiff's compensation (€1000, €3000) were lower compared to the ones described in the literature. The limited case law regarding compensation for hand and wrist injuries in Greece may explain the low compensation payments. Additionally, more than half of the cases were initially examined and treated by residents in plastic, orthopedic or general surgery, and failure in diagnosis was attributed to them by the plaintiff. In one case a high-pressure injury was assessed and managed by a general surgeon, who did not have experience in the management of this pattern of injury.

In the present study we reviewed only the claims related to hand and wrist trauma that went to a trial. It cannot be interpreted as representative of all malpractice claims in hand and wrist trauma. At present, there is no official authority in Greece where all negligence claims can be registered. Therefore, we cannot estimate the total amount of negligence claims for hand and wrist trauma that were filed between 2000 and 2019 and the number of claims that were settled outside court (Table 1).

CONCLUSION

This is the first report of medical negligence claims related to hand and wrist injuries that went to a trial in Greece. We presented six cases of hand and wrist trauma that reached the court room and their decisions. The main cause for filing a claim was missed diagnosis, which resulted in delayed management and in loss of a finger in 50% of cases. Hand and wrist injuries are common with possible long-term disability if treated inadequately. Therefore, a better understanding of the factors that lead to successful claims will help surgeons improve their practice to minimize legal implications and litigation.

ARTICLE HIGHLIGHTS

Research background

Medical negligence claims have presented an upward trend over the last decades worldwide, with hand and wrist liability representing a significant burden of orthopedic surgery lawsuits. Hand and wrist injuries are common, affecting mainly young and economically productive people. However, even small injuries may lead to long-term disability if treated inadequately, with affected people becoming unable to work, socialize and perform routine daily activities.

Research motivation

Literature addressing the issue of malpractice in hand and wrist surgery has been scarce, with most studies being performed in Europe and the United States. However, there are no studies related to liability in hand and wrist trauma and surgery in Greece.

Research objectives

The purpose of this study was to identify medical malpractice claims in hand and wrist surgery in Greece, to define the reasons for filing a claim and to define the reasons of successful litigations. Additionally, the results of the study were compared with the international malpractice data.

Research methods

This is a retrospective study of all medical malpractice claims for hand and upper extremity surgery that went to a trial attributed to all surgical specialties in Greece over a 20-year period. Claims were further analyzed to identify claims related to hand and wrist trauma and surgery.

Research results

We presented six medical malpractice cases related to hand and wrist trauma that ended in a trial. Missed diagnosis and subsequent failure of initial management of the injury was the main reason for filing a claim. In half of the cases mismanagement resulted in complete or partial loss of a finger. Two cases are still open, two cases were closed in favor of the defendant, and two cases were closed in favor of the plaintiff with a mean compensation of €2000.

Research conclusions

This is the first report of medical negligence claims related to hand and wrist trauma in Greece. A missed diagnosis of hand and wrist injury can result in long-term disability for a patient and has been the main reason for a malpractice claim. In the present study, missed diagnosis resulted in partial or complete loss of a finger in half of the cases.

Research perspectives

Better understanding of the factors that lead to successful claims can result in the improvement of services to hand trauma patients and will help surgeons improve their practice to minimize legal implications and litigation.

REFERENCES

1 **de Putter CE**, Selles RW, Polinder S, Panneman MJ, Hovius SE, van Beeck EF. Economic impact of hand and wrist injuries: health-care costs and productivity costs in a population-based study. *J Bone Joint Surg Am* 2012; **94**: e56 [PMID: 22552678 DOI: 10.2106/JBJS.K.00561]

2 **Rosberg HE**, Carlsson KS, Cederlund RI, Ramel E, Dahlin LB. Costs and outcome for serious hand and arm injuries during the first year after trauma - a prospective study. *BMC Public Health* 2013; **13**: 501 [PMID: 23706070 DOI: 10.1186/1471-2458-13-501]

3 **Crowe CS**, Massenburg BB, Morrison SD, Chang J, Friedrich JB, Abady GG, Alahdab F, Alipour V, Arabloo J, Asaad M, Banach M, Bijani A, Borzì AM, Briko NI, Castle CD, Cho DY, Chung MT, Daryani A, Demoz GT, Dingels ZV, Do HT, Fischer F, Fox JT, Fukumoto T, Gebre AK, Gebremichael B, Haagsma JA, Haj-Mirzaian A, Handiso DW, Hay SI, Hoang CL, Irvani SSN, Jozwiak JJ, Kalhor R, Kasaeian A, Khader YS, Khalilov R, Khan EA, Khundkar R, Kisa S, Kisa A, Liu Z, Majdan M, Manafi N, Manafi A, Manda AL, Meretoja TJ, Miller TR, Mohammadian-Hafshejani A, Mohammadpourhodki R, Mohseni Bandpei MA, Mokdad AH, Naimzada MD, Ndwandwe DE, Nguyen CT, Nguyen HLT, Olagunju AT, Olagunju TO, Pham HQ, Pribadi DRA, Rabiee N, Ramezanzadeh K, Ranganathan K, Roberts NLS, Roever L, Safari S, Samy AM, Sanchez Riera L, Shahabi S, Smarandache CG, Sylte DO, Tesfay BE, Tran BX, Ullah I, Vahedi P, Vahedian-Azimi A, Vos T, Woldeyes DH, Wondmieneh AB, Zhang ZJ, James SL. Global trends of hand and wrist trauma: a systematic analysis of fracture and digit amputation using the Global Burden of Disease 2017 Study. *Inj Prev* 2020; **26**: i115-i124 [PMID: 32169973 DOI: 10.1136/injuryprev-2019-043495]

4 **Telich-Tarriba JE**, Velazquez E, Theurel-Cuevas A, Shinji-Perez K, Anaya-Ayala JE, Jimenez-Murat Y, Cardenas-Mejia A. Upper Extremity Patterns of Injury and Management at a Plastic and Reconstructive Surgery Referral Center in Mexico City. *Ann Plast Surg* 2018; **80**: 23-26 [PMID: 28737558 DOI: 10.1097/SAP.0000000000001182]

5 **Ajwani SH**, Halai SM, Mohil RS. Litigation in Hand and Wrist Related Injuries and Surgery. *Ortop Traumatol Rehabil* 2018; **20**: 205-209 [PMID: 30152770 DOI: 10.5604/01.3001.0012.2128]

6 **Pappas ND**, Moat D, Lee DH. Medical malpractice in hand surgery. *J Hand Surg Am* 2014; **39**: 168-170 [PMID: 24369944 DOI: 10.1016/j.jhsa.2013.06.021]

7 **Mahdavian Delavary B**, Cremers JE, Ritt MJ. Hand and wrist malpractice claims in The Netherlands: 1993-2008. *J Hand Surg Eur Vol* 2010; **35**: 381-384 [PMID: 20032001 DOI: 10.1177/1753193409355735]

8 **Gidwani S**, Zaidi SM, Bircher MD. Medical negligence in orthopaedic surgery: a review of 130 consecutive medical negligence reports. *J Bone Joint Surg Br* 2009; **91**: 151-156 [PMID: 19190045 DOI: 10.1302/0301-620X.91B2.21567]

9 **Khan IH**, Giddins G. Analysis of NHSLA claims in hand and wrist surgery. *J Hand Surg Eur Vol* 2010; **35**: 61-64 [PMID: 19786409 DOI: 10.1177/1753193409347422]

10 **Trevatt AE**, Smith OJ, Needleman J, Banerjee A. An analysis of the most common types of hand injury mistakes and their cost in the acute setting. *Med Leg J* 2016; **84**: 206-211 [PMID: 27553446 DOI: 10.1177/0025817216664663]

11 **Morrison CM**, Thompson NW, Herbert KJ, Brennen MD. Missed injuries in the acutely traumatised hand. *Ulster Med J* 2003; **72**: 22-25 [PMID: 12868699]

12 **Miranda BH**, Spilsbury ZP, Rosala-Hallas A, Cerovac S. Hand trauma: A prospective observational study reporting diagnostic concordance in emergency hand trauma which supports centralised service improvements. *J Plast Reconstr Aesthet Surg* 2016; **69**: 1397-1402 [PMID: 27542593 DOI: 10.1016/j.bjps.2016.06.030]

13 **Ring J**, Talbot C, Price J, Dunkow P. Wrist and scaphoid fractures: a 17-year review of NHSLA litigation data. *Injury* 2015; **46**: 682-686 [PMID: 25697859 DOI: 10.1016/j.injury.2015.01.017]

14 **Matsen FA**, Stephens L, Jette JL, Warme WJ, Huang JI, Posner KL. The quality of upper extremity orthopedic care in liability claims filed and claims paid. *J Hand Surg Am* 2014; **39**: 91-99 [PMID: 24315491 DOI: 10.1016/j.jhsa.2013.10.014]

15 **Dailiana HZ**, Kotsaki D, Varitimidis S, Moka S, Bakarozi M, Oikonomou K, Malizos NK. Injection injuries: seemingly minor injuries with major consequences. *Hippokratia* 2008; **12**: 33-36 [PMID: 18923762]

16 **de Jong JP**, Nguyen JT, Sonnema AJ, Nguyen EC, Amadio PC, Moran SL. The incidence of acute traumatic tendon injuries in the hand and wrist: a 10-year population-based study. *Clin Orthop Surg* 2014; **6**: 196-202 [PMID: 24900902 DOI: 10.4055/cios.2014.6.2.196]

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ORIGINAL ARTICLE

Retrospective Study

Efficacy of remdesivir for hospitalized COVID-19 patients with end stage renal disease

Vijairam Selvaraj, Amos Lal, Arkadiy Finn, Joshua Ray Tanzer, Muhammad Baig, Atin Jindal, Kwame Dapaah-Afriyie, George Bayliss

ORCID number: Vijairam Selvaraj 0000-0002-8507-9891; Amos Lal 0000-0002-0021-2033; Arkadiy Finn 0000-0002-1630-1137; Joshua Ray Tanzer 0000-0002-5393-2974; Muhammad Baig 0000-0001-5444-6161; Atin Jindal 0000-0002-1832-3479; Kwame Dapaah-Afriyie 0000-0003-1957-8497; George Bayliss 0000-0002-7508-9762.

Author contributions: Selvaraj V, Finn A and Lal A were responsible for the conception and design of the work, screening of papers and drafting the manuscript; Jindal A was responsible for the literature review and contributed to manuscript writing; Tanzer JR and Baig M performed analysis and final approval; Jindal A, Dapaah-Afriyie K and Bayliss G contributed to research oversight, data review and manuscript revision.

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Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were

Vijairam Selvaraj, Arkadiy Finn, Muhammad Baig, Atin Jindal, Kwame Dapaah-Afriyie, Department of Medicine, Miriam Hospital, Warren Alpert Medical School of Brown University, Providence, RI 02906, United States

Amos Lal, Department of Medicine, Division of Pulmonary and Critical Care, Mayo Clinic, Rochester, MN 55905, United States

Joshua Ray Tanzer, Department of Biostatistics Core, Lifespan Group, Providence, RI 02906, United States

George Bayliss, Department of Medicine, Rhode Island Hospital and Alpert Medical School, Bayliss, Division of Kidney and Hypertension, Brown University, Providence, RI 02906, United States

Corresponding author: Amos Lal, FACP, MBBS, Assistant Professor, Department of Medicine, Division of Pulmonary and Critical Care, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, United States. manavamos@gmail.com

Abstract

BACKGROUND

Since the beginning of corona virus disease 2019 (COVID-19) pandemic, there has been a widespread use of remdesivir in adults and children. There is little known information about its outcomes in patients with end stage renal disease who are on dialysis.

AIM

To assess the clinical outcomes with use of remdesivir in adult patients with end stage kidney failure on hemodialysis.

METHODS

A retrospective, multicenter study was conducted on patients with end stage renal disease on hemodialysis that were discharged after treatment for COVID-19 between April 1, 2020 and December 31, 2020. Primary endpoints were oxygen requirements, time to mortality and escalation of care needing mechanical ventilation.

RESULTS

obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All authors declare no conflict of interest.

Data sharing statement: No additional data are available.

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Specialty type: Critical care medicine

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Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
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A total of 45 patients were included in the study. Twenty patients received remdesivir, and 25 patients did not receive remdesivir. Most patients were caucasian, females with diabetes mellitus and hypertension being the commonest comorbidities. There was a trend towards reduced oxygen requirement (beta = -25.93, X^2 (1) = 6.65, P = 0.0099, probability of requiring mechanical ventilation (beta = -28.52, X^2 (1) = 22.98, P < 0.0001) and mortality (beta = -5.03, X^2 (1) = 7.41, P = 0.0065) in patients that received remdesivir compared to the control group.

CONCLUSION
Larger studies are justified to study the effects of remdesivir in this high-risk population with end stage kidney disease on dialysis.

Key Words: COVID-19; Remdesivir; End stage renal disease; Dialysis; Hemodialysis; Kidney disease

Core Tip: Little known information exists regarding the efficacy of remdesivir in corona virus disease 2019 patients with end stage renal disease on dialysis. Use of remdesivir was associated with a trend towards reduced oxygen requirement, reduced probability of progression to mechanical ventilation and better prognosis. Larger studies are justified in this high risk, vulnerable population.

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INTRODUCTION

Corona virus disease 2019 (COVID-19) is a clinical syndrome arising from infection with severe acute respiratory syndrome - coronavirus 2 (SARS-CoV-2) coronavirus that has led to several hospitalizations and intensive care unit admissions. Remdesivir, a viral RNA polymerase inhibitor, has demonstrated in vitro activity against viruses such as Middle East Respiratory Syndrome - CoV (MERS-CoV), Ebola, and SARS-CoV1.

In the Adaptive COVID-19 Treatment Trial-1 (ACTT-1), remdesivir was noted to reduce the median time to recovery when compared to the placebo group (10 *vs* 15 d) [1]. The Infectious Diseases Society of America (IDSA) recommended the use of remdesivir in hospitalized patients with severe COVID-19 with SpO2 < 94%, including patients on supplemental oxygen or mechanical ventilation[2]. The World Health Organization (WHO) issued a 'weak or conditional' recommendation against the use of remdesivir in hospitalized COVID-19 patients[3]. Despite this, the use of remdesivir is widespread in hospitalized COVID-19 patients. Many of the clinical trials on remdesivir excluded COVID-19 patients with severe renal dysfunction (CrCl < 30 mL/min/1.73m^2). Little is known about clinical outcomes with use of remdesivir in COVID-19 patients with severe renal dysfunction or end-stage renal disease (ESRD) who are on hemodialysis (HD).

As remdesivir has poor water solubility, Sulfobutylether-β-Cyclodextrin (SBECD) is added to the intravenous preparation as a vehicle. Dialysis and renal replacement therapy readily remove SBECD, and significant accumulation of SBECD only occurs when dialysis is held for prolonged periods in ESRD patients. Voriconazole is another medication that has been safely used in patients with kidney failure using the same carrier (SBECD)[4].

Our hypothesis is that the addition of remdesivir to dexamethasone as part of the treatment regimen in COVID-19 patients with ESRD may have impact on the overall length of stay, need for supplemental oxygen, mortality, and mechanical ventilation. The aim of this study was to evaluate the feasibility and efficacy of using remdesivir in

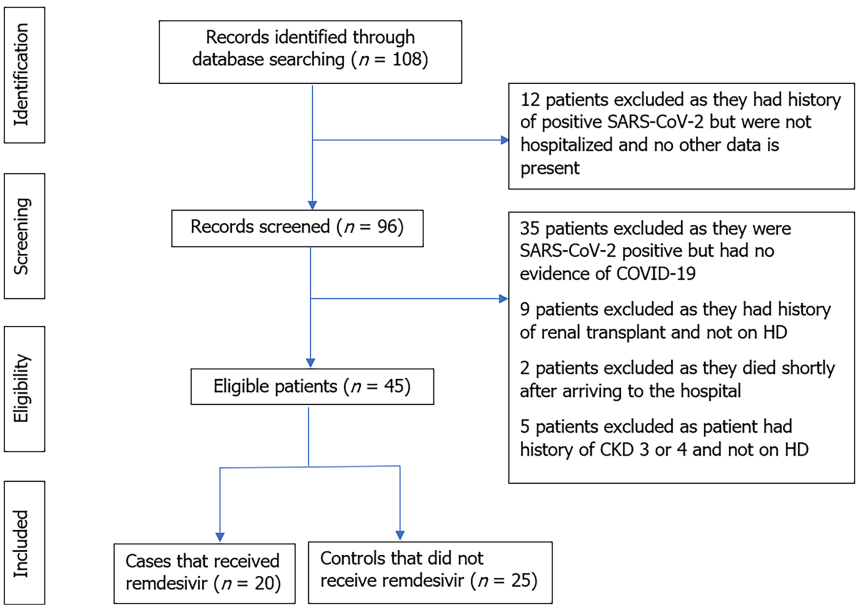

Figure 1 Flow chart outlining patient selection. SARS-CoV-2: Severe acute respiratory syndrome-coronavirus 1; COVID-19: Corona virus disease 2019; CKD: Chronic kidney disease; HD: Hemodialysis.

patients with COVID-19 and ESRD on HD.

MATERIALS AND METHODS

We collected data from two quaternary, acute care hospitals, Rhode Island Hospital (RIH) and The Miriam Hospital (TMH), located in Providence, Rhode Island. All hospitalized patients above the age of 18 years with ESRD on HD from April 1 to December 31, 2020, with a positive polymerase chain reaction (PCR) nasopharyngeal or oropharyngeal SARS-CoV-2 swab were screened for potential study inclusion (Figure 1). ESRD was defined as a GFR of less than 15 mL/min/1.73m^2 according to the chronic kidney disease epidemiology collaboration (CKD-EPI) formula. The study was reviewed and approved by the Institutional Review Board of TMH. Data was collected by physicians in the Division of Hospital Medicine at Miriam Hospital (an affiliate of Warren Alpert Medical School of Brown University).

Patients with moderate disease included patients with CRP levels between 50-200 mg/L (normal 0-10 mg/L) and 2-6L/min of oxygen requirement. Patients with severe disease included patients with CRP levels greater than 200 mg/L and oxygen requirements greater than 6 L/min. Prone positioning was instituted in all patients with moderate to severe disease if they could tolerate it.

Remdesivir group selection

All patients with ESRD on HD hospitalized with PCR-confirmed COVID-19 in both hospitals were screened for inclusion. To be considered eligible for study inclusion, patients had to meet the following criteria: (1) Hospitalized for at least 48 h, aged ≥18 years; (2) SARS-CoV-2 infection confirmed by RNA PCR test; (3) SpO2 ≤ 94% on room air or requiring supplemental oxygen; and (4) Presence of radiographic evidence of pulmonary infiltrates. These patients were given 200mg of intravenous (iv) remdesivir on day one, followed by 100 mg once daily for 2-10 d or until discharge, death or if there was elevated AST/ALT, with levels greater than ten times the upper limit of normal.

Control group selection

For the purposes of this study, we created a control group consisting of hospitalized ESRD patients on HD with PCR-confirmed COVID-19 who did not receive remdesivir (during the same study period). To identify controls, we screened all patients with ESRD on HD who were admitted to both hospitals from April 1 to December 31, 2020 and did not receive remdesivir. After identifying those patients and to minimize selection bias, we used the following inclusion criteria: (1) Hospitalized for at least 48

Table 1 Baseline characteristics of study population

	Remdesivir (*n* = 20)	Control (*n* = 25)
Mean age (yr)	64.20 (± 15.16)	68.32 (± 12.67)
Age groups in years (*n*, %)		
18-40	2 (10)	1 (4)
41-64	5 (25)	7 (28)
Above 65	13 (65)	17 (68)
Females (*n*, %)	11 (55)	12 (48)
Race or ethnic group (*n*, %)		
White or Caucasian	9 (45)	12 (48)
Hispanic	5 (25)	9 (36)
Black or African American	2 (10)	2 (8)
Other	4 (20)	2 (8)
Tobacco use (*n*, %)	11 (55)	14 (56)
Diabetes mellitus (*n*, %)	13 (65)	20 (80)
Hypertension (*n*, %)	19 (95)	24 (96)
Coronary artery disease/peripheral vascular disease (*n*, %)	8 (40)	9 (36)
Congestive heart failure (*n*, %)	10 (50)	12 (48)
History of lung disease- no. (%)	6 (30)	9 (36)
Obesity (BMI>30 kg/m^2) (*n*, %)	8 (40)	12 (48)
Arrhythmia (*n*, %)	6 (30)	9 (36)
Length of stay - d (± SD)	13.00 (± 7.35)	12.16 (± 8.38)
Treatment (*n*, %)		
Corticosteroids	20 (100)	17 (68)
Antibiotics	13 (65)	13 (52)
Therapeutic anticoagulation	9 (45)	11 (44)

h, aged ≥18 years; (2) SARS-CoV-2 infection confirmed by PCR test; (3) SpO2 ≤ 94% on room air or requiring supplemental oxygen; and (4) Presence of radiographic evidence of pulmonary infiltrates.

Patients who met the following criteria were excluded: (1) Patients < 18 years of age; (2) Patients with ESRD who received renal transplant and are not on dialysis; and (3) Patients with AST, ALT > 10 times the upper limit of normal. The Nephrology service at Miriam Hospital (an affiliate of Alpert Medical School of Brown University) followed these patients while they were admitted. Patients also received antibiotics if there was a concern for superimposed bacterial infection in addition to the other interventions keeping in line with the institutional standard of care.

Endpoints

Our primary endpoint was comparing the oxygen requirements, time to mortality and escalation of care needing mechanical ventilation in patients that received remdesivir *vs* control group.

Data collection

Data were obtained from the Epic Electronic Medical Record system and recorded in a standardized form. Demographic data, laboratory findings, maximum oxygen requirements in Liters Per Minute (LPM), length of stay (LOS), and comorbid conditions were ascertained. Outcome measures were assessed through the date of study completion, hospital discharge or death; whichever came first.

Statistical analysis

To compare rates of oxygen and ventilator use, generalized linear modeling was used. Estimation was by maximum likelihood using SAS proc genmod software[5]. Mean oxygen use was modeled first as a normal distribution with an identity link, and the progression to mechanical ventilation was modeled as a binomial distribution with a logit link. For the length of stay and patient disposition, survival analysis was used, estimation by SAS proc phreg[6]. Here the length of stay is modeled as a ratio for patients who discharge *vs* patients who do not survive. The complete outcome data was available for both the cases and controls until death or discharge from the hospital. The risk of patient health deterioration as a function of time is modeled given covariates. Model selection was based on expert medical knowledge as well as the visual examination of residual plots.

Patient experience of COVID-19 pneumonia is highly variable, differences between patients were modeled as conditional on patient health status. Comparisons were made between patients with diabetes because this is a known risk population that would be highly susceptible to disease. Additionally, to identify the specific patients with severe condition, comparisons were also made based on d dimers. Grouping patients by rate of d dimers was selected because there were clear groupings among respondents. The histogram demonstrated a bimodal distribution, with some patients having very few d dimers, and some having many (skew = 2.64, kurtosis = 7.30). To account for this, patients above the mean were classified as "high d dimer" and patients below the mean classified as "low d dimer." The three-way interaction could then be modeled as a 2 (remdesivir or control) × 2 (diabetic or not diabetic) × 2 (high or low d dimer) ANOVA style design with interactions. While there were data available on corticosteroids, the observational nature of the study raised concerns that this may be a biased estimate because treatments were not given at random. As the research question mainly focused on the clinical outcomes with use of remdesivir, only patients' health characteristics were used as control variables, rather than introducing the complexity of various drug interactions within a small study sample.

Before analyzing the data, a brief power analysis was done to calibrate the limitations of the sample size. This was accomplished using G × Power software and the equations provided by Schoenfeld[7]. For the general regression models (oxygen, ventilator use), it was estimated that the effect of remdesivir needed to be large to be significant, accounting for 28% of the variance (2% is considered small, 13% medium, and 26% large). The effects of the additional covariates would also need to be large, accounting for an additional 25% of the variance. The survival analysis had better power, sensitive to a small to moderate effect size, risk ratio 2.32 (convention is 1.68 small, 3.47 medium, 6.71 Large)[8]. While the sample is smaller than would be preferred, the urgency of this research question outweighs the risk of statistical power.

RESULTS

A total of 108 charts were reviewed, of which only 45 met the inclusion criteria. A total of 20 patients received remdesivir while 25 patients were in the control group. Baseline statistics are reported in Table 1. There was no significant difference in length of stay in patients that received remdesivir (M = 13.00 ± 7.35 d) compared to patients that did not receive remdesivir (M = 12.16 ± 8.38 d). Table 2 has the main effect parameter estimates for the primary research questions and covariates, and Table 3 provides the estimated means by risk group for all three endpoints. Oxygen usage was considered first. The main effect of remdesivir was significant and the parameter was negative, indicating that across patients, those who were on remdesivir tended to use less oxygen (beta = -25.93, X^2 (1) = 6.65, P = 0.0099). That said, the three-way interaction term was significant (X^2 (1) = 6.37, P = 0.0116), indicating that the means varied based on patient risk conditions. Comparing remdesivir and control groups within risk groups, differences were only significant among patients who did not have diabetes (see Table 3).

Examining the covariates, the only significant finding at alpha = 0.05 was for sex, such that women tended to have lower oxygen need on average (beta = -9.49, X^2 (1) = 4.43, P = 0.0198). In addition, there was a trend for older patients and patients who used tobacco toward higher oxygen use (age: beta = 0.32, X^2 (1) = 3.25, P = 0.0712; tobacco use: beta = 8.49, X^2 (1) = 3.82, P = 0.0507). We anticipate that with larger sample size these results would reach the threshold of statistical significance.

Table 2 Main effect parameter estimates for the primary outcomes and covariates

	Outcome: Max O2			Outcome: Ventilation			Outcome: Time to Mortality		
Variable	**PE**	**X^2 (1)**	***p***	**PE**	**X^2 (1)**	***P* value**	**PE**	**X^2 (1)**	***P* value**
Age	0.32	3.25	0.0712	0.04	0.56	0.4562	0.05	1.75	0.1860
Tobacco use	8.59	3.82	0.0507	1.29	0.91	0.3399	-0.89	0.91	0.3398
Female Sex	-9.49	5.43	0.0198	-2.94	3.80	0.0511	0.05	< 0.01	0.9529
Black, Hispanic, and Other races	7.02	2.69	0.1011	2.14	1.96	0.1614	1.18	1.91	0.1672
Obesity	5.35	1.36	0.2444	1.46	0.74	0.3904	0.32	0.16	0.6932
Diabetes	-20.59	5.21	0.0224	-4.06	3.61	0.0575	-4.17	9.25	0.0024
High d dimers	-21.50	2.22	0.1358	-0.01	< 0.01	0.9971	-5.86	7.41	0.0065
Remdesivir	-25.93	6.65	0.0099	-28.52	22.98	< 0.0001	-5.03	7.42	0.0065

PE stands for parameter estimate. For Max O2, this is the average difference between the specified group and the overall mean. For ventilation, this represents the log odds difference between the specified group and the overall odds of being on a ventilator. For time to mortality, this represents the difference in risk of mortality as a function of time for the specified group relative to the overall risk of mortality for corona virus disease 2019 patients. Because age was specified as a continuous value, the values in PE represent the change in mean, odds, or risk for a one-year increase or decrease in age.

Next the progression to mechanical ventilation was considered. As before, remdesivir use was associated with much better outcome (beta = -28.52, X^2 (1) = 22.98, P < 0.0001). The three-way interaction term was not significant, reducing the model fit overall, however the interactions between remdesivir and each of diabetes and high d dimer status was significant (P < 0.0001), indicating dependencies between patient characteristics and health outcomes. Examining the conditional probabilities of mechanical ventilation need, remdesivir was found to be helpful for patients who were not diabetic and had low d dimer values (P < 0.0001). No covariates showed statistically significant association with the risk of needing a ventilator; female sex reached very close to statistical significance (X^2 (1) = 3.80, P = 0.0511), indicating less risk of ventilator use on average (beta = 2.94).

Finally, the time to mortality was examined, providing similar results to the previous analyses. The main effect of remdesivir was significant (X^2 (1) = 7.41, P = 0.0065) indicating on average patients on remdesivir had a better prognosis (beta = -5.03). The three-way interaction was not significant (X^2 (1) = 0.63, P = 0.4262), however all two-way interactions were significant or close to significant (remdesivir-high d dimers: X^2 (1) = 3.56, P = 0.0591; remdesivir-diabetes: X^2 (1) = 4.59, P = 0.0322; high d dimers-diabetes: X^2 (1) = 4.58, P = 0.0324) indicating dependent risks given patient characteristics. Again, it was specifically patients who did not have diabetes and had low d dimers for whom remdesivir demonstrated to significantly reduced risk (P = 0.0032, risk ratio < 0.01). No covariates demonstrated significant association with COVID-19 pneumonia prognosis.

DISCUSSION

Our study demonstrated a trend towards lesser oxygen requirement in the group of ESRD patients on HD who received remdesivir for the treatment of COVID-19 pneumonia. There was also a trend towards lower progression to mechanical ventilation in patients with COVID-19 that received remdesivir as compared to the control group. There was a trend towards better prognosis in terms of mortality in patients that received remdesivir compared to patients in the control group. However, due to the smaller number this trend did not reach statistical significance. None of the patients' treatment was interrupted due to hepatotoxicity. To our knowledge, only case series have been previously published on the safety of remdesivir in COVID-19 patients with ESRD.

Remdesivir is a monophosphoramidate prodrug of a nucleoside analogue and an inhibitor of the viral RNA-dependent RNA polymerase (RDRP). Intracellularly, the prodrug is rapidly converted into GS-704277 and subsequently into a monophosphate form that is finally converted into the active triphosphate form. Dephosphorylation of

Table 3 Group mean comparisons

D dimers	Diabetes	Condition	Mean	Z	*P* value	Cohen's d
Outcome: Max O2						
High	Yes	Remdesivir	28.80	-0.75	0.2260	0.43
		Control	36.81			
	No	Remdesivir	46.23	2.38	0.0087	1.76
		Control	13.22			
Low	Yes	Remdesivir	13.99	-0.33	0.3712	0.09
		Control	15.72			
	No	Remdesivir	8.79	-2.06	0.0199	1.38
		Control	34.72			
Outcome: Probability of being on a ventilator						
D dimers	Diabetes	Condition	% on ventilator	Z	*p*	Risk ratio
High	Yes	Remdesivir	6.16	-1.21	0.1125	0.11
		Control	55.34			
	No	Remdesivir	67.92	-0.07	0.4708	0.90
		Control	75.47			
Low	Yes	Remdesivir	8.22	0.27	0.3955	1.62
		Control	5.07			
	No	Remdesivir	0.00	-4.45	< 0.0001	0.00
		Control	75.66			
Outcome: Time to mortality						
D dimers	Diabetes	Condition	Hazard ratio	Z	*p*	Risk ratio
High	Yes	Remdesivir	-3.13	0.11	0.4570	5.78
		Control	-4.92			
	No	Remdesivir	-5.98	-0.02	0.4930	0.89
		Control	-5.86			
Low	Yes	Remdesivir	-4.84	-0.12	0.4512	0.52
		Control	-4.17			
	No	Remdesivir	-5.03	-2.72	0.0032	0.01
		Control	0.00			

Cohen's d effect size is conventionally defined as small = 0.2, medium = 0.5, and large = 0.8. Effect sizes for risk ratios are conventionally defined as small = 0.60 or 1.68, medium = 0.29 or 3.47, and large = 0.15 or 6.71.

the monophosphate form produces the nucleoside core (GS-441524), which becomes the predominant circulating plasma metabolite. The triphosphate form acts as an analog of adenosine triphosphate (ATP) and competes for incorporation by RDRP, causing premature chain termination and inhibition of viral replication. Originally developed as an investigational drug for Ebola virus, remdesivir has potent in vitro inhibitory activity against SARS-CoV1, MERS coronavirus, and SARS-CoV2. Remdesivir is usually intravenously administered at a dose of 200 mg once followed by 100 mg daily for a total of 5-10 d in adults and children ≥ 40 kg. The plasma $t_{1/2}$ of parent remdesivir is 1-2 hours, however the $t_{1/2}$ of GS-441524 is approximately 20-25 hours[9,10].

The intravenous preparation of remdesivir also contains a solubilizing agent, SBECD. Every 100 mg of remdesivir contains 3-6 g of SBECD (maximum recom-

mended threshold dose 250 mg/kg per day)[11]. Animal studies have shown that SBECD accumulation may only cause hepatic and renal toxicity at doses 50 to 100 times higher than the present patients' exposure during a 5-to-10-day course of remdesivir[12,13]. SBECD does not undergo significant tubular reabsorption and remains in an ionized state after glomerular filtration. Only less than 10% of remdesivir is renally excreted while 49% is recovered in the urine as GS-441524. In a case series by Davis *et al*, remdesivir's half-life in 66% of the COVID-19 patients with ESRD was twice as long as in healthy volunteers. While there was a decline in remdesivir concentrations by the end of the dosing interval, GS-441524 levels were also considerably higher than reference values. Despite this, post-HD concentrations of GS-441524 were 45%-49% lower than pre-HD measurements[14].

The results from our feasibility study are hypothesis generating. We see interesting trends towards lower oxygen requirements, and reduced progression to mechanical ventilation in the ESRD patients that received remdesivir as a part of the treatment for COVID-19. If remdesivir is an efficacious treatment as hypothesized, it would be expected that patients receiving this treatment would have better outcomes. This was observed in the data, at least for patients who were lower risk (i.e., not diabetic, low d dimer rates). This provides early support for remdesivir, though larger studies could show the effect of remdesivir on these patient centric outcomes.

Our study has many limitations. Firstly, only 68% of the patients in the control group received dexamethasone. However, all the patients in the remdesivir group received dexamethasone. This is mainly because some patients in the control group presented before July 2020 when dexamethasone use was not considered standard of care. In place of dexamethasone, alternative treatments such as hydroxychloroquine and convalescent plasma were used. Steroids were only used in these patients if they were in septic shock requiring vasopressors. Secondly, the sample size was relatively small. The study may not have been adequately powered to detect a significant difference. However, being a feasibility study, we did not expect the results to be statistically significant. Lastly, being a retrospective study, the study design has inherent biases such as selection and confounding biases.

CONCLUSION

The use of remdesivir in COVID-19 patients with ESRD showed a trend towards lesser oxygen requirements, lower progression to mechanical ventilation and survived longer. Our feasibility study is hypothesis generating and these patterns need further exploration with larger studies. Further research is also needed to study the clinical effects of remdesivir in COVID-19 patients with CKD stage 4 or 5 that are not on hemodialysis.

ARTICLE HIGHLIGHTS

Research background

Little known information exists regarding the efficacy of remdesivir in COVID-19 patients with end stage renal disease on dialysis.

Research motivation

With increasing use of remdesivir in COVID-19 patients we need more information about specific group of patients who could potentially benefit from the use of this medication and its safety profile.

Research objectives

To assess the clinical outcomes with use of remdesivir in adult patients with end stage kidney failure on hemodialysis.

Research methods

A multicenter, retrospective study was conducted on COVID-19 patients with end stage renal disease on hemodialysis that were discharged from the hospital between April 1st and December 31st, 2020. The primary outcomes were oxygen requirements, time to mortality and escalation of care needing mechanical ventilation.

Research results

A total of 45 patients were included in the study. Twenty patients received remdesivir, while 25 patients did not receive remdesivir. Most of the patients were females, Caucasians, and had diabetes mellitus and hypertension as the commonest comorbidities. There was a trend towards reduced oxygen requirement (beta = -25.93, X^2 (1) = 6.65, P = 0.0099, probability of requiring mechanical ventilation (beta = -28.52, X^2 (1) = 22.98, P < 0.0001) and mortality (beta = -5.03, X^2 (1) = 7.41, P = 0.0065) in patients that received remdesivir compared to the control group.

Research conclusions

Larger studies are justified to study the effects of remdesivir in this high-risk population with end stage kidney disease on dialysis.

Research perspectives

We believe that larger studies (both observational and randomized clinical trials) are warranted to further confirm the findings of this study.

REFERENCES

1 **Beigel JH**, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020; **383**: 1813-1826 [PMID: 32445440 DOI: 10.1056/NEJMoa2007764]

2 **Bhimraj A**, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, Edwards KM, Gandhi R, Muller WJ, O'Horo JC, Shoham S, Murad MH, Mustafa RA, Sultan S, Falck-Ytter Y. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin Infect Dis* 2020 [PMID: 32338708 DOI: 10.1093/cid/ciaa478]

3 **Rochwerg B**, Agarwal A, Siemieniuk RA, Agoritsas T, Lamontagne F, Askie L, Lytvyn L, Leo YS, Macdonald H, Zeng L, Amin W, Burhan E, Bausch FJ, Calfee CS, Cecconi M, Chanda D, Du B, Geduld H, Gee P, Harley N, Hashimi M, Hunt B, Kabra SK, Kanda S, Kawano-Dourado L, Kim YJ, Kissoon N, Kwizera A, Mahaka I, Manai H, Mino G, Nsutebu E, Preller J, Pshenichnaya N, Qadir N, Sabzwari S, Sarin R, Shankar-Hari M, Sharland M, Shen Y, Ranganathan SS, Souza JP, Stegemann M, De Sutter A, Ugarte S, Venkatapuram S, Dat VQ, Vuyiseka D, Wijewickrama A, Maguire B, Zeraatkar D, Bartoszko JJ, Ge L, Brignardello-Petersen R, Owen A, Guyatt G, Diaz J, Jacobs M, Vandvik PO. A living WHO guideline on drugs for covid-19. *BMJ* 2020; **370**: m3379 [PMID: 32887691 DOI: 10.1136/bmj.m3379]

4 **Kiser TH**, Fish DN, Aquilante CL, Rower JE, Wempe MF, MacLaren R, Teitelbaum I. Evaluation of sulfobutylether-β-cyclodextrin (SBECD) accumulation and voriconazole pharmacokinetics in critically ill patients undergoing continuous renal replacement therapy. *Crit Care* 2015; **19**: 32 [PMID: 25645660 DOI: 10.1186/s13054-015-0753-8]

5 **Hilbe JM**. Generalized linear models. *The American Statistician* 1994; **48**: 255-265

6 **Perperoglou A**, le Cessie S, van Houwelingen HC. A fast routine for fitting Cox models with time varying effects of the covariates. *Comput Methods Programs Biomed* 2006; **81**: 154-161 [PMID: 16426701 DOI: 10.1016/j.cmpb.2005.11.006]

7 **Schoenfeld DA**. Sample-size formula for the proportional-hazards regression model. *Biometrics* 1983; **39**: 499-503 [PMID: 6354290]

8 **Cohen J**. A power primer. *Psychol Bull* 1992; **112**: 155-159 [PMID: 19565683 DOI: 10.1037//0033-2909.112.1.155]

9 **Sheahan TP**, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO, Spahn JE, Bauer L, Sellers S, Porter D, Feng JY, Cihlar T, Jordan R, Denison MR, Baric RS. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 2020; **11**: 222 [PMID: 31924756 DOI: 10.1038/s41467-019-13940-6]

10 **Wang M**, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020; **30**: 269-271 [PMID: 32020029 DOI: 10.1038/s41422-020-0282-0]

11 **Adamsick ML**, Gandhi RG, Bidell MR, Elshaboury RH, Bhattacharyya RP, Kim AY, Nigwekar S, Rhee EP, Sise ME. Remdesivir in Patients with Acute or Chronic Kidney Disease and COVID-19. *J Am Soc Nephrol* 2020; **31**: 1384-1386 [PMID: 32513665 DOI: 10.1681/ASN.2020050589]

12 **Sörgel F**, Malin JJ, Hagmann H, Kinzig M, Bilal M, Eichenauer DA, Scherf-Clavel O, Simonis A, El Tabei L, Fuhr U, Rybniker J. Pharmacokinetics of remdesivir in a COVID-19 patient with end-stage renal disease on intermittent haemodialysis. *J Antimicrob Chemother* 2021; **76**: 825-827 [PMID: 33251541 DOI: 10.1093/jac/dkaa500]

13 **Luke DR**, Tomaszewski K, Damle B, Schlamm HT. Review of the basic and clinical pharmacology of sulfobutylether-beta-cyclodextrin (SBECD). *J Pharm Sci* 2010; **99**: 3291-3301 [PMID: 20213839 DOI: 10.1002/jps.22109]

14 **Davis MR**, Pham CU, Cies JJ. Remdesivir and GS-441524 plasma concentrations in patients with end-stage renal disease on haemodialysis. *J Antimicrob Chemother* 2021; **76**: 822-825 [PMID: 33152758 DOI: 10.1093/jac/dkaa472]

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ORIGINAL ARTICLE

Prospective Study

Epidemiology of electrical burns and its impact on quality of life - the developing world scenario

Giriraj Gandhi, Atul Parashar, Ramesh K Sharma

ORCID number: Giriraj Gandhi 0000-0001-8879-6485; Atul Parashar 0000-0003-1617-6732; Ramesh K Sharma 0000-0001-6078-4714.

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Country/Territory of origin: India

Giriraj Gandhi, Atul Parashar, Ramesh K Sharma, Department of Plastic Surgery, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Corresponding author: Atul Parashar, MBBS, MCh, MS, Professor, Department of Plastic Surgery, Post Graduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India. atulparashar@hotmail.com

Abstract

BACKGROUND

Electrical burns are devastating injuries and can cause deep burns with significant morbidity and delayed sequelae. Epidemiological data regarding the etiology, socioeconomic differences and geographic variation are necessary to assess the disease burden and plan an effective preventive strategy. These severe injuries often lead to amputations and thus hamper quality of life in the long term

AIM

To identify the population at maximum risk of sustaining electrical burns. We also studied the impact of electrical burns on these patients in terms of quality of life as well as return to work.

METHODS

The study was conducted at a tertiary referral teaching hospital over a period of eighteen months. All patients with a history of sustaining electrical burns and satisfying the inclusion criteria were included in the study. All relevant epidemiological parameters and treatment details were recorded. The patients were subsequently followed up at 3 mo, 6 mo and 9 mo. The standardized Brief Version of the Burn Specific Health Scale (BSHS-B) was adopted to assess quality of life. Statistical analysis was conducted using IBM SPSS statistics (version 22.0). A P value of < 0.05 was considered statistically significant.

RESULTS

A total of 103 patients were included in the study. The mean age of the patients was 31.83 years (range 18-75 years). A significant majority (91.3%) of patients were male. The mean total body surface area (TBSA) in these patients was 21.1%. In most of the patients (67%), the injury was occupation-related. High voltage injuries were implicated in 72.8% of patients. Among the 75 high voltage burn patients, 31 (41%) required amputation. The mean number of surgeries the patients underwent in hospital was 2.03 (range 1 to 4). The quality of life

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parameters amongst the patients sustaining high voltage electrical burns were poorer when compared to low voltage injuries at all follow-up intervals across nine domains. In eight of these domains, the difference was statistically significant. Similarly, the scores among the amputees were poorer when compared to non-amputees. The difference was statistically significant in six domains.

CONCLUSION
Electrical burns remain a problem in the developing world. Most injuries are occupation-related. The quality of life in patients with high voltage burns and amputees remains poor. Work resumption was almost impossible for amputees. These patients could not regain pre-injury status. Steps should be taken to create awareness and to implement an effective preventive strategy to safeguard against electrical injuries.

Key Words: Electrical burns; Quality of life; Amputation; Return to work; Occupational therapy; High voltage injuries

Core Tip: Electrical burns remain a problem in the developing world. Most injuries are occupation-related. The quality of life in patients with high voltage burns and amputees remains poor. Work resumption was almost impossible for amputees. These patients could not regain pre-injury status. Steps should be taken to create awareness and implement an effective preventive strategy to safeguard against electrical injuries.

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INTRODUCTION

Electrical appliances are used in domestic as well as industrial settings on a daily basis, and it is difficult to imagine normal life without electricity. Electrical injuries are probably as old as the discovery of electricity itself. The first recorded case of electrical injury was in 1879 in France when a carpenter suffered a low voltage injury (250 V) when operating a generator[1], and today electrical injury is considered the most common cause of occupation-related injury in developing as well as developed nations [2,3].

An electrical injury does not only involve the superficial layers of the skin but can injure the deeper tissue and can cause multiorgan damage and even death[4,5]. Electrical injuries occur due to passage of the electric current through the body and can be challenging to manage due to progressive necrosis as a result of injury to the microvasculature. The injury may lead to limb loss and disfigurement of the victim which will have a lasting impact on the ability of the individual to resume work (Figure 1). Most electrical injuries are preventable provided there are appropriate safety precautions. Epidemiological data regarding the etiology, socioeconomic differences and geographic variation are necessary before an effective prevention strategy can be planned[6,7]. Patients with electrical burns can suffer cognitive disturbances including slower thinking, impaired concentration, language and memory problems, as well as emotional distress[8,9]. Therefore, patients can have long-term residual effects affecting their quality of life. Knowledge of the characteristics of the injury and mechanism by which the injuries are sustained in our area we can help formulate specific preventive strategies. Those people who are at maximum risk of sustaining these injuries can be educated in terms of preventive measures. This will help reduce the morbidity and mortality associated with this injury.

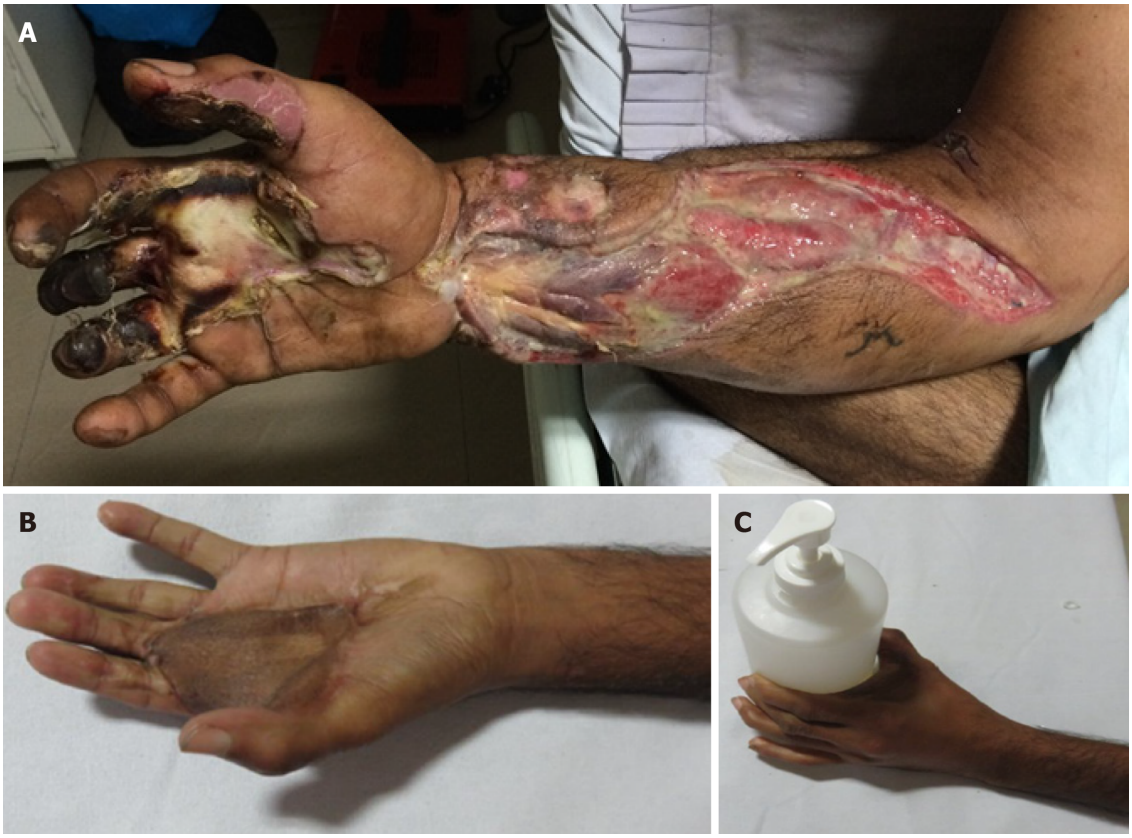

Figure 1 The injury may lead to limb loss and disfigurement of the victim which will have a lasting impact on the ability of the individual to return to work. A: Appearance on day 5 following fasciotomy in a high voltage electrical burns patient showing a gangrenous middle finger and ring finger along with nonviable tendons; B: Following skin necrosis due to electrical burns, debridement and a groin flap were performed; C: Same patient shown in Figure 1A and B using his injured hand to hold a bottle.

MATERIALS AND METHODS

Patient selection

The study was conducted in the Department of Plastic Surgery, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, over a period of eighteen months. This prospective case series consisted of all patients presenting to the Advanced Trauma Centre, PGIMER with electrical burns. Patients who had pre-existing comorbidities, or who were incoherent/intubated were excluded from the study. Patients less than 18 years of age were also excluded as they would not be able to complete the quality of life questionnaire satisfactorily.

Patient evaluation and follow-up

A thorough history and physical examination was undertaken to determine the mechanism of injury, and an evaluation of possible associated life-threatening injuries was carried out. The wounds were evaluated and the need for emergency procedures such as fasciotomy for compartment syndrome were carried out when required.

Immediate complications were ruled out or addressed and resuscitation of the patient was started after determining the percentage of total body surface area (TBSA) involved (calculated using the Lund and Browder chart). Fluid resuscitation was guided by the Parkland formula. Adequate resuscitation was confirmed by maintaining adequate urine output.

An electrocardiogram was performed to rule out arrhythmia and necessary treatment was given if required. Urine myoglobin was determined in all patients with electrical burns. Routine blood investigations including serum electrolytes were evaluated to rule out any anomalies and if necessary corrective treatment was given.

The patient's course was followed in the ward and epidemiological data were collected using a burn proforma and surgical procedures undertaken were recorded. Follow-up was carried out at 3 mo, 6 mo and 9 mo. The standardized and valid Brief Version of the Burn Specific Health Scale (BSHS-B) was adopted to assess health-related quality of life (HRQOL) in patients with extensive severe burns in 40 items

among nine domains: heat sensitivity, affect, hand function, treatment regimens, work, sexuality, interpersonal relationships, simple abilities, and body image[10]. The items were scored using a five point Likert scale with 0, extremely; 1, quite a bit; 2, moderately; 3, a little bit; and 4, none (not at all). Higher scores indicated greater HRQOL. Among the specific instruments available for measuring burn patients' quality of life, BSHS-B is the most widely used[11].

Statistical analysis

Discrete categorical data are represented either as a number or a percentage (%); Continuous data are represented as either the mean and standard deviation or the median and interquartile range. The normality of quantitative data was checked using the Kolmogorov-Smirnov tests of normality. For normally distributed data the means of BSHS in 3 types of electrical burns were compared using One-Way ANOVA followed by the post hoc Multiple Comparisons test. For normally distributed data, the Student t-test was applied to compare 2 groups. For comparison of 2 groups of skewed data the Mann-Whitney U-test was used. Proportions were compared using the Chi square or Fisher's exact test, depending on their applicability. For time related variables of skewed data the Wilcoxon Signed rank test was applied; for normally distributed data ANOVA was carried out. Analysis was conducted using IBM SPSS statistics (version 22.0). A P value of < 0.05 was considered statistically significant.

RESULTS

A total of 103 patients who satisfied the inclusion criteria were enrolled in our study.

Patients were aged 18 years to 75 years with a mean age of 31.83 years. 65% of patients were less than 30 years of age with the majority (46.6%) between 21 and 30 years, 91.3% were male and 8.7% were female. Sixty-nine patients (67%) had occupation-related injuries. Seventy-five patients (72.8%) had high voltage electrical burns and only 28 patients (27.2%) had low voltage electrical burns (Table 1). Data regarding the exact mechanism of the burns were collected (Table 2). Thirty-three patients were injured due to contact with a live wire either in the field, roof or the factory. A total of 22 patients had burns related to working with a transformer. Fifteen patients were injured by a home appliance, 8 by farming machinery and 7 youngsters while playing came into contact with a live wire. Six patients were injured at a construction site. Two patients were injured when flying a kite.

Fifty-eight patients (56.3%) had pure contact burns and 30 patients (29.1%) had pure electrical flash burns. Fifteen patients (14.6%) had a mixed injury with a flash as well as a contact burn. The TBSA of the burns ranged from 1% to 90%. The mean area was 22% with a standard deviation of 18.3%. The 25th percentile was 10%, 50th percentile was 18%, and the 75th percentile was 18%.

Of the 103 patients, 40 patients underwent an amputation. A total of 32 patients who suffered a high voltage electrical burn underwent upper limb amputation at different levels. Eight patients with low voltage electrical burns also underwent amputation but this was limited to finger amputation only. Of the 32 patients with high voltage electrical burns who had upper limb amputation, 8 patients had bilateral upper limb amputation at various levels. Seventeen patients also underwent lower limb amputation of which 7 had bilateral lower limb amputation.

Patients with electrical burns are likely to have "progressive necrosis" and hence may need multiple surgeries. The patients usually required two debridements with a debridement in the first 24 h after resuscitation and a relook debridement after another 48 h. In most cases definitive cover was feasible during the second intervention (Figure 2). However, some patients required multiple debridements before the wound was ready for definitive cover. The maximum number of surgeries in a single patient was 4 (Table 3).

Of the total number of patients, 13 (12.6%) succumbed to the injury. The cause of death included acute renal failure, cardiac arrhythmia, and sepsis due to extensive exposed areas.

Of 103 patients, there were 13 deaths and 17 patients were lost to follow-up during the study period. We followed up the remaining 73 patients at 3 mo, 6 mo and 9 mo.

The 40 questions in the BSHS were divided in 9 domains. The quality of life in patients with low voltage electrical burns *vs* those with high voltage electrical burns were recorded.

The mean of scores for all the questions and the standard deviation in the 9 domains at 3 mo, 6 mo and 9 mo are shown in Table 4.

Table 1 Characteristics of electrical burn injuries

Age distribution	Minimum age 18 yr, %	Maximum age 75 yr, %
Sex distribution	Male 94 (91.3)	Female 9 (8.7)
Occupation-related injury	Yes 69 (67)	No 34 (33)
High voltage *vs* low voltage burns	High voltage 75 (72.8)	Low voltage 28 (27.2)

Table 2 Mechanism of sustained injury

Mechanism of injury	Frequency (*n*)	Percent (%)
Construction site	6	5.8
Domestic line repair	2	1.9
Farming machinery	8	7.8
Flying kite	2	1.9
Home appliance	15	14.6
Live wire in field	15	14.6
Live wire in factory	7	6.8
Live wire on roof	11	10.7
Loading in truck	3	2.9
Playing	7	6.8
Transformer	22	21.4
Welding	5	4.9
Total	103	100.0

Table 3 Mean number of surgeries performed with standard deviation and percentiles

Number of surgeries		
Mean number of surgeries (*n*)		2.03
SD		0.842
Minimum number of surgeries (*n*)		1
Maximum number of surgeries (*n*)		4
Percentiles	25	1.00
	50	2.00
	75	3.00

When the *t* test was applied to the data in Table 4, differences in the domains when compared were significant in all except hand function at 3 and 6 mo, treatment regimen at 3 mo, 6 mo and 9 mo, and return to work at 3 mo, 6 mo and 9 mo (Table 5).

We also compared the quality of life amongst the patients who underwent amputation (Figure 3) *vs* those who did not undergo amputation. The mean total scores at 3 mo, 6 mo and 9 mo and the standard deviation are represented in Table 6.

We applied the *t* test to determine if the differences in the scores were significant. Comparisons between amputees and non-amputees showed that the differences in heat sensitivity, treatment regimens and body image were non-significant. All the other parameters were significant at 3 mo, 6 mo and 9 mo (Table 7).

Table 4 Mean scores in patients with high voltage and low voltage burns as per various domains at 3 mo, 6 mo and 9 mo

Domain	Voltage (*n*)	3 mo, mean ± SD	6 mo, mean ± SD	9 mo, mean ± SD
Heat sensitivity	High voltage (49)	12.55 (4.92)	15.14 (4.03)	16.73 (3.41)
	Low voltage (24)	15.71 (4.57)	17.46 (3.01)	18.21 (2.13)
Affect	High voltage (49)	16.12 (7.14)	19.00 (6.59)	20.82 (6.77)
	Low voltage (24)	23.33 (4.07)	25.46 (3.34)	26.5 (2.72)
Hand function	High voltage (49)	11.29 (6.29)	13.88 (6.25)	15.04 (6.09)
	Low voltage (24)	12.08 (5.93)	15.63 (3.94)	17.50 (3.48)
Treatment regimens	High voltage (49)	13.31 (4.35)	14.61 (4.19)	15.9 (4.05)
	Low voltage (24)	14.96 (4.71)	16.38 (3.89)	17.29 (3.22)
Work	High voltage (49)	6.33 (5.83)	7.96 (6.11)	8.73 (6.26)
	Low voltage (24)	8.83 (5.29)	10.50 (5.32)	11.71 (5.47)
Sexuality	High voltage (49)	8.14 (2.89)	9.24 (2.90)	9.63 (2.95)
	Low voltage (24)	10.75 (1.89)	11.21 (1.53)	11.54 (1.10)
Interpersonal relations	High voltage (49)	8.82 (3.97)	10.39 (3.80)	11.69 (3.76)
	Low voltage (24)	13.08 (2.80)	14.58 (2.13)	15.08 (1.67)
Simple abilities	High voltage (49)	6.78 (3.08)	8.85 (2.74)	9.98 (2.68)
	Low voltage (24)	9.0 (2.6)	10.71 (1.4)	11.46 (1.06)
Body image	High voltage (49)	6.39 (3.19)	8.45 (2.93)	10.37 (2.95)
	Low voltage (24)	11.38 (3.28)	13.33 (2.44)	14.50 (1.84)

Table 5 *P* value of the various domains in patients sustaining high voltage *vs* low voltage electrical burns

Domains	3 mo, *t* value (*P* value)	6 mo, *t* value (*P* value)	9 mo, *t* value (*P* value)
Heat sensitivity	- 2.63 (0.010)	-2.49 (0.015)	- 1.93 (0.057)
Affect	- 4.59 (0.000)	- 4.52 (0.000)	-3.95 (0.000)
Hand function	-0.52 (0.606)	-1.25 (0.215)	-1.84 (0.071)
Treatment regimens	-1.48 (0.142)	-1.73 (0.088)	- 1.47 (0.146)
Work	-1.78 (0.080)	-1.74 (0.086)	-1.98 (0.051)
Sexuality	-4.02 (0.000)	-3.11 (0.003)	-3.06 (0.003)
Interpersonal relations	-4.71 (0.000)	-5.03 (0.000)	-4.21 (0.000)
Simple abilities	-3.04 (0.003)	-3.12 (0.003)	-2.60 (0.011)
Body image	-6.22 (0.000)	-7.05 (0.000)	-6.28 (0.000)

DISCUSSION

Electrical burns are devastating injuries and can cause deep burns with significant morbidity, leading to prolonged hospital admission and multiple surgeries to achieve complete wound healing. These injuries are also responsible for amputation of limbs making the patient dependent on caregivers even for basic activities of daily living if multiple limbs are involved. Even after limb salvage surgery, the patient may have to undergo multiple admissions for reconstruction of tendons and nerves in the affected limb before adequate functionality of the limb is achieved. In the present study we attempted to examine the epidemiology of this injury and identify individuals at maximum risk of this injury.

We enrolled patients from 18 years to 75 years of age with 65% of patients below 30 years of age and a mean age of 31.83 years. Buja *et al*[12] in their study included patients with an age distribution of 2 years to 67 years and a mean age of 33.6 years. Ambikavathy Mohan in his study of electrical burns in South India included almost

Table 6 Mean scores in patients undergoing amputation and those not undergoing amputation at 3 mo, 6 mo and 9 mo

Domain	Amputee *vs* non-amputee (*n*)	3 mo, mean ± SD	6 mo, mean ± SD	9 mo, mean ± SD
Heat sensitivity	Amputee (30)	13.64 (4.77)	16.17 (3.41)	17.47 (3.05)
	Non-amputee (43)	13.56 (5.22)	15.72 (4.18)	17.05 (3.18)
Affect	Amputee (30)	14.33 (6.82)	17.80 (6.86)	20.17 (6.91)
	Non-amputee (43)	21.40 (5.84)	23.44 (5.08)	24.44 (5.30)
Hand function	Amputee (30)	7.83 (5.77)	11.13 (6.17)	13.17 (6.62)
	Non-amputee (43)	14.14 (5.00)	16.77 (3.84)	17.72 (3.51)
Treatment regimens	Amputee (30)	14.13 (4.01)	15.43 (3.62)	16.97 (3.43)
	Non-amputee (43)	13.65 (4.86)	15.02 (4.52)	15.93 (4.08)
Work	Amputee (30)	4.47 (4.71)	6.03 (5.38)	7.10 (6.20)
	Non-amputee (43)	9.02 (5.70)	10.72 (5.60)	11.53 (5.46)
Sexuality	Amputee (30)	7.93 (3.40)	9.10 (3.33)	9.53 (3.25)
	Non-amputee (43)	9.74 (2.16)	10.44 (1.99)	10.77 (2.02)
Interpersonal relations	Amputee (30)	8.17 (3.87)	10.43 (4.01)	11.67 (3.73)
	Non-amputee (43)	11.65 (3.72)	12.70 (3.54)	13.60 (3.30)
Simple abilities	Amputee (30)	5.40 (2.88)	7.87 (2.86)	9.27 (3.01)
	Non-amputee (43)	8.98 (2.31)	10.62 (1.41)	11.3 (1.30)
Body image	Amputee (30)	7.03 (3.80)	9.10 (3.52)	11.23 (3.21)
	Non-amputee (43)	8.72 (3.99)	10.72 (3.55)	12.07 (3.31)

Table 7 *P* value of the various domains among amputees and non-amputees

Domains	3 mo, *t* value (*P* value)	6 mo, *t* value (*P* value)	9 mo, *t* value (*P* value)
Heat sensitivity	-0.063 (0.950)	-0.482 (0.631)	-0.564 (0.574)
Affect	4.743 (0.000)	4.040 (0.000)	2.989 (0.004)
Hand function	4.973 (0.000)	4.810 (0.000)	3.814 (0.000)
Treatment regimens	-0.447 (0.656)	-0.413 (0.681)	-1.139 (0.259)
Work	3.601 (0.001)	3.575 (0.001)	3.230 (0.002)
Sexuality	2.781 (0.007)	2.153 (0.035)	2.001 (0.049)
Interpersonal relations	3.872 (0.000)	2.549 (0.013)	2.340 (0.022)
Simple abilities	5.868 (0.000)	5.390 (0.000)	3.952 (0.000)
Body image	1.814 (0.074)	1.927 (0.058)	1.076 (0.286)

50% of patients aged less than 30 years. These were young adults and most of them the sole earners in the family. Sustaining an electrical burn and losing the ability to work is a great loss to the family as well as society in general which has huge economic consequences[13]. In the present study, 91.3% of patients were male and only 8.7% were female. These results may be due to occupational predisposition among the male population. This is consistent with previous data regarding the sex distribution of electrical burns[14,15]. The electrical burns in 67% patients were occupation-related and 33% were due to unrelated causes. Electrical burns are considered the most common job related-injury in both developing as well as developed countries[2,3]. Our findings are consistent with the available literature.

Amongst the 103 patients, 72.8% were injured by a high voltage electric current, whereas 27.2% sustained burns by a low voltage source. High voltage injuries are more distressing causing larger body mass necrosis and have a higher chance of amputation and requiring extensive reconstruction[16]. 41% of patients with high voltage burns underwent amputation. On the other hand, only 8 patients with low

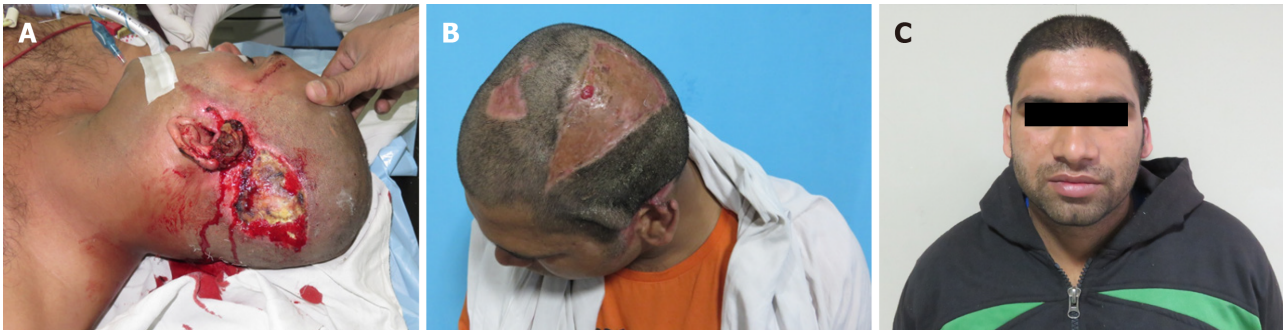

Figure 2 In most cases definitive cover was feasible during the second intervention. A: Electrical contact burns with the entry point at the left parietal region; B: Transposition flap cover after second debridement; C: Same patient shown in Figure 2A and B at 3 mo follow-up.

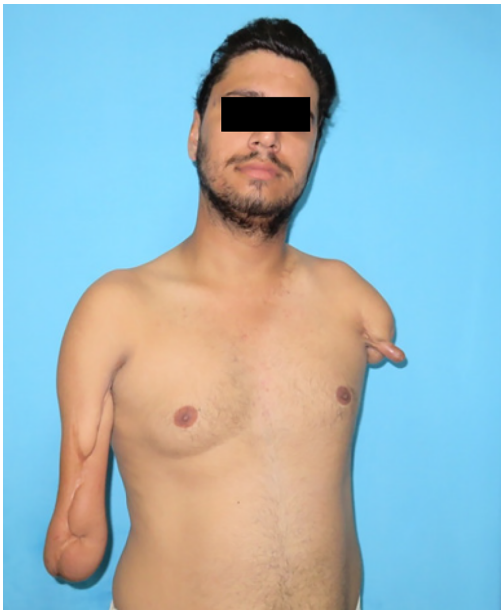

Figure 3 Bilateral amputee following electrical burns.

voltage burns underwent minor amputation of fingers. Also all 13 deaths during the study period occurred in patients with high voltage electrical burns.

71% of patients had a contact burn component, and 43.7% of patients had a flash burn component. 29.1% of patients had pure flash burns. The contact burn injuries were deeper and required multiple surgeries and flap cover. Flash burns which were limited to the superficial layer of the dermis healed with regular dressings within 2 weeks of the injury. In general, flash burns are superficial and usually do not damage deeper tissues. Surgery is required in these patients and sometimes multiple procedures may be required, but amputations are not usually required[17].

The mean TBSA in these patients was 21.1% with a standard deviation of 18.3%, and the range was from 1% to 90%. In the study by Kym *et al*[18] a mean TBSA of 14% was observed. Agakhani *et al*[19] found that the mean TBSA was 13.5%. The study by Hamid Karimi *et al*[20] in Iran found that the mean TBSA was 13.2%. The reason for the slightly higher mean TBSA in our study can be attributed to inter-observer variation in estimating the burns and to the large number of cases of electrical flash burns with larger TBSA burns.

Forty of the 103 patients (38.8%) underwent amputation. Of the 75 high voltage burn patients, 32 (42%) underwent amputation. Nine patients with low voltage electrical burns (32%) underwent amputation, but these were mainly minor amputations. Agakhani *et al*[19] reported similar results. The study by Kym *et al*[18] in South Korea demonstrated that 625 patients (74.7%) underwent amputation, but most of these were minor. They reported an amputation rate of 15.6% in the low tension group. This high rate of amputation following electrical burns indicates the morbidity associated with these burns and suggests that prevention is better than cure. It also

shows the importance of limb salvage by timely fasciotomy and early stable wound coverage after adequate debridement[21].

Thirty-two of our patients had upper limb amputation and 8 of these patients underwent bilateral amputation. Seventeen patients underwent lower limb amputation of which 7 had bilateral lower limb amputation. This is consistent with other studies[22]. In general, upper limbs are affected as they are frequently in contact with the electrical source.

The mean number of surgeries the patients underwent was 2.03 and ranged from 1 to 4. The 25th percentile was 1, 50th percentile was 2 and the 75th percentile was 3. Extensive raw areas following flash burns required 2 surgeries consisting of split thickness skin grafts.

Early adequate debridement is the key to successful reconstructive procedures. The injury is usually most severe in the small muscle branches, where blood flow is slower [22]. Sometimes complete damage is not initially evident. As the smaller vessels become thrombosed tissue damage then becomes evident. This creates the illusion of progressive tissue necrosis. Performing a flap and then having problems of pus discharge from below the flap is distressing both for the patient as well as the surgeon. We therefore found it prudent to occasionally have a second look when we had doubts about the viability of the tissue. This in our view prevented problems with both over debridement as well as under debridement. Frankly necrotic and devitalized tissue was removed in the first surgery and indeterminate tissue was left behind. Then further surgery was performed after 48 to 72 h to provide definitive cover. The only disadvantage of this technique is increasing management by one stage and the patient undergoing anesthesia an additional time and therefore increasing the cost of management. As our hospital is a government hospital the cost factor did not have much bearing, but this approach may increase the cost of management in a private setup. Hence this method was not followed in all patients.

During our study period, a total of 13 deaths (12.6%) were observed. The patients with a higher percentage of flash burns succumbed to sepsis, while acute renal failure and cardiac events were the cause of death amongst patients with contact burns. Mortality is reported to be between 3% and 15% in the U.S.[23]. A possible reason for the number of deaths being higher is that ours is a tertiary referral center with a lot of complex cases being referred to us on a regular basis.

The morbidity associated with burns is huge especially if the patient undergoes major amputation. It may be impossible for patients to return to work[24] and they may also become dependent on caregivers even for activities of daily living. This has an impact on the psychology of the patient.

The patients in our study were followed up at 3 mo, 6 mo and 9 mo to determine their quality of life. We compared quality of life based on the domains in patients with high voltage electrical burns *vs* low voltage electrical burns. In the total heat sensitivity domain the difference in the score was significant at all stages of follow-up. Patients with a flash component and large surface who underwent grafting had more problems regarding heat sensitivity. The difference in the score of the affect of high voltage electrical burns and low voltage electrical burns was significant at all stages. This may be due to the fact that usually high voltage burns are more devastating and have a poor affect as compared to patients with low voltage electrical burns. The hand function scores between the two groups showed that patients with low voltage burns fared better, but the difference was not statistically significant different between the groups at all stages of follow-up.

In general, patients with low voltage electrical burns had more trouble coping with the treatment regimen. This may be due to the fact that a lot of these patients required grafts and thorough post-graft skin care is required. The difference between the low voltage and high voltage groups was not significant, possibly because some patients in the high voltage group required grafts and they too needed to take care of the skin thus confounding the results.

With regard to work, the difference in scores between the low voltage and high voltage groups was significant, and patients sustaining low voltage electrical burns were significantly better at 3 mo, 6 mo and 9 mo. This is because high voltage electrical burns are usually more destructive[16].

Amongst the other domains, sexuality, interpersonal relationship, simple abilities and body image, patients with low voltage electrical burns were significantly better placed than those with high voltage electrical burns. We also compared the quality of life of amputees *vs* non-amputees. The domains of affect, hand function, sexuality, work, interpersonal relationship and simple abilities were significantly different and patients with amputation were significantly poorly placed as compared to non-amputees. The difference between the score for body image was non-significant. The

reason for this could be due to amputees not liking their "incomplete" body and non-amputees not being able to accept their bodies with extensive scars.

As 67% of electrical burns are related to occupation we strongly feel that a good education program for the at-risk population would be extremely beneficial.

From the available data it is clear that a prevention strategy should include the following 2 aspects: (1) Strict implementation of existing laws; and (2) An education program aimed at the at-risk population and the general public regarding the devastating outcome of electrical burn injuries and essential safety measures.

Strict implementation of existing laws can be ensured by heavy fines for the contractor or the builder responsible for breaking the law. Sign boards indicating danger depicted pictorially should be used. These sign boards will get the message across even to the uneducated population keeping them away from the areas where accidents are likely to happen. Various education programs regarding the effects of these devastating injuries and safety measures to be undertaken for prevention will go a long way to reduce the incidence of such injuries. Today we live in a world where communication is very easy and has become a powerful tool. There are countless means of mass communication including the internet, social media, television and radio. Only constant reminders will probably finally reduce accidental burn victims in our country[25] and we can use all these media to our advantage to spread the message.

CONCLUSION

In conclusion, electrical burns are still a major problem in India and most injuries are occupation-related. Furthermore, extensive injuries need to be managed in a tertiary care center using a multidisciplinary approach. Quality of life in patients with high voltage electrical burns and amputees is poor. Thus, steps should be taken to create awareness as well as plan and implement a good preventive strategy for electrical burns

ARTICLE HIGHLIGHTS

Research background

We have come a long way since the discovery of electricity and have become totally dependent on it. Yet there are numerous hazards associated with it. The accidental injuries sustained from electricity can potentially cripple individuals making them completely dependent on others for activities of daily living. There are a limited number of studies investigating the causes and characteristics of electrical injuries and the quality of life in these patients following treatment. In-depth evaluation of the circumstances of injuries and overall quality of life in this particular subset of patients has not been thoroughly evaluated.

Research motivation

Knowledge of the characteristics of electrical burn injuries and understanding the circumstances in which these injuries are sustained can help to formulate specific preventive strategies. The subjects who are at maximum risk of sustaining these injuries can be educated on these preventive measures. This will help reduce the morbidity and mortality associated with these devastating injuries.

Research objectives

To study the epidemiology of electrical burns and to define the population which is at maximum risk of sustaining such injuries. The impact of electric burns on these patients and their quality of life along with the potential of returning to previous work were also evaluated.

Research methods

This prospective study was conducted over a period of 18 mo at a tertiary care teaching hospital. All patients presenting to the Trauma Center with a history of sustaining electrical burns and satisfying the inclusion criteria were included in the study. The course of the patient in hospital was followed and epidemiological data were collected using a burn proforma. Follow up was carried out at 3 mo, 6 mo and 9

mo. The standardized and valid Brief Version of the Burn Specific Health Scale (BSHS-B) was adopted to assess health-related quality of life (HRQOL). The normality of quantitative data was assessed by the Kolmogorov-Smirnov test. Normally distributed data were compared using One-Way ANOVA followed by the post hoc Multiple Comparisons test. For time related variables of skewed data the Wilcoxon Signed rank test was applied; for normally distributed data ANOVA was carried out. Analysis was conducted using IBM SPSS statistics (version 22.0). A P value of < 0.05 was considered statistically significant.

Research results

These injuries were more common in males and in the younger population. The majority of injuries were occupation-related and mostly accidental in nature, mainly due to ignorance as well as carelessness on the part of the victims. Hence, many injuries and resultant morbidities could have been prevented by mass education and awareness. A significant number of patients were uneducated. Thus, they had to take menial jobs without being aware of the appropriate safety measures. There was also a lack of awareness amongst their supervisors. Patients had a combination of contact and flash burns. The variety of associated injuries in these patients made a multidisciplinary approach vital for effective management. The patients underwent a variety of surgeries depending on the extent of the initial injury, of which amputation was the most devastating. Limb salvage necessitated multiple complex procedures which required intricate planning and execution. The quality of life among patients sustaining high voltage electrical burns and amputees was poor.

Research conclusions

Electrical burns cause extensive damage requiring multiple surgeries and reconstructive techniques. This makes it a major economic burden for the patient as well as the government. In addition, there are various social and rehabilitative challenges for the patient as well as his or her family. The patients who underwent multiple limb amputations became dependent on caregivers even for basic activities of daily living for the rest of their lives. It is a major challenge for these patients to return to pre-injury status due to the significant stigma of initial injury and persistent tissue damage. This underscores the importance of effective preventive strategies to reduce these injuries.

Research perspectives

Future studies should be carried out to determine the efficacy of various preventive strategies to decrease the frequency of these injuries and to reduce the morbidity and mortality associated with electrical burns.

REFERENCES

1 **Acosta AS**, Azarcon-Lim J, Ramirez AT. Survey of electrical burns in Philippine General Hospital. *Ann N Y Acad Sci* 1999; **888**: 12-18 [PMID: 10842615 DOI: 10.1111/j.1749-6632.1999.tb07938.x]

2 **Mohammadi AA**, Amini M, Mehrabani D, Kiani Z, Seddigh A. A survey on 30 mo electrical burns in Shiraz University of Medical Sciences Burn Hospital. *J International Society for Burn Injuries* 2008; **34**: 111-113

3 **Opara KO**, Chukwuanukwu TO, Ogbonnaya IS, Nwadinigwe CU. Pattern of severe electrical injuries in a Nigerian regional burn centre. *Nigerian J Clinical Practice* 2006; **9**: 124-127

4 **Arnoldo BD**, Purdue GF, Kowalske K, Helm PA, Burris A, Hunt JL. Electrical injuries: a 20-year review. *J Burn Care Rehabilitation* 2004; **25**: 479-484

5 **Hussmann J**, Kucan JO, Russell RC, Bradley T, Zamboni WA. Electrical injuries--morbidity, outcome and treatment rationale. *J International Society for Burn Injuries* 1995; **21**: 530-535

6 **Liao CC**, Rossignol AM. Landmarks in burn prevention. *Burns* 2000; **26**: 422-434 [PMID: 10812263 DOI: 10.1016/s0305-4179]

7 **Linares AZ**, Linares HA. Burn prevention: the need for a comprehensive approach. *Burns* 1990; **16**: 281-285 [PMID: 2257071 DOI: 10.1016/0305-4179]

8 **Cherington M**. Central nervous system complications of lightning and electrical injuries. *Semin Neurol* 1995; **15**: 233-240 [PMID: 8570925 DOI: 10.1055/s-2008-1041028]

9 **Primeau M**, Engelstatter GH, Bares KK. Behavioral consequences of lightning and electrical injury. *Semin Neurol* 1995; **15**: 279-285 [PMID: 8570930 DOI: 10.1055/s-2008-1041033]

10 **Kildal M**, Andersson G, Fugl-Meyer AR, Lannerstam K, Gerdin B. Development of a brief version of the Burn Specific Health Scale (BSHS-B). *J Trauma* 2001; **51**: 740-746 [PMID: 11586169 DOI: 10.1097/00005373-200110000-00020]

11 **Yoder LH**, Nayback AM, Gaylord K. The evolution and utility of the burn specific health scale: A

systematic review. *Burns* 2010; **36**: 1143-1156 [PMID: 20382480 DOI: 10.1016/j.burns.2010.01.004]
12 **Electrical burn injuries**. An eight-year review. In: Buja Z, Arifi H, Hoxha E. Annals of Burns and Fire Disasters, 2010
13 **Gilboa D**, Friedman M, Tsur H. The burn as a continuous traumatic stress: implications for emotional treatment during hospitalization. *J Burn Care Rehabil* 1994; **15**: 86-91; discussion 91
14 **Patil SB**, Khare NA, Jaiswal S. Changing patterns in electrical burn injuries in a developing country: should prevention programs focus on the rural population? *J Burn Care Res* 2010; **31**: 931-934
15 **Ramakrishnan KM**, Ramachandran K, Jayaraman V. Electrical burns treated in an Indian hospital. *Burns* 1991; **17**: 481-483
16 **Chudasama S**, Goverman J, Donaldson JH, van Aalst J, Cairns BA, Hultman CS. Does voltage predict return to work and neuropsychiatric sequelae following electrical burn injury? *Ann Plast Surg* 2010; **64**: 522-525 [PMID: 20395807 DOI: 10.1097/SAP.0b013e3181c1ff31]
17 **Handschin AE**, Vetter S, Jung FJ, Guggenheim M, Kunzi W, Giovanoli P. A case-matched controlled study on high-voltage electrical injuries vs thermal burns. *J Burn Care Res* 2009; **30**: 400-407
18 **D Kym**, DK Seo, GY Hur2, JW Lee. Epidemiology Of Electrical Injury: Differences Between Low-And High-Voltage Electrical Injuries During A 7-Year Study Period In South Korea
19 **Aghakhani K**, Heidari M, Tabatabaee SM, Abdolkarimi L. Effect of current pathway on mortality and morbidity in electrical burn patients. *Burns* 2015; **41**: 172-176
20 **Karimi H**, Momeni M, Vasigh M. Long term outcome and follow up of electrical injury. *J Acute Disease* 2015; 107-111
21 **Maghsoudi H**, Adyani Y, Ahmadian N. Electrical and lightning injuries. *J Burn Care Res* 2007; **28**: 255-261 [PMID: 17351442 DOI: 10.1097/BCR.0B013E318031A11C]
22 **Hunt JL**, McManus WF, Haney WP, Pruitt BA Jr. Vascular lesions in acute electric injuries. *J Trauma* 1974; **14**: 461-473 [PMID: 4152263 DOI: 10.1097/00005373-197406000-00003]
23 **Bingham H**. Electrical burns. *Clin Plast Surg* 1986; **13**: 75-85 [PMID: 3956083]
24 **Wick R**, Gilbert JD, Simpson E, Byard RW. Fatal electrocution in adults--a 30-year study. *Med Sci Law* 2006; **46**: 166-172 [PMID: 16683472 DOI: 10.1258/rsmmsl.46.2.166]
25 **Puri V**. Mass media magic- the power to Empower. *Indian J Burns* 2014; **22**: 1-2

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MINIREVIEWS

Point-of-care ultrasound for critically-ill patients: A mini-review of key diagnostic features and protocols

Yie Hui Lau, Kay Choong See

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Yie Hui Lau, Department of Anaesthesiology, Intensive Care and Pain Medicine, Tan Tock Seng Hospital, Singapore 308433, Singapore

Kay Choong See, Division of Respiratory & Critical Care Medicine, National University Hospital, Singapore 119074, Singapore

Corresponding author: Yie Hui Lau, MBBS, Doctor, Department of Anaesthesiology, Intensive Care and Pain Medicine, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore. yie_hui_lau@ttsh.com.sg

Abstract

Point-of-care ultrasonography (POCUS) for managing critically ill patients is increasingly performed by intensivists or emergency physicians. Results of needs surveys among intensivists reveal emphasis on basic cardiac, lung and abdominal ultrasound, which are the commonest POCUS modalities in the intensive care unit. We therefore aim to describe the key diagnostic features of basic cardiac, lung and abdominal ultrasound as practised by intensivists or emergency physicians in terms of accuracy (sensitivity, specificity), clinical utility and limitations. We also aim to explore POCUS protocols that integrate basic cardiac, lung and abdominal ultrasound, and highlight areas for future research.

Key Words: Critical care; Echocardiography; Point-of-care testing; Sensitivity and specificity; Ultrasonography

Core Tip: Point-of-care ultrasound (POCUS) is increasingly being used by intensivists and emergency physicians for the care of critically-ill patients. This mini-review highlights key findings in basic cardiac, lung and abdominal ultrasound, and introduces several POCUS-based protocols, which have practical utility for patient management.

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INTRODUCTION

Diagnostic errors in medicine and intensive care are prevalent, with autopsy studies showing substantial misdiagnoses[1]. Point-of-care ultrasonography (POCUS) fills a void to reduce diagnostic uncertainty and some features may also guide prognosis and management. However, image acquisition and interpretation needs to be done with skill and caution to avoid inadvertent over- or underdiagnosis of abnormalities. POCUS misdiagnoses due to inexperience may lead to errors in the treatment that may worsen patients' outcomes or even be fatal[2]. Each POCUS practitioner must be mindful of this, and follow up or evaluate with alternatives where applicable. It is still important that any form of POCUS should be preceded by clinical examination, which provides complementary information for diagnosis and treatment.

There is an increase in the application of POCUS for managing critically ill patients, performed by intensivists or emergency physicians, who are neither radiologists nor sonographers. POCUS is inexpensive, non-invasive and can be readily available at the bedside. It is thus an important skill-set for anyone who takes care of critically ill patients.

POCUS may be too brief to have in depth interrogation of any pathology found and more detailed scanning is not practical in a busy intensive care unit (ICU) or emergency department. Excessive time taken for image acquisition and measurements may delay other clinical assessment or treatment. If abnormalities are found or if a comprehensive evaluation is required, a formal transthoracic echocardiogram or follow up computed tomography (CT) imaging can then be arranged at a more opportune time.

Results of needs surveys among intensivists reveal emphasis on basic cardiac, lung and abdominal ultrasound[3], which are the commonest POCUS modalities in the ICU. We thus aim to describe the key diagnostic features of basic cardiac, lung and abdominal ultrasound as practised by intensivists or emergency physicians in terms of accuracy (sensitivity, specificity), clinical utility and limitations. We also aim to explore POCUS-based protocols that integrate these ultrasound features.

BASIC CRITICAL CARE ECHOCARDIOGRAPHY

Basic critical care echocardiography (CCE) typically involves obtaining 4 echocardiography views (parasternal long axis, parasternal short axis, apical four- chamber, subcostal views) to answer urgent questions at the bedside, regarding myocardial contractility, left ventricular filling, right ventricular dilatation, or the presence of other obvious abnormalities (*e.g.* large pericardial effusion). Myocardial contractility is usually described in terms of regional wall motion abnormalities such as hypokinesia, dyskinesia or akinesia. Image acquisition and interpretation requiring all 4 of these views require skill and competency in order to complete the assessment in a timely manner. CCE is most often used to evaluate causes of shock, cardiac arrest or acute cardiopulmonary failure. Some key features of basic CCE are summarised in Table 1; examples in Figure 1.

BASIC LUNG ULTRASOUND

Lung ultrasound has also gained popularity because of its relative portability. The added benefit compared to chest radiographs and CT imaging, is that the patient's clinical course can be conveniently followed up over time with no radiation risk. Lung ultrasound has been shown to reduce the use of chest radiographs and CT scans in critically ill patients by 26% and 47% respectively[4]. The diagnostic accuracy rates of lung ultrasound for cardiogenic pulmonary edema (94% *vs* 65%, $P = 0.03$) and for pneumonia (83% *vs* 66% $P = 0.016$) are better if paired with CCE, than compared to lung ultrasound alone[5]. Some of the key features and the clinical utility of these features are described in Table 2, with examples in Figure 2.

General limitations to lung ultrasound include a large body habitus, presence of subcutaneous emphysema and thoracic dressings; these limit obtaining adequate windows[6]. Lack of access to training and ultrasound machines also limit more widespread application of lung ultrasound. However, compared to CCE, competency in lung ultrasound can be achieved more quickly with a minimum of 10 scans[7].

ABDOMINAL ULTRASOUND

While basic cardiac and lung ultrasound features have generally been well-characterized individually, abdominal ultrasound features have instead been studied in the context of integrated protocols. The Focused Assessment with Sonography for Trauma (FAST) incorporates scanning the abdomen, heart, pericardial and pleural spaces in a trauma patient. This subsequently incorporated basic thoracic injury

Table 1 Characteristics of basic critical care echocardiography

	Key features	Accuracy % (95%CI)	Clinical utility	Limitations
Pericardial effusion	Echo-free space between heart and the parietal layer of the pericardium. 15 mL: Minimum detectable by echocardiography; > 50 mL: Pathological. Nature of the fluid-non-echogenic space (serous fluid), echogenic fluid (blood, pus)	ED physicians using a combination of parasternal short and long axis, apical and subcostal views: (1) Sensitivity 96 (90.4-98.9); (2) Specificity 98 (95.7-98.7); (3) PPV 92.5 (85.8- 96.7); and (4) NPV 98.9 (97.3-99.7). Accuracy: 97.5 (95.7-98.7)[29]	Diagnostic, as a cause of dyspnea; Characterisation of fluid; Estimate size of effusion; Guide approach for pericardiocentesis	Pleural effusion, pericardial fat pad may be mistaken as pericardial effusion. Limited echo windows may affect the sensitivity and specificity of CCE. 4 standard views should be done to assess if the effusion is localised or global[30]
Pericardial tamponade	A pericardial effusion with: (1) Diastolic RV collapse; (2) Systolic RA collapse < 1/3 of cardiac cycle (earliest sign); (3) A plethoric IVC with minimal respiratory variation; and (4) Doppler: Exaggerated respiratory cycle changes in mitral and tricuspid valve in-flow velocities (peak E wave velocity will drop at least 25% (mitral) 40% (tricuspid) in expiration compared to inspiration (suggestive of pulsus paradoxus)	(1) Sensitivity 48-60; Specificity 75-90[31] (sensitivity and specificity improves as the severity increases); (2) RA collapse. Sensitivity 55-97; Specificity 33-100[31]. Absence of both RA systolic, RV diastolic collapse: NPPV 90; Sensitivity 95-97; Specificity 40; (3) Sensitivity 92% but not specific[32]; and (4) Pulsus paradoxus itself: Sensitivity 82% (95%CI: 72%–92%); in the presence of pericardial effusion, positive LR 3.3 (95%CI: 1.8-6.3) and negative LR 0.03 (95%CI: 0.01-0.24)[31]	Identifying tamponade as cause of shock. If found to be the cause of cardiac arrest, and had pericardiocentesis after diagnosis, survival to discharge increased by 15.4% (compared to 1.4% without POCUS)[33]	(1) Plethoric IVC may be caused by chronic lung disease, congestive cardiac failure, tricuspid regurgitation; (2) Patients on mechanical ventilation will not demonstrate plethora because inspiration is generated by positive pressure and hence IVC expands rather than collapses[34]; (3) Doppler techniques require more advanced practitioners of POCUS; and (4) Respiratory variation of the mitral and tricuspid inflows should not be used as a sole criterion for tamponade without the presence of chamber collapse, IVC dilation, or abnormal hepatic vein flows (blunting or reversal of diastolic flows in expiration)
Right ventricular dilation and dysfunction	(1) RV dilatation in PE: Diameter-> 42 mm (base), > 35 mm (mid-level). Longitudinal dimension > 86 mm[35]; (2) RV dysfunction in PE, TAPSE < 17.5 mm, indicated abnormal, RV systolic, function[36]; (3) RV hypokinesis; (4) Right heart thrombi; (5) Ventricular interdependence; (6) Leftward septal displacement; and (7) McConnell sign (Normal contraction or sparing of the RV apex with hypokinesis of midportion of the RV free wall)	(1) Enlargement of the RV compared to the LV. Sensitivity 55. Specificity 86[37]; (2) RV dysfunction indicated by abnormal TAPSE Sensitivity 87. Specificity 91. AUC 0.96 (95%CI: 0.87-1.00)[36]; (3) RV hypokinesis for diagnosis of PE. Sensitivity 70. Specificity 33. Predictor of 30-d mortality in PE. Sensitivity 52.4 (43.7-61.0). Specificity 62.7 (59.5-65.8). NPV 90.6 (88.1-92.7). PPV 16.1 (12.8-19.9)[38]; (4) –; (5) –; (6) –; and (7) Sensitivity 70%. Specificity 33; PPV 67; NNV 36 [30]	To identify acute cor pulmonale or pulmonary embolism. Various echocardiographic signs can be used to rule in PE, but none can rule it out. This is due to the known variability of PE presentation, clot burden, and physiologic reserve that contribute to pulmonary vascular resistance and acute RH strain[36]. RV dysfunction in PE found to be predictor of early mortality[38]. Presence of right heart thrombi is associated with an increased risk of death in 30 d	Obtaining adequate RV views in critically ill patients may be challenging, especially post abdominal-surgery with a smaller subcostal window. There are numerous methods available to measure RV size and function, yet the parameter that is the most accurate in the critically ill is controversial[39]. McConnell's sign may also be present in RV infarct and not just PE (*i.e.* Not specific for PE)
Left ventricular dysfunction [40]	(1) 2D Biplane; (2) Visual ejection fraction; (3) MAPSE < 12 mm; and (4) E-point septal separation > 7 mm	(1) -; (2) Predicts LVEF < 50%. AUROC 0.8 (0.70-0.90); (3) Predicts LVEF < 50% AUROC 0.73 (0.62-0.84); and (4) Predicts EF < 30%. Sensitivity 100 (95%CI: 62.9-100). Specificity 51.6 (95% CI: 38.6-64.5)[41]	(1) Allows more informed risk counselling, prognostication. Patients with no cardiac activity on PoCUS were much less likely to achieve ROSC, had shorter mean resuscitation times[42]; and (2) Relatively easy and rapid. Internal Medicine physicians were able to identify normal versus decreased LVSF with high sensitivity, specificity, and "good" interrater agreement compared to formal echocardiography after completing a training program[43]	(1) Requires optimal acquisition of endocardial borders, time consuming, requires training; (2) and (3) are rarely done
Variation of IVC diameter with respiration	(1) Collapsibility index, measured 4cm caudal to the right atrium, with a deep standardised inspiration; (2) Distensibility index during intermittent positive pressure ventilation; and (3) IVC collapse of > 50 %	(1) Fluid responsiveness: Depending on whether a standardised or non- standardised spontaneous breath was taken: Sensitivity 66-93 Specificity 99-98[44,45]; (2) Comparable to pulse pressure variation in predicting fluid responsiveness (AUROC 0.75 ± 0.07); (3) Cut off value of 16.5%. Sensitivity 71.4; Specificity 76.5[46]; and (4) In predicting CVP < 8 mmHg: PPV of 87, NPV of 96,	Assessment of fluid responsiveness to avoid unnecessarily fluid boluses. The degree to which the CVP falls during spontaneous inspiration depends upon 3 variables: Cardiac function; The drop in pleural pressure; Venous return	Requires a spontaneously breathing patient, able to cooperate and perform a standardised breath. Accuracy affected by point of measurement along the IVC and the angle of insonation, given the cylindrical nature of the IVC and especially for the use of M-Mode measurements. IVC may be dilated in valvulopathies, pulmonary hypertension or in highly trained athletes[25]. May not accurately indicate volume status because venous return can be affected by

	AUROC 0.93	other factors *e.g.* vascular tone. IVC collapsibility may be confounded by pressure within the abdominal cavity *e.g.* Intra-abdominal hypertension, ascites, IPPV

AUROC: Area under receiver operating characteristic; CVP: Central venous pressure; ED: Emergency department; IPPV: Intermittent positive pressure ventilation; IVC: Inferior vena cava (plethoric IVC defined as diameter > 2.1 cm and < 50% inspiratory reduction); LR: Likelihood ratio; LV: Left ventricle; LVEF: Left ventricular ejection fraction; LVSF: Left ventricular systolic function; MAPSE: Mitral annular plane systolic excursion; NPV: Negative predictive value; PE: Pulmonary embolism; PPV: Positive predictive value; RA: Right atrial; ROSC: Return of spontaneous circulation; RV: Right ventricle; TAPSE: Tricuspid annular plane systolic excursion.

assessment in form of extended FAST (E-FAST). In FAST, abdominal sonography focuses on detecting free fluid in the abdominal cavity which indicates hemoperitoneum associated with significant abdominal injuries. The 4 sonographic views in the FAST exam are the 4 Ps: Pericardial, perihepatic, perisplenic, pelvic regions. The limitations of FAST are that it has low accuracy in the very early post-injury phase, and does not detect retroperitoneal bleeding well. It does not detect early solid organ injuries not accompanied by significant bleeding. It does not replace traditional imaging modalities if there are penetrating injuries[8]. Extended FAST further incorporates basic lung ultrasound to detect pneumothoraces or hemothorax, which has a sensitivity of 78.6%-95.3% (68.1%-99.2%) and specificity of 98.2%-99.8% (97.0%-99.9%) compared to traditional clinical examination and radiological imaging with chest X-ray or CT[8]. Other than FAST, abdominal POCUS in the critical care setting also includes assessing the bladder (to detect retention of urine), kidneys (for hydronephrosis *etc.*), gallbladder (for cholecystitis *etc.*), and abdominal aorta (for abdominal aortic aneurysms). Some examples are shown in Figure 3.

POCUS PROTOCOLS

Since 2001, intensivists and emergency physicians have come up with protocols that integrate the key features of basic cardiac, lung and abdominal ultrasound. These protocols are used to confirm or eliminate certain diagnoses in a stepwise manner. Clinicians perform POCUS as an extension of the physical examination in a problem-oriented approach, and scans are often repeated post intervention.

As with all ultrasound procedures, POCUS is operator dependent. Some of the protocols described also require advanced CCE competencies. The more recent protocols tend to integrate multiple POCUS modalities, and have stepwise diagnostic questions to be answered depending on the clinical context. For lung ultrasound, different protocols have different number of points to assess, which is based on the clinical experience of the authors. Some other examples, which are used to explore causes of shock and cardiac arrest, are listed in Table 3. We also included some protocols which only involved one POCUS modality due to its integration in other protocols (BLUE protocol)[9], or the unique pathophysiological question it tries to answer (VeXUS)[10]. The clinical benefits of the protocols described below are still pending further study.

The C.A.U.S.E. protocol[11] aims to detect the common diagnoses that may explain a cardiac arrest, such as cardiac tamponade, severe hypovolemia, pulmonary embolism and pneumothorax. It involves 2 sonographic perspectives of the thorax: The 4 chamber view (the subcostal view is recommended), and the anteromedial views of the lung and pleura at the second intercostal space, at the midclavicular line.

Table 2 Characteristics of basic lung ultrasound

	Key features	Accuracy %	Clinical utility	Limitations
A-Pattern	Horizontal artifact indicating normal lung surface indicating PAOP ≤ 13 mmHg	Sensitivity 67; Specificity 90 [47]	Dry inter-lobular septa. Aeration, response to PEEP and recruitment. Diagnosis/exclusion of large PE	For diagnosis of PE, requires ability to perform DVT scans to support findings. A-pattern may manifest in large pulmonary embolism but not in cases of smaller pulmonary emboli in the peripheral lung parenchyma near the pleural surface may be detected by lung ultrasound[48], classical described as hypoechoic, pleural-based parenchymal alteration with > 85% of these lesions wedge-shaped[49]. A-lines may be seen in cases of pneumothorax, COPD/asthma
Pneumothorax	May have A pattern due to reflection of air at the parietal pleura. During M-Mode: (1) "Stratosphere"/"Bar code" sign, instead of a seashore sign. During B-Mode; (2) Loss of lung sliding; and (3) Lung point-transition of normal lung sliding/B lines to a pneumothorax pattern (no lung sliding or B lines) at a critical point, during a respiratory cycle	(1) Sensitivity 86-91, Specificity 91-99[6,50]; (2) Sensitivity 67, Specificity 100, PPV 100, NPV 91; and (3) Sensitivity 66. Specificity 100[51]	Early detection in trauma in the emergency department, even for non-radiologists	Absence of "lung sliding" alone may not confirm the presence of pneumothorax. Small, apical pneumothoraces may be false negatives but usually do not require any intervention. False positives in non-trauma critically ill patients due to: (1) Dyspnea; (2) Single lung intubation or esophageal intubation; (3) Lung and pleura adhering together due to ARDS/chronic pleurodesis, cancer, phrenic nerve palsy, large infiltrates/pleural effusion, pulmonary contusions; and (4) Presence of several A lines in patients with asthma/COPD[52]
Occult pneumothorax (detected on CT scan but missed on chest radiography)	(1) Abolition of lung sliding alone; (2) Absent lung sliding plus the A line sign. The A line sign is the presence of A-lines *without* associated B lines (In normal lung, A lines will be with artifacts such as B lines, and lung sliding); also known as the stratosphere sign; and (3) The lung point	(1) Sensitivity 100, Specificity 78; (2) Sensitivity 95, Specificity 94; and (3) Sensitivity 79, Specificity 100[53]	Reduced need for CT scans, transportation, ionising radiation. Earlier detection of pneumothorax.	Among controls without pneumothorax, some may have absent lung sliding (false positive)
B-profile	B-lines are vertical ring-down artifacts that do not fade with increasing depth, and move with lung sliding, and obliterate A lines. > 3 is considered pathological. Alveolar-interstitial syndrome. > 2 Comet-tails 7 mm apart, indicating thickened interlobular septa	Sensitivity 97-98, Specificity88-95[54]	Diagnosis of acute hemodynamic pulmonary edema. Other differentials: Generalised–acute or chronic interstitial lung disease, acute lung injury/acute respiratory distress syndrome. Focal–related to pneumonia, pulmonary contusion, lung tumours, other pulmonary consolidating processes[55]. May be due to Gravity-related dependent edema may be present in dependent areas. May be used with other POCUS modalities *e.g.* CCE to diagnose underlying cause of interstitial syndrome	Comet tails, which are short (1cm) reverberation artifacts, may be mistaken as B-lines. Unlike B-lines, comet tails do not obliterate A-lines, fades with increasing depth. They may be present in normal lung[55]. Lacks utility in patient with known pre-existing interstitial syndrome unless there

				are prior scans for comparison. False positives: (1) Physiological B-lines may be present in 10% of healthy population; and (2) Older persons may have more B-lines and chest areas positive
Consolidation	Hypoechoic tissue with hyperechoic punctiform images (air-bronchograms). C-profile in the BLUE protocol: Anterior lung consolidation or thick, irregular pleural line[40]	Sensitivity 92-93, Specificity 92-100[54,56]		Atelectasis may appear similar and be misinterpreted as consolidation (false positive). This can be differentiated from consolidation by the lung pulse and dynamic air bronchogram[57]
Pleural effusion	Fluid collection in pleural space, above diaphragm. Able to detect as little as 15 mm. Quantification of amount of pleural effusion: A pleural effusion ≥ 800 mL is predicted when interpleural distance was > 45 mm (right) or > 50 mm (left)	Sensitivity 91-93, Specificity 92-93[56] (Right side) Sensitivity 94, Specificity 76 (Left side), Sensitivity 100, Specificity 67	Non-invasive, radiation-free detection of pleural effusion which can also guide bedside drainage. Avoids need for transportation for CT-imaging. May show features which further characterises the type of effusion; septations, debris, heterogeneous fluid collections which are suggestive of an exudative effusion; anechoic, homogenous fluid which suggests transudative effusion. Guides location for thoracocentesis. At least 2 cm of interpleural distance required as a minimum indication for thoracocentesis	In patients with an elevated hemidiaphragm, inappropriate diaphragm visualization may lead to mistaking effusion for sub-diaphragmatic ascites. May be confused with pericardial effusion. Peri-procedure complications and injury may occur if the heart/subdiaphragmatic organs are overlooked thinking a pericardial/subdiaphragmatic effusion is a pleural effusion. Loculated effusions may be missed or misjudged with inadequate scanning especially in posterior areas

ARDS: Acute respiratory distress syndrome; COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; DVT: Deep vein thrombosis PAOP: Pulmonary artery occlusion pressure; PE: Pulmonary embolism; PEEP: Positive end expiratory pressure; PLAPS: Posterolateral alveolar and/or pleural syndrome, a posterior continuation of the lower BLUE point.

The SESAME protocol[12] was initially described for shock or cardiac arrest, aiming to identify the commonest causes, or easiest causes to diagnose or manage. It uses a single microconvex probe which is available on most ultrasound systems. The steps are as follows: (1) Lung ultrasound (BLUE followed by FALLS protocol), because of convenience and it quickly indicates if a fluid challenge is appropriate; (2) Lower femoral vein vascular ultrasound or abdominal ultrasound to detect deep vein thrombosis or free fluid in the abdomen respectively; and (3) This is followed by pericardial and cardiac ultrasound. The benefit of this protocol is that it uses a single "universal" probe which saves time in a crisis.

The PIEPEAR[13] protocol is a 7-step protocol used in the setting of acute clinical deterioration of a critically ill patient. It describes a thought process, and incorporates POCUS assessments: (1) Identifying deranged physiological systems; (2) Screening for causes; (3) Focused ultrasound exam; (4) Making a presumptive diagnosis; (5) Exploring an etiology, including other investigations; (6) Initiating treatment; and (7) Repeating the focused ultrasound to assess the response to treatment, and titrating the treatment accordingly. It includes a 12-step lung and cardiac ultrasound sequence involving inferior vena cava (IVC), right ventricle (RV), left ventricle (LV) systolic and diastolic function, and afterload

Table 3 Point-of-care ultrasonography protocols in intensive care unit and emergency departments

Modalities used	Protocols (Year described)	Clinical utility	Limitations
Lung ultrasound only	BLUE protocol[9] (2008). (1) Nude profile (No abnormalities, A-profile with no DVT); (2) B-profile: Anterior lung rockets with lung sliding. Causes: Acute pulmonary oedema; (3) Pulmonary embolism (A-profile with DVT); (4) Pneumothorax (A'-profile with lung point); and (5) Pneumonia, 4 profiles (B' profile, A/B, C-profile, no-V-PLAPS profile)	Diagnosis in acute respiratory failure. A simple, dichotomous protocol which uses a single microconvex probe without need for advanced techniques (1) Accuracy 90.5%, Sensitivity 89%, Specificity 97%, PPV 87%, NPV 99%; (2) Sensitivity 97% (89%-100%), Specificity 95% (91%-98%)[9, 58], LR+ 21.1, LR- 0.03; (3) Sensitivity 81% (58%-95%), Specificity 99% (98%-100%), LR+ 193, LR- 0.19; (4) Sensitivity 88% (52%-100%) Specificity 100% (99%-100%), LR+ (infinity), LR- 0.11; and (5) All 4 profiles: Sensitivity 89 (80%-95%), Specificity: 94 (90%-97%), LR+ (15.8), LR- (0.11)	Pneumonia can generate a B-profile without anterior consolidation. Initial publication excluded patients post hoc with multiple diagnoses
Abdominal ultrasound only	VExUS[10] (2020). Evaluates IVC congestion and severity of congestion in 3 organs: Liver, gut, kidneys	(1) Indicates risk of post-cardiac surgery acute kidney injury related to venous congestion; (2) Potentially may guide fluid interventions to improve organ perfusion; and (3) Severe VExUS grade C and subsequent development of subsequent AKI after cardiac surgery. Sensitivity 27% (CI 15%-47%); Specificity 96% (CI 89%-99%) (+LR: 6.37 CI 2.19-18.5)	(1) Does not identify the source of venous congestion; (2) Currently not yet validated in other clinical settings or successful interventions to change outcomes; (3) Includes difficult and complex image acquisition and measurements; (4) Hepatic vein Doppler may be influenced by tricuspid regurgitation; pulsatile portal vein flow and IVC dilatation have been reported in healthy athletic volunteers (potential false positive)[10]; and (5) Hepatic and portal vein Doppler waveforms may be abnormal in cirrhotics due to arterio-portal shunting, such as reversal of portal venous flow; pulsatile or helical portal venous flow[59]
Cardiac and lung ultrasound	C.A.U.S.E[11] (2008). 4 chamber view of the heart + lung ultrasound. Diagnosis of (1) Pericardial tamponade; (2) Tension pneumothorax; (3) Pulmonary embolus; and (4) Hypovolemia	Aims to detect the 4 leading causes of non-arrhythmogenic cardiac arrest without interfering with resuscitation (1) Poor to moderate sensitivity as routine screening in all patients suspected of pulmonary emboli, but good to excellent specificity; and (2) Collapsed IVC or < 5 mm should prompt fluid resuscitation. > 20 mm suggests pump failure (congestive heart failure, cardiac tamponade, PE)	
	FALLS (Fluid Administration Limited by Lung Sonography) protocol[60] 2013. Combines CCE and BLUE-protocol lung ultrasound to assess causes of circulatory failure	(1) For expediting a diagnosis; (2) Guides fluid management in acute circulatory failure *e.g.* cessation of inappropriate fluid boluses; (3) Sequentially rules out obstructive, cardiogenic, then hypovolemic shock for expediting the diagnosis of distributive (usually septic) shock[60]; and (4) Allows earlier fluid therapy before confirmation of sepsis	(1) Absence of cardiac windows will limit earlier parts of the protocol, requires lung ultrasound (PE section); (2) Presence of diffuse lung rockets (B-profile, B' profile) on initial assessment will exclude patients from this protocol because fluid administration cannot be guided by transformation of A-lines to B-lines, but fluids can be given using other POCUS findings; and (3) Cardiogenic shock due to RV failure (with low wedge pressure) will not be easily diagnosed as it is usually associated with A-profile. Do ECG to rule out right sided myocardial infarction
	ORACLE[15] (2020). O: Left ventricular functiOn, R = Right ventricular disease, A = vAlve disease, C = periCardium, L = Lung ultrasound, E = hEmodynamic parameters	(1) ICU, COVID-19 patients; and (2) Cardiac and pulmonary evaluations	(1) Intermediate to advanced echo skills required with several measurements required; and (2) Requires at least 20 min in trained hands, may take longer for novices
	PIEPIER (2018)[13]. 12 step lung ultrasound + CCE: IVC, RV, LV systolic and diastolic function, and afterload deduction/calculation	A stepwise approach to diagnosing causes of cardio-respiratory failure, including consideration of etiology, interventions and reassessments	Requires experience for image interpretation, diagnosis and intermediate echocardiography
Cardiac, lung, venous	ASE POCUS protocol for COVID-19 pandemic[16] (2020). (1) Cardiac (basic views); (2) Lung (8 or 12 point); and (3) Vascular [IVC, leg veins (optional)]	(1) Outlines structures to be imaged, parameters to assess and measure, and disease associations; (2) May assist in the initial cardiopulmonary assessment of patients with COVID-19; (3) Also includes device cleaning checklist; and (4) Mentions need for storing and documenting POCUS results to reduce the need for repeat examination	In the case of difficult image acquisition, and it may be more efficient for a skilled sonographer to rapidly scan the patient, rather than have a POCUS operator struggle with prolonged attempts

Cardiac, lung and abdominal ultrasound	SHoC-ED[42] (2018). Combines ACES (abdominal and cardiothoracic evaluation with sonography in shock), and RUSH (rapid ultrasound in Shock and Hypotension)	Cardiac: Assess LV/RV function, size and presence of pericardial effusion. Lung: Base of lung-lung sliding. Abdominal-free fluid, AAA, IVC for size and collapsibility	An RCT in ED involving patients with undifferentiated hypotension did not detect significant difference in 30 d or hospital survival, media fluid administered, inotrope administration
Cardiac, lung, venous and abdominal	GUCCI (2019)[14]. (1) Acute respiratory failure: Lung ultrasound + cardiac + vascular ultrasound; and (2) Shock: Cardiac + lung + vascular + abdominal ultrasound	Guide diagnosis and interventions in acute respiratory failure, shock and cardiac arrest (*e.g.* Defibrillation)	Needs competency in other modes of POCUS
	SESAME (2015)[12]. 5 steps: (1) Lung ultrasound (BLUE followed by FALLS protocol); (2) Lower femoral vein vascular ultrasound "V-point": A distal, lower superficial femoral vein; (3) Abdominal ultrasound; (4) Pericardium; and (5) Cardiac ultrasound	Severe shock or cardiac arrest. Assess for tension pneumothorax, hypovolemia, pulmonary embolism, pericardial tamponade, free abdominal fluid as a cause of cardiac arrest	(1) Uses a single microconvex probe, which may not be available on all ultrasound systems; (2) Limitations due to body habitus; (3) Evaluates for VTE only at the "V-point", which is different from other VTE POCUS protocols which require assessment of 2 or more points on the lower limb veins[61]. 50% of patients with massive PE have DVT at the V-point, *i.e.* may be absent in 50%. Examining at one isolated point may not be as comprehensive as other protocols, but the author justifies this to avoid spending excessive time where there is low yield; and (4) Presence of DVT is used to "rule in" pulmonary embolism" as a cause of cardiac arrest[62]

AAA: Abdominal aortic aneurysm; AKI: Acute kidney injury; A4C: Apical 4 chamber; CCE: Critical care echocardiography; DVT: Deep vein thrombosis; ED: Emergency department; FAST: Focused assessment with sonography for trauma; IVC: Inferior vena cava; LR+: Positive likelihood ratio; LR-: Negative likelihood ratio; LV: Left ventricle; PE: Pulmonary embolism; PLAPS: Posterolateral alveolar and/or pleural syndrome; PLax: Parasternal long axis; POCUS: Point-of-care-ultrasound; RCT: Randomised controlled trial; RUSH: Rapid Ultrasound in Shock and Hypotension; RV: Right ventricle; VEXus: Venous Excess Ultrasonography Score; VTE: Venous thromboembolism; ICU: Intensive care unit.

deduction/calculation.

Another protocol is the Global Ultrasound Check for the Critically Ill (GUCCI) protocol, which integrates multiple protocols[14] and is organised based on 3 syndromes (acute respiratory failure, shock, cardiac arrest) and includes ultrasound-guided procedures. Compared to PIEPEAR, it has specific diagnostic questions to be answered, and has direct, specific management implications.

The ORACLE[15] protocol was designed for ICU patients with coronavirus disease 2019 (COVID-19) infections (O: Left ventricular functiOn, R: Right ventricular disease, A: vAlve disease, C: PeriCardium, L: Lung ultrasound, E: hEmodynamic parameters). It was designed such that POCUS is performed in a structured way while reducing additional staff (*e.g.* sonographers) exposure to infection. Images were acquired during ward rounds and offline measurements were done outside patient rooms.

FUTURE DIRECTIONS AND RESEARCH

POCUS has proven to be essential in triaging cases in the current COVID-19 pandemic, due to availability of relatively portable devices which are easy to disinfect. It reduces the logistical challenge of transporting patients to radiology suites or echocardiography units. The American Society of Echocardiographers (ASE) protocol combines cardiac, lung and vascular ultrasound and is an option for COVID-19 patients where cardiopulmonary disease requires evaluation. An added advantage of intensivists using POCUS is reducing exposure to other personnel and locations, permitting conservation of personal protective equipment[16].

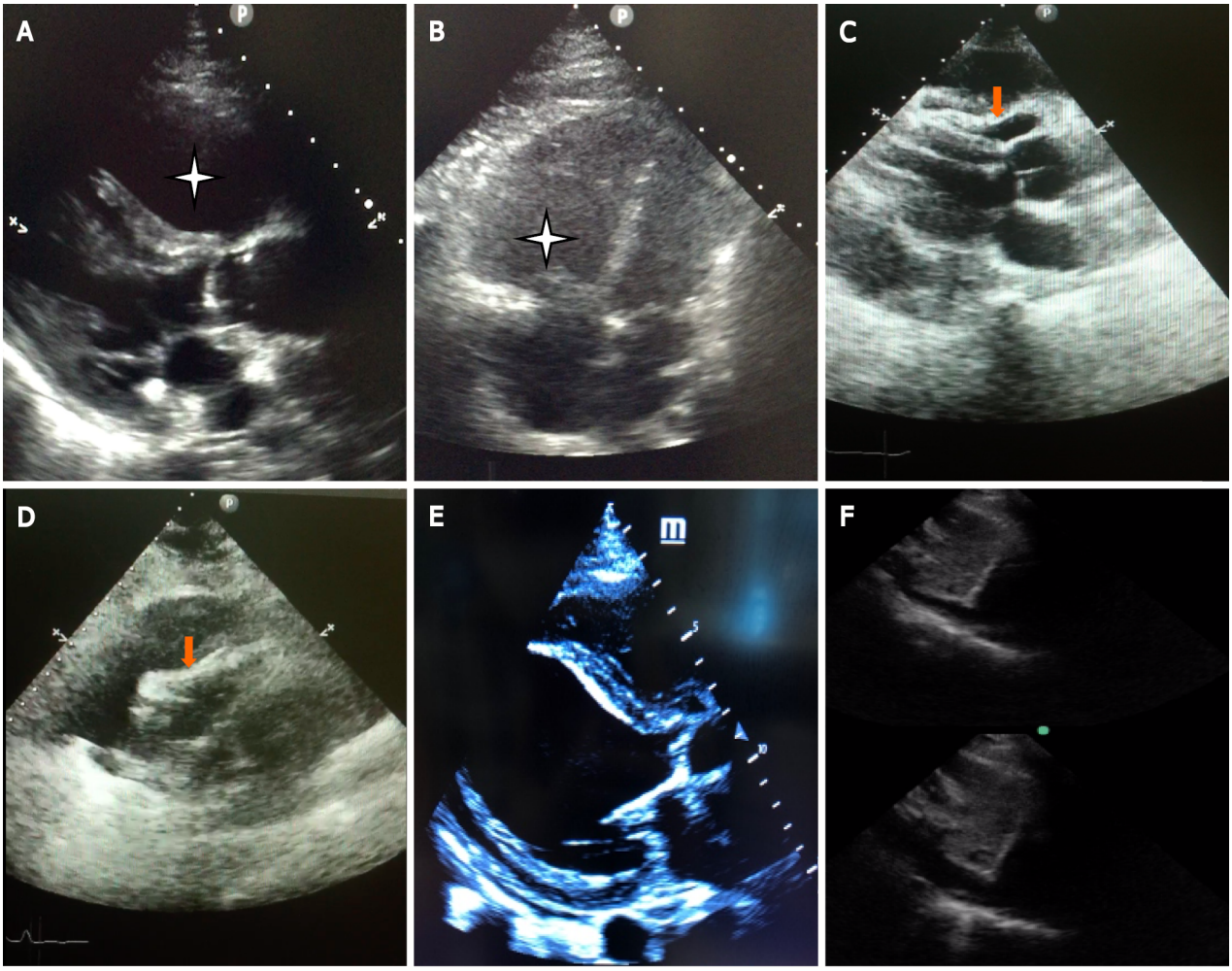

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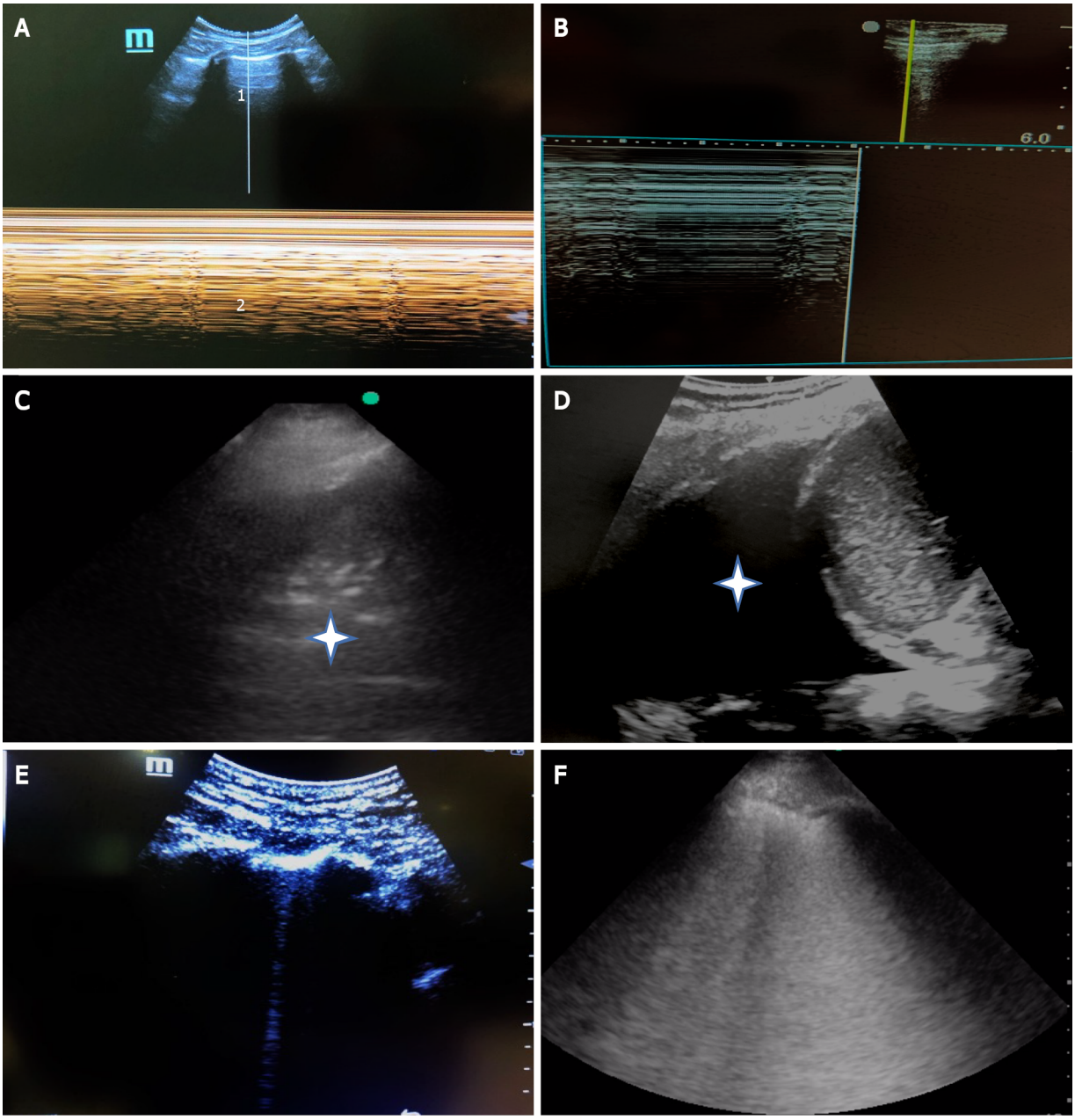
Figure 1 Key features in basic critical care echocardiography. A: Dilated right ventricle [Parasternal long axis (PLAX)]; B: Dilated right ventricle (Apical 4 chamber view); C: Pericardial tamponade-Pericardial effusion with diastolic collapse of right ventricle (PLAX view); D: Pericardial tamponade–Pericardial effusion with systolic collapse of right atrium [subcostal long axis (SLAX) view]; E: Left ventricular dysfunction-minimal thickening and contraction of basal anteroseptal and inferolateral wall with severe hypokinesia (PLAX view); F: Inferior vena cava variation of > 50% with foreceful spontaneous respiration-"sniff test" (SLAX view).

Recently, POCUS has started to appear in the secondary survey of adult cardiac life support (ACLS) algorithm, and can be considered especially if it does not interfere with algorithm. This is to identify potentially reversible causes for cardiac arrest[17] or to detect return of spontaneous circulation (ROSC). Depending on the type of shock or history preceding cardiac arrest, targeted CCE may identify clues to the underlying cause such as a plethoric IVC and absence of lung sliding associated with tension pneumothorax, or small/normal ventricles and collapsed IVC due to hypovolemic shock. CCE may also identify tamponade, thrombus-in-transit, myocardial infarction as a cause of cardiac arrest[18]. However, the International Liaison Committee on Resuscitation (ILCOR) task force recommends that the individual performing POCUS is trained to minimise interruptions to chest compressions. With regards to prognostication, ILCOR currently suggests *against* the use of POCUS for prognostication during cardiopulmonary resuscitation due to weak evidence for any CCE findings in predicting outcomes. Although a single small randomized controlled trial (RCT) found no improvement in outcomes with use of cardiac ultrasound during cardiopulmonary resuscitation, this result is not definitive and more research is required[19].

There are other modalities of POCUS, although less commonly performed, that can be useful in the ICU. These include airway ultrasound, screening for deep vein thrombosis (DVT), diaphragm ultrasound and ultrasound to assess the optic nerve sheath diameter. Pre-procedural airway ultrasound improves safety prior to a percutaneous tracheostomy[20]. Diaphragm ultrasound can be used to detect diaphragm dysfunction with great accuracy[21]. Optic nerve sheath diameter ultrasound allows detection of raised intracranial pressure at the bedside and can be used for prognostication post cardiac arrest[22]. Evidence for utility of these POCUS modalities in changing patient-centred outcomes is still lacking. Additionally, the training requirements and learning trajectory remain areas for further development and research.



DOI: 10.5492/wjccm.v11.i2.70 **Copyright** © The Author(s) 2022.

Figure 2 Key features in basic lung ultrasound. A: M-mode lung ultrasound-normal a lines (1), and seashore sign (2); B: M-mode lung ultrasound-pneumothorax Bar code/stratosphere sign; C: Consolidation with air bronchograms (Asterisk); D: Pleural effusion (large); E: 1 single B line-normal; F: B profile, > 3 B lines (confluent)-pathological.

Currently, there has also been increasing interest in the use of artificial intelligence that provides real-time guidance for probe placement, aids acquisition of optimal images[23], and helps to reduce exposure of healthcare workers to highly infectious cases[24]. Such technology has also been used to help users identify anatomy and do measurements of cardiac function[23]. Whether these algorithms are able to replace a trained sonographer, improve scan durations and accuracy, and improve healthcare delivery or patient outcomes remain uncertain. Robot-assisted ultrasonography, with scans conducted by operators remotely, has also been described. These devices are 5G-powered with robotic arms manipulated by an operator in another room using a simulated robotic hand[25].

There are currently few studies evaluating if CCE or multi-organ POCUS has any effect on mortality, which might be confounded by many other factors. One retrospective study found that POCUS done on ED patients prior to interventions such as fluid boluses are associated with care delays and increased in-hospital mortality compared to critically ill patients with no POCUS[26]. Also, being a diagnostic and monitoring tool, the therapies given are variable depending on the clinician so it will be hard to link POCUS's utility directly with mortality. More studies are nonetheless needed to explore the effect of POCUS on patient-centred outcomes.

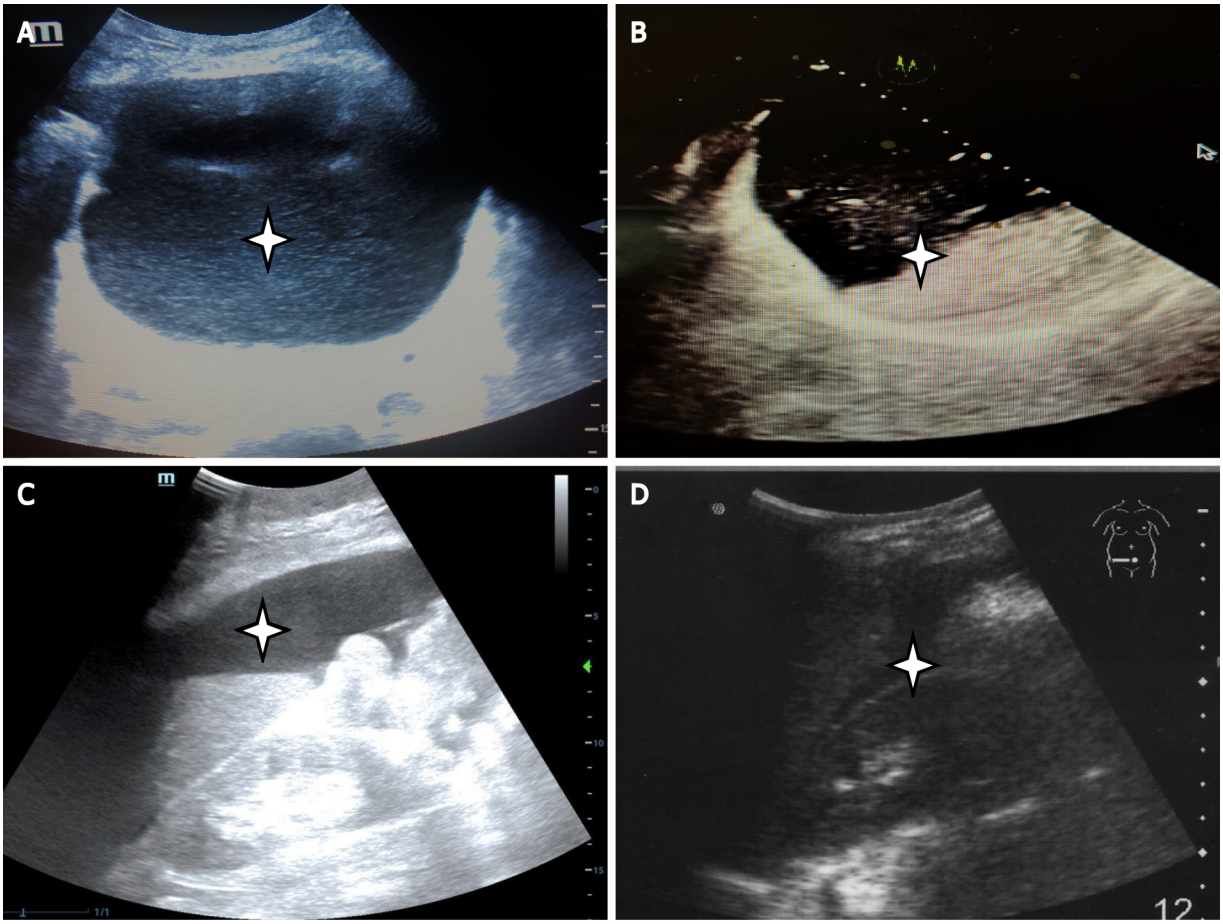


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Figure 3 Key features in abdominal ultrasound. A: Bladder overdistension due to acute retention of urine (Asterisk); B: Incomplete gastric emptying (presence of semi-digested food in the stomach, Asterisk), which will indicate need for rapid sequence induction for intubation; C: Ascites (Asterisk); D: Free fluid in the hepato-renal pouch. In cases with abdominal trauma, this indicates intra-peritoneal bleeding (Asterisk).

Given the multitude of POCUS protocols described, there will unlikely be head-to-head studies or standardization of included devices. Each medical unit needs to adopt POCUS protocols that are relevant to its clinical practice. This process must involve multi-disciplinary stakeholders and trainers so that it remains relevant during different parts of a patient's hospitalisation. This then leads to standardised curricula so that there can be quality assurance and reduction of inter-operator differences. More importantly, the systemic adoption of POCUS protocols can allow patient-centric outcomes to be studied. Needless to say, access to a point-of-care ultrasound machine is critical in adoption of POCUS on a regular basis. Given how each patient's critical illness, response to treatment and subsequent trajectory lie on a continuum, it would be useful if the unit has a picture archiving and communication system (PACS) to allow different healthcare providers involved in the care of the patient at different stages of the hospitalisation to compare the images. This system also can be used for POCUS education or competency assessment of POCUS learners by their supervisors. Even without a PACS system, this also can be achieved on ultrasound systems which allow storage of video or still clips. Such documentation may be increasingly important for oversight of POCUS practice, which is one of the concerns raised by the Joint Commission in naming POCUS as one of the top 10 health technology *hazards* in 2020[27].

Hand-held POCUS as an extension of physical exam (i.e. stethoscope) is becoming more popular. If POCUS is integrated with structured assessments such as ACLS (Advanced cardiac life support), advanced trauma life support (ATLS), CERTAIN (Checklist for Early Recognition and Treatment of Acute Illness and iNjury), and teams are equipped with ultrasound devices, it can provide additional information at the bedside which may change management. This includes right-siting of patients to the relevant medical disciplines (*e.g.* a dissecting aortic aneurysm sent to a hospital with cardiac surgery facilities), or pericardiocentesis in a patient who has shock due to tamponade. Pitfalls of incorporating POCUS to routine assessments include inappropriate use of this tool, misdiagnoses by inexperienced operators, excessive time taken, and distraction from clinical assessment and critical resuscitation tasks. POCUS was associated with longer pauses during cardio-pulmonary resuscitation especially comparing between ultrasound-fellowship trained *vs* non-fellowship trained operators[28]. If it becomes integrated

in such structured assessments, teams must be mindful of the caveats and ultrasound operators should be adequately trained, with safety mechanisms inbuilt (*e.g.* strict timekeeping for pulse-checks and interruptions in cardiopulmonary resuscitation). Such training may also need to focus on POCUS views which are more easily accessed during a resuscitation situation such as anterior lung, and subcostal echocardiography windows.

The quality of handheld devices is still lacking compared to traditional point-of-care- ultrasound systems, which may lead to poorer image quality or artefacts and misinterpretation. This is an area that is rapidly expanding with newer devices that are smaller coming out in the market, including probes that can be connected to smart devices, and recently artificial intelligence-integrated handheld devices.

CONCLUSION

Cardiac, lung and abdominal ultrasound should be part of the skillset of doctors managing critically ill patients. Being operator dependent, the accuracy of POCUS in detecting or excluding abnormalities may be influenced by the operator's experience. The influence of POCUS findings on treatment also depends on clinician experience. Several protocols combining different POCUS modalities have been described but the validity of these protocols in different settings still needs to be studied. There is a growing body of evidence describing the accuracy of POCUS applications, and with growing experience and competency one hopes that the accuracy will improve. POCUS should be considered a tool to confirm a diagnosis, as an extension of physical examination. More evidence is needed to recommend it as standard of care.

FOOTNOTES

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Country/Territory of origin: Singapore

ORCID number: Yie Hui Lau 0000-0003-1754-7515; Kay Choong See 0000-0003-2528-7282.

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REFERENCES

1 **Winters B**, Custer J, Galvagno SM Jr, Colantuoni E, Kapoor SG, Lee H, Goode V, Robinson K, Nakhasi A, Pronovost P, Newman-Toker D. Diagnostic errors in the intensive care unit: a systematic review of autopsy studies. *BMJ Qual Saf* 2012; **21**: 894-902 [PMID: 22822241 DOI: 10.1136/bmjqs-2012-000803]
2 **Blanco P**, Volpicelli G. Common pitfalls in point-of-care ultrasound: a practical guide for emergency and critical care physicians. *Crit Ultrasound J* 2016; **8**: 15 [PMID: 27783380 DOI: 10.1186/s13089-016-0052-x]
3 **Lau YH**, Loh CH, Fong WK, Siddiqui S, Tan CK, Tan JJ, See KC. Point-of-Care Ultrasound Training Among Intensivists in Singapore: A Multicentre Survey. *Ann Acad Med Singap* 2020; **49**: 630-642 [PMID: 33241251]
4 **Peris A**, Tutino L, Zagli G, Batacchi S, Cianchi G, Spina R, Bonizzoli M, Migliaccio L, Perretta L, Bartolini M, Ban K, Balik M. The use of point-of-care bedside lung ultrasound significantly reduces the number of radiographs and computed tomography scans in critically ill patients. *Anesth Analg* 2010; **111**: 687-692 [PMID: 20733164 DOI: 10.1213/ANE.0b013e3181e7cc42]
5 **Bataille B**, Riu B, Ferre F, Moussot PE, Mari A, Brunel E, Ruiz J, Mora M, Fourcade O, Genestal M, Silva S. Integrated use of bedside lung ultrasound and echocardiography in acute respiratory failure: a prospective observational study in ICU. *Chest* 2014; **146**: 1586-1593 [PMID: 25144893 DOI: 10.1378/chest.14-0681]
6 **Bouhemad B**, Zhang M, Lu Q, Rouby JJ. Clinical review: Bedside lung ultrasound in critical care practice. *Crit Care* 2007; **11**: 205 [PMID: 17316468 DOI: 10.1186/cc5668]
7 **See KC**, Ong V, Wong SH, Leanda R, Santos J, Taculod J, Phua J, Teoh CM. Lung ultrasound training: curriculum

implementation and learning trajectory among respiratory therapists. *Intensive Care Med* 2016; **42**: 63-71 [PMID: 26474994 DOI: 10.1007/s00134-015-4102-9]

8 **Montoya J**, Stawicki SP, Evans DC, Bahner DP, Sparks S, Sharpe RP, Cipolla J. From FAST to E-FAST: an overview of the evolution of ultrasound-based traumatic injury assessment. *Eur J Trauma Emerg Surg* 2016; **42**: 119-126 [PMID: 26038031 DOI: 10.1007/s00068-015-0512-1]

9 **Lichtenstein DA**. BLUE-protocol and FALLS-protocol: two applications of lung ultrasound in the critically ill. *Chest* 2015; **147**: 1659-1670 [PMID: 26033127 DOI: 10.1378/chest.14-1313]

10 **Beaubien-Souligny W**, Rola P, Haycock K, Bouchard J, Lamarche Y, Spiegel R, Denault AY. Quantifying systemic congestion with Point-Of-Care ultrasound: development of the venous excess ultrasound grading system. *Ultrasound J* 2020; **12**: 16 [PMID: 32270297 DOI: 10.1186/s13089-020-00163-w]

11 **Hernandez C**, Shuler K, Hannan H, Sonyika C, Likourezos A, Marshall J. C.A.U.S.E.: Cardiac arrest ultra-sound exam--a better approach to managing patients in primary non-arrhythmogenic cardiac arrest. *Resuscitation* 2008; **76**: 198-206 [PMID: 17822831 DOI: 10.1016/j.resuscitation.2007.06.033]

12 **Lichtenstein DA**. How can the use of lung ultrasound in cardiac arrest make ultrasound a holistic discipline. The example of the SESAME-protocol. *Med Ultrason* 2014; **16**: 252-255 [PMID: 25110767 DOI: 10.11152/mu.2013.2066.163.dal1]

13 **Yin W**, Li Y, Wang S, Zeng X, Qin Y, Wang X, Chao Y, Zhang L, Kang Y, Ccusg CCUSG. The PIEPEAR Workflow: A Critical Care Ultrasound Based 7-Step Approach as a Standard Procedure to Manage Patients with Acute Cardiorespiratory Compromise, with Two Example Cases Presented. *Biomed Res Int* 2018; **2018**: 4687346 [PMID: 29992144 DOI: 10.1155/2018/4687346]

14 **Tavares J**, Ivo R, Gonzalez F, Lamas T, Mendes JJ. Global Ultrasound Check for the Critically lll (GUCCI)-a new systematized protocol unifying point-of-care ultrasound in critically ill patients based on clinical presentation. *Open Access Emerg Med* 2019; **11**: 133-145 [PMID: 31372068 DOI: 10.2147/OAEM.S199137]

15 **García-Cruz E**, Manzur-Sandoval D, Rascón-Sabido R, Gopar-Nieto R, Barajas-Campos RL, Jordán-Ríos A, Sierra-Lara Martínez D, Jiménez-Rodríguez GM, Murillo-Ochoa AL, Díaz-Méndez A, Lazcano-Díaz E, Araiza-Garaygordobil D, Cabello-López A, Melano-Carranza E, Bucio-Reta E, González-Ruiz FJ, Cota-Apodaca LA, Santos-Martínez LE, Fernández-de la Reguera G, Ramos-Enríquez Á, Rojas-Velasco G, Álvarez-Álvarez RJ, Baranda-Tovar F. Critical care ultrasonography during COVID-19 pandemic: The ORACLE protocol. *Echocardiography* 2020; **37**: 1353-1361 [PMID: 32862474 DOI: 10.1111/echo.14837]

16 **Johri AM**, Galen B, Kirkpatrick JN, Lanspa M, Mulvagh S, Thamman R. ASE Statement on Point-of-Care Ultrasound during the 2019 Novel Coronavirus Pandemic. *J Am Soc Echocardiogr* 2020; **33**: 670-673 [PMID: 32503704 DOI: 10.1016/j.echo.2020.04.017]

17 **Long B**, Alerhand S, Maliel K, Koyfman A. Echocardiography in cardiac arrest: An emergency medicine review. *Am J Emerg Med* 2018; **36**: 488-493 [PMID: 29269162 DOI: 10.1016/j.ajem.2017.12.031]

18 **Paul JA**, Panzer OPF. Point-of-care Ultrasound in Cardiac Arrest. *Anesthesiology* 2021; **135**: 508-519 [PMID: 33979442 DOI: 10.1097/ALN.0000000000003811]

19 **Merchant RM**, Topjian AA, Panchal AR, Cheng A, Aziz K, Berg KM, Lavonas EJ, Magid DJ; Adult Basic and Advanced Life Support, Pediatric Basic and Advanced Life Support, Neonatal Life Support, Resuscitation Education Science, and Systems of Care Writing Groups. Part 1: Executive Summary: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2020; **142**: S337-S357 [PMID: 33081530 DOI: 10.1161/CIR.0000000000000918]

20 **Osman A**, Sum KM. Role of upper airway ultrasound in airway management. *J Intensive Care* 2016; **4**: 52 [PMID: 27529028 DOI: 10.1186/s40560-016-0174-z]

21 **Santana PV**, Cardenas LZ, Albuquerque ALP, Carvalho CRR, Caruso P. Diaphragmatic ultrasound: a review of its methodological aspects and clinical uses. *J Bras Pneumol* 2020; **46**: e20200064 [PMID: 33237154 DOI: 10.36416/1806-3756/e20200064]

22 **Zhang YW**, Zhang S, Gao H, Li C, Zhang MX. Prognostic Role of Optic Nerve Sheath Diameter for Neurological Outcomes in Post-Cardiac Arrest Patients: A Systematic Review and Meta-Analysis. *Biomed Res Int* 2020; **2020**: 5219367 [PMID: 33426054 DOI: 10.1155/2020/5219367]

23 **Akkus Z**, Aly YH, Attia IZ, Lopez-Jimenez F, Arruda-Olson AM, Pellikka PA, Pislaru SV, Kane GC, Friedman PA, Oh JK. Artificial Intelligence (AI)-Empowered Echocardiography Interpretation: A State-of-the-Art Review. *J Clin Med* 2021; **10** [PMID: 33808513 DOI: 10.3390/jcm10071391]

24 **Cheema BS**, Walter J, Narang A, Thomas JD. Artificial Intelligence-Enabled POCUS in the COVID-19 ICU: A New Spin on Cardiac Ultrasound. *JACC Case Rep* 2021; **3**: 258-263 [PMID: 33619470 DOI: 10.1016/j.jaccas.2020.12.013]

25 **Yu RZ**, Li YQ, Peng CZ, Ye RZ, He Q. Role of 5G-powered remote robotic ultrasound during the COVID-19 outbreak: insights from two cases. *Eur Rev Med Pharmacol Sci* 2020; **24**: 7796-7800 [PMID: 32744706 DOI: 10.26355/eurrev_202007_22283]

26 **Mosier JM**, Stolz U, Milligan R, Roy-Chaudhury A, Lutrick K, Hypes CD, Billheimer D, Cairns CB. Impact of Point-of-Care Ultrasound in the Emergency Department on Care Processes and Outcomes in Critically Ill Nontraumatic Patients. *Crit Care Explor* 2019; **1**: e0019 [PMID: 32166263 DOI: 10.1097/CCE.0000000000000019]

27 **ECRI**. Institute Top 10 health technology hazards for 2020. [cited 10 August 2021]. Available from: https://www.ecri.org/Landing-2020-top-ten-health-technology-hazards

28 **Clattenburg EJ**, Wroe P, Brown S, Gardner K, Losonczy L, Singh A, Nagdev A. Point-of-care ultrasound use in patients with cardiac arrest is associated prolonged cardiopulmonary resuscitation pauses: A prospective cohort study. *Resuscitation* 2018; **122**: 65-68 [PMID: 29175356 DOI: 10.1016/j.resuscitation.2017.11.056]

29 **Mandavia DP**, Hoffner RJ, Mahaney K, Henderson SO. Bedside echocardiography by emergency physicians. *Ann Emerg Med* 2001; **38**: 377-382 [PMID: 11574793 DOI: 10.1067/mem.2001.118224]

30 **Casazza F**, Bongarzoni A, Capozi A, Agostoni O. Regional right ventricular dysfunction in acute pulmonary embolism and right ventricular infarction. *Eur J Echocardiogr* 2005; **6**: 11-14 [PMID: 15664548 DOI: 10.1016/j.euje.2004.06.002]

31 **Pérez-Casares A**, Cesar S, Brunet-Garcia L, Sanchez-de-Toledo J. Echocardiographic Evaluation of Pericardial Effusion

and Cardiac Tamponade. *Front Pediatr* 2017; **5**: 79 [PMID: 28484689 DOI: 10.3389/fped.2017.00079]

32 **Gaspari R**, Weekes A, Adhikari S, Noble VE, Nomura JT, Theodoro D, Woo M, Atkinson P, Blehar D, Brown SM, Caffery T, Douglass E, Fraser J, Haines C, Lam S, Lanspa M, Lewis M, Liebmann O, Limkakeng A, Lopez F, Platz E, Mendoza M, Minnigan H, Moore C, Novik J, Rang L, Scruggs W, Raio C. Emergency department point-of-care ultrasound in out-of-hospital and in-ED cardiac arrest. *Resuscitation* 2016; **109**: 33-39 [PMID: 27693280 DOI: 10.1016/j.resuscitation.2016.09.018]

33 **Alerhand S**, Carter JM. What echocardiographic findings suggest a pericardial effusion is causing tamponade? *Am J Emerg Med* 2019; **37**: 321-326 [PMID: 30471929 DOI: 10.1016/j.ajem.2018.11.004]

34 **Himelman RB**, Kircher B, Rockey DC, Schiller NB. Inferior vena cava plethora with blunted respiratory response: a sensitive echocardiographic sign of cardiac tamponade. *J Am Coll Cardiol* 1988; **12**: 1470-1477 [PMID: 3192844 DOI: 10.1016/s0735-1097(88)80011-1]

35 **Stone MB**, Huang JV. Inferior Vena Cava Assessment: Correlation with CVP and Plethora in Tamponade. *Glob Heart* 2013; **8**: 323-327 [PMID: 25690633 DOI: 10.1016/j.gheart.2013.11.004]

36 **Fields JM**, Davis J, Girson L, Au A, Potts J, Morgan CJ, Vetter I, Riesenberg LA. Transthoracic Echocardiography for Diagnosing Pulmonary Embolism: A Systematic Review and Meta-Analysis. *J Am Soc Echocardiogr* 2017; **30**: 714-723.e4 [PMID: 28495379 DOI: 10.1016/j.echo.2017.03.004]

37 **Rudski LG**, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; **23**: 685-713; quiz 786 [PMID: 20620859 DOI: 10.1016/j.echo.2010.05.010]

38 **Park JH**, Kim JH, Lee JH, Choi SW, Jeong JO, Seong IW. Evaluation of right ventricular systolic function by the analysis of tricuspid annular motion in patients with acute pulmonary embolism. *J Cardiovasc Ultrasound* 2012; **20**: 181-188 [PMID: 23346287 DOI: 10.4250/jcu.2012.20.4.181]

39 **Kucher N**, Rossi E, De Rosa M, Goldhaber SZ. Prognostic role of echocardiography among patients with acute pulmonary embolism and a systolic arterial pressure of 90 mmHg or higher. *Arch Intern Med* 2005; **165**: 1777-1781 [PMID: 16087827 DOI: 10.1001/archinte.165.15.1777]

40 **Orde S**, Slama M, Yastrebov K, Mclean A, Huang S; College of Intensive Care Medicine of Australia and New Zealand [CICM] Ultrasound Special Interest Group [USIG]. Subjective right ventricle assessment by echo qualified intensive care specialists: assessing agreement with objective measures. *Crit Care* 2019; **23**: 70 [PMID: 30845976 DOI: 10.1186/s13054-019-2375-z]

41 **Atkinson PR**, Beckett N, French J, Banerjee A, Fraser J, Lewis D. Does Point-of-care Ultrasound Use Impact Resuscitation Length, Rates of Intervention, and Clinical Outcomes During Cardiac Arrest? *Cureus* 2019; **11**: e4456 [PMID: 31205842 DOI: 10.7759/cureus.4456]

42 **Stenberg Y**, Wallinder L, Lindberg A, Walldén J, Hultin M, Myrberg T. Preoperative Point-of-Care Assessment of Left Ventricular Systolic Dysfunction With Transthoracic Echocardiography. *Anesth Analg* 2021; **132**: 717-725 [PMID: 33177328 DOI: 10.1213/ANE.0000000000005263]

43 **McKaigney CJ**, Krantz MJ, La Rocque CL, Hurst ND, Buchanan MS, Kendall JL. E-point septal separation: a bedside tool for emergency physician assessment of left ventricular ejection fraction. *Am J Emerg Med* 2014; **32**: 493-497 [PMID: 24630604 DOI: 10.1016/j.ajem.2014.01.045]

44 **Johnson BK**, Tierney DM, Rosborough TK, Harris KM, Newell MC. Internal medicine point-of-care ultrasound assessment of left ventricular function correlates with formal echocardiography. *J Clin Ultrasound* 2016; **44**: 92-99 [PMID: 26179460 DOI: 10.1002/jcu.22272]

45 **Caplan M**, Durand A, Bortolotti P, Colling D, Goutay J, Duburcq T, Drumez E, Rouze A, Nseir S, Howsam M, Onimus T, Favory R, Preau S. Measurement site of inferior vena cava diameter affects the accuracy with which fluid responsiveness can be predicted in spontaneously breathing patients: a post hoc analysis of two prospective cohorts. *Ann Intensive Care* 2020; **10**: 168 [PMID: 33306164 DOI: 10.1186/s13613-020-00786-1]

46 **Preau S**, Bortolotti P, Colling D, Dewavrin F, Colas V, Voisin B, Onimus T, Drumez E, Durocher A, Redheuil A, Saulnier F. Diagnostic Accuracy of the Inferior Vena Cava Collapsibility to Predict Fluid Responsiveness in Spontaneously Breathing Patients With Sepsis and Acute Circulatory Failure. *Crit Care Med* 2017; **45**: e290-e297 [PMID: 27749318 DOI: 10.1097/CCM.0000000000002090]

47 **Mohammad Abdelfattah W**, Mohiedden O, Saad-eldeen Elgammal S, Mohammad Elsayed K, Said Mowafy SM, Mohammad Abdalla R. Distensibility index of inferior vena cava and pulse pressure variation as predictors of fluid responsiveness in mechanically ventilated shocked patients. *J Emerg Med, Trauma Acute Care* 2020 [DOI: 10.5339/jemtac.2020.2]

48 **Lichtenstein DA**, Mezière GA, Lagoueyte JF, Biderman P, Goldstein I, Gepner A. A-lines and B-lines: lung ultrasound as a bedside tool for predicting pulmonary artery occlusion pressure in the critically ill. *Chest* 2009; **136**: 1014-1020 [PMID: 19809049 DOI: 10.1378/chest.09-0001]

49 **Jiang L**, Ma Y, Zhao C, Shen W, Feng X, Xu Y, Zhang M. Role of Transthoracic Lung Ultrasonography in the Diagnosis of Pulmonary Embolism: A Systematic Review and Meta-Analysis. *PLoS One* 2015; **10**: e0129909 [PMID: 26076021 DOI: 10.1371/journal.pone.0129909]

50 **Reissig A**, Kroegel C. Transthoracic ultrasound of lung and pleura in the diagnosis of pulmonary embolism: a novel non-invasive bedside approach. *Respiration* 2003; **70**: 441-452 [PMID: 14665764 DOI: 10.1159/000074195]

51 **Chan KK**, Joo DA, McRae AD, Takwoingi Y, Premji ZA, Lang E, Wakai A. Chest ultrasonography *vs* supine chest radiography for diagnosis of pneumothorax in trauma patients in the emergency department. *Cochrane Database Syst Rev* 2020; **7**: CD013031 [PMID: 32702777 DOI: 10.1002/14651858.CD013031.pub2]

52 **Lichtenstein D**, Mezière G, Biderman P, Gepner A. The "lung point": an ultrasound sign specific to pneumothorax. *Intensive Care Med* 2000; **26**: 1434-1440 [PMID: 11126253 DOI: 10.1007/s001340000627]

53 **Blaivas M**, Lyon M, Duggal S. A prospective comparison of supine chest radiography and bedside ultrasound for the

diagnosis of traumatic pneumothorax. *Acad Emerg Med* 2005; **12**: 844-849 [PMID: 16141018 DOI: 10.1197/j.aem.2005.05.005]

54 **Lichtenstein DA**, Mezière G, Lascols N, Biderman P, Courret JP, Gepner A, Goldstein I, Tenoudji-Cohen M. Ultrasound diagnosis of occult pneumothorax. *Crit Care Med* 2005; **33**: 1231-1238 [PMID: 15942336 DOI: 10.1097/01.ccm.0000164542.86954.b4]

55 **Lichtenstein D**, Goldstein I, Mourgeon E, Cluzel P, Grenier P, Rouby JJ. Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. *Anesthesiology* 2004; **100**: 9-15 [PMID: 14695718 DOI: 10.1097/00000542-200401000-00006]

56 **Yue Lee FC**, Jenssen C, Dietrich CF. A common misunderstanding in lung ultrasound: the comet tail artefact. *Med Ultrason* 2018; **20**: 379-384 [PMID: 30167593 DOI: 10.11152/mu-1573]

57 **Hansell L**, Milross M, Delaney A, Tian DH, Ntoumenopoulos G. Lung ultrasound has greater accuracy than conventional respiratory assessment tools for the diagnosis of pleural effusion, lung consolidation and collapse: a systematic review. *J Physiother* 2021; **67**: 41-48 [PMID: 33353830 DOI: 10.1016/j.jphys.2020.12.002]

58 **Lichtenstein DA**. Lung ultrasound in the critically ill. *Ann Intensive Care* 2014; **4**: 1 [PMID: 24401163 DOI: 10.1186/2110-5820-4-1]

59 **Lichtenstein D**. FALLS-protocol: lung ultrasound in hemodynamic assessment of shock. *Heart Lung Vessel* 2013; **5**: 142-147 [PMID: 24364005]

60 **Iranpour P**, Lall C, Houshyar R, Helmy M, Yang A, Choi JI, Ward G, Goodwin SC. Altered Doppler flow patterns in cirrhosis patients: an overview. *Ultrasonography* 2016; **35**: 3-12 [PMID: 26169079 DOI: 10.14366/usg.15020]

61 **Lee JH**, Lee SH, Yun SJ. Comparison of 2-point and 3-point point-of-care ultrasound techniques for deep vein thrombosis at the emergency department: A meta-analysis. *Medicine (Baltimore)* 2019; **98**: e15791 [PMID: 31145304 DOI: 10.1097/MD.0000000000015791]

62 **Lichtenstein D**, Malbrain ML. Critical care ultrasound in cardiac arrest. Technological requirements for performing the SESAME-protocol--a holistic approach. *Anaesthesiol Intensive Ther* 2015; **47**: 471-481 [PMID: 26578398 DOI: 10.5603/AIT.a2015.0072]

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ORIGINAL ARTICLE

Retrospective Study

Treatment with neurohormonal inhibitors and prognostic outcome in pulmonary arterial hypertension with risk factors for left heart disease

Riccardo Scagliola, Claudio Brunelli, Manrico Balbi

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Riccardo Scagliola, Claudio Brunelli, Manrico Balbi, Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, Genova 16132, Genova, Italy

Corresponding author: Riccardo Scagliola, MD, Doctor, Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, Largo R. Benzi No. 10, Genova 16132, Genova, Italy. risca88@live.it

Abstract

BACKGROUND

Despite major advances in pharmacologic treatment, patients with pulmonary arterial hypertension (PAH) still have a considerably reduced life expectancy. In this context, chronic hyperactivity of the neurohormonal axis has been shown to be detrimental in PAH, thus providing novel insights on the role of neurohormonal blockade as a potential therapeutic target.

AIM

To evaluate the application and prognostic effect of neurohormonal inhibitors (NEUi) in a single-center sample of patients with idiopathic PAH and risk factors for left heart disease.

METHODS

We analyzed data retrospectively collected from our register of right heart catheterizations performed consecutively from January 1, 2005 to October 31, 2018. Patients on beta-blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker or mineralocorticoid receptor antagonist at the time of right heart catheterization were classified as NEUi users and compared to NEUi non-recipients.

RESULTS

Complete data were available for 57 PAH subjects: 27 of those (47.4%) were taking at least one NEUi at the time of right heart catheterization and were compared with the remaining 36 NEUi non-recipients. NEUi users were older and had a higher cardiovascular risk profile compared to non-recipients. Additionally, NEUi non-users had a higher probability of dying during the course of follow-up than NEUi recipients (56.7% *vs* 25.9%, log-rank $P = 0.020$).

CONCLUSION
The above data highlighted a subgroup of patients with PAH and comorbidities for left heart disease in which NEUi use has shown to be associated with improved survival. Future prospective studies are needed to identify the most appropriate therapeutic strategies in this subset population.

Key Words: Pulmonary arterial hypertension; Left heart disease; Neurohormonal inhibitors; Prognostic outcome; Right heart catheterization; Pharmacological treatment

Core Tip: In this observational study we underscored an increase in risk predictors for left heart disease among patients with idiopathic pulmonary arterial hypertension. Data were retrospectively collected from a single-center sample of patients with idiopathic pulmonary arterial hypertension who underwent right heart catheterization from January 1, 2005 to October 31, 2018. Among them, subjects treated with neurohormonal inhibitors showed a significantly better prognostic outcome during the course of follow-up as compared to neurohormonal inhibitor non-recipients.

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a life-threatening cause of right ventricular failure, characterized by endothelial dysfunction and pulmonary vascular remodeling[1]. Despite major advances in pharmacologic treatment, patients with PAH still have a considerably reduced life expectancy. In this context, chronic hyperactivity of the neurohormonal axis has been shown to be detrimental in PAH, thus providing novel insights on the role of neurohormonal blockade as a potential therapeutic target [2]. To date, neurohormonal inhibitors (NEUi) are not currently labelled in PAH by contemporary guidelines, while they are used to treat PAH subjects with concomitant risk factors for left heart disease (LHD), for which they are instead scheduled for[3,4].

In recent years, further investigations have challenged the paradigm according to which PAH and pulmonary hypertension (PH) due to LHD are considered two separate pathophysiological entities. The AMBITION (Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) trial found a higher than expected prevalence of risk predictors for LHD among PAH patients[5]. In the same way, data from the COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Arterial Hypertension) and other registry reports showed a significant trend towards an increased age and a higher percentage of cardiovascular comorbidities at diagnosis of PAH, together with a weaker response to targeted PAH therapy[6,7]. So the emerging definition of 'atypical PAH' or 'PAH with comorbidities' has been coined to identify such a hybrid PH phenotype with a purely precapillary hemodynamic profile and risk predictors for LHD, in which a concealed post-capillary involvement may be supposed[8,9]. In this way, the favorable impact of NEUi in this subset population has been hypothesized, by targeting cardiovascular risk factors and hidden LHD.

MATERIALS AND METHODS

We evaluated retrospectively collected data of subjects who underwent right heart catheterization (RHC) in a single-center cohort followed in the Cardiology Unit of University Hospital San Martino in Genoa, Italy from January 1, 2005 up to October 31, 2018. Following the current European Society of Cardiology and European Respiratory Society guidelines for the diagnosis and treatment of pulmonary hypertension[3], PAH was defined hemodynamically by mean pulmonary arterial pressure ≥ 25 mmHg, together with pulmonary artery wedge pressure ≤ 15 mmHg and pulmonary vascular resistance > 3 Wood units, in the absence of other identifiable etiologies of precapillary PH.

We selected patients with idiopathic PAH and complete information about demographics, biochemical data and drug therapy at the time of RHC. Patients with PAH and associated clinical conditions, such as PH due to lung disease and/or hypoxia, chronic thromboembolic PH or PH related

to unclear or multifactorial mechanisms, were ruled out of the observational analysis. Subjects with a diagnosis of LHD (defined by instrumental signs of left ventricular systolic or diastolic dysfunction or left heart valvular disease) did not undergo hemodynamic assessment by RHC and were excluded from the study population, according to our guidelines recommended study protocol[3,10].

In order to rule out occult post-capillary PH in patients suspected of having PAH, rapid fluid administration of 500 mL 0.9% NaCl solution within 5 min (by pressure cuff, C-fusor 500, Smiths Medical, Minneapolis, MN, United States) was performed, and the response of pulmonary artery wedge pressure to shifts in volume status was recorded within 2 min after the fluid challenge[11,12].

Patients on beta-blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker or mineralocorticoid receptor antagonist at the time of RHC were classified as NEUi users and compared with NEUi non-recipients. Comparisons between NEUi users and NEUi non-users were performed in terms of demographics, cardiovascular risk factors, biochemical samples, hemodynamic parameters and prognostic outcome.

This study was conducted in accordance with the principles of the Declaration of Helsinki, and the ethics committee of the Medical University of Genoa approved the protocol. Due to the retrospective design, written informed consent to participate in the study was not applicable.

Statistical analysis was carried out using the Statistica 13.1 software for Windows (StatSoft, Inc., Tulsa, OK, United States). Quantitative variables were expressed either as number (percentage of total) or mean ± standard deviation. The statistical significance of the results between the two groups was determined by means of either χ^2 test or *t*-test, as appropriate. Death from any cause was assessed by Kaplan-Meyer survival analysis. A P value < 0.05 was considered statistically significant.

RESULTS

Complete data were available for 57 patients affected by idiopathic PAH. The majority of them were female (64.9%), mean age was 63.6 ± 10.6 years and mean follow-up period was 4.2 ± 3.0 years. Mean pulmonary arterial pressure, pulmonary artery wedge pressure and pulmonary vascular resistance were 45.0 ± 14.9 mmHg, 11.0 ± 2.8 mmHg and 8.8 ± 5.0 Wood units, respectively. Twenty-seven patients (47.4%) were under treatment with at least one NEUi at the time of RHC and constituted the NEUi user group: 15 (26.3%) were taking angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and 12 (21.1%) beta-blockers, while 6 (10.5%) were taking mineralocorticoid receptor antagonists. The remaining 36 subjects of the study population belonged to the NEUi non-recipients.

The two groups were comparable in terms of PAH-specific drugs taken during the follow-up period, as well as of prognostic determinants for PAH provided by the current European guidelines, including World Health Organization functional class, 6-min walking distance, right atrial pressure, cardiac index and N-terminal pro-brain natriuretic peptide plasmatic levels (P = not significant). NEUi users were significantly older (67.6 ± 11.9 years *vs* 60.1 ± 14.5 years, P = 0.039), had a lower glomerular filtration rate (58.7 ± 22.7 mL/min/1.73 m^2 *vs* 73.7 ± 24.7 mL/min/1.73 m^2, P = 0.022), a higher body mass index (25.9 ± 4.4 *vs* 23.5 ± 3.5, P = 0.025), an increased prevalence of smoking habits (51.9% *vs* 20.0%, P = 0.025) and increased systemic arterial hypertension (74.1% *vs* 40.0%, P = 0.020) compared to non-recipients. Additionally, 5 NEUi recipients (18.5%) underwent coronary artery revascularization compared to NEUi non-users (P = 0.046). Baseline characteristics and statistical results are summarized in Table 1. NEUi non-users had a higher probability of dying during the course of follow-up than NEUi recipients (56.7% *vs* 25.9%, log-rank P = 0.020) (Figure 1).

DISCUSSION

The reported data detected a significantly higher cardiovascular risk profile in the study population, encountering more than 50% of subjects with arterial hypertension and more than 30% with smoking habits and dyslipidemia. Albeit limited by the retrospective nature of the investigation, the small size and the single-center origin of the sample examined, these findings are in agreement with the results from the AMBITION trial and substantiated by registry data supporting that PAH with cardiovascular comorbidities is a codified PH entity in clinical practice[5,7]. However, to date these data have not been acknowledged by the current international guidelines on PH, which still fail to consider patients with PAH and cardiovascular comorbidities as belonging to a defined clinical subset[3,13]. This lack in the current state of regard for PH has limited further speculation on the potential therapeutic effects of NEUi in these kinds of patients. In this regard, the analysis of the two patient populations studied herein showed a significantly higher cardiovascular risk profile for LHD among NEUi users, in whom a better prognostic outcome has been observed compared to NEUi non-recipients.

A plausible explanation to these observations comes from the beneficial effects of NEUi use on cardiovascular comorbidities, which tended to cluster in the NEUi users group acting mainly on systemic inflammation and microvascular circulation, with consequent worsening of right ventricular impairment and survival[14,15]. In the same line, data from the literature pointed out a plausible

Table 1 Baseline characteristics of the study population

Variable	NEUi non-users, *n* = 30	NEUi users, *n* = 27	*P*
Age in yr	60.1 ± 14.5	67.6 ± 11.9	0.039
Men/Women, *n* (%)	11 (36.7)/19 (63.3)	9 (33.3)/18 (66.7)	0.988
Follow-up in yr	4.0 ± 2.7	4.5 ± 3.3	0.504
Dead at follow-up, *n* (%)	17 (56.7)	7 (25.9)	0.038
BMI in kg/m^2	23.5 ± 3.5	25.9 ± 4.4	0.025
Arterial hypertension, *n* (%)	12 (40.0)	20 (74.1)	0.020
Smoking habits, *n* (%)	6 (20.0)	14 (51.9)	0.025
Dyslipidemia, *n* (%)	7 (23.3)	12 (44.4)	0.160
Diabetes mellitus, *n* (%)	2 (6.7)	5 (18.5)	0.339
Supraventricular arrhythmias, *n* (%)	4 (13.3)	7 (25.9)	0.386
Coronary artery disease, *n* (%)	0 (0)	5 (18.5)	0.046
eGFR in mL/min/1.73 m^2 [CKD-EPI]	73.7 ± 24.7	58.7 ± 22.7	0.022
WHO-FC	2.2 ± 0.76	2.3 ± 0.47	0.572
6MWD in m	383.9 ± 129.7	374.3 ± 145.1	0.845
NT-proBNP in ng/mL	714.9 ± 692.4	808.7 ± 617.9	0.593
Systolic PAP in mmHg	74.7 ± 26.3	71.0 ± 21.3	0.569
Diastolic PAP in mmHg	27.5 ± 11.6	26.3 ± 9.6	0.681
Mean PAP in mmHg	46.2 ± 16.1	43.6 ± 13.6	0.509
Right atrial pressure in mmHg	8.3 ± 3.9	10.5 ± 5.0	0.063
PAWP in mmHg	10.5 ± 2.9	11.7 ± 2.5	0.105
PVR in Wood unit	9.0 ± 5.4	8.6 ± 4.6	0.789
Cardiac index in L/min/m^2	2.6 ± 0.9	2.4 ± 0.6	0.258

BMI: Body mass index; NEUi: Neurohormonal inhibitors; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: Estimated glomerular filtration rate; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAP: Pulmonary arterial pressure; PAWP: Pulmonary artery wedge pressure; PVR: Pulmonary vascular resistance; 6MWD: 6-min walking distance; WHO-FC: World Health Organization functional class.

overlap between idiopathic PAH and PH due to LHD in terms of pathophysiologic mechanisms, prognostic outcomes and response to targeted PAH-specific treatment[11,14]. In the analysis conducted by Obokata *et al*[16], the activation of the endothelin signaling pathway seemed to contribute to right ventricular functional impairment in subjects with heart failure with preserved ejection fraction, while endothelin-1 is also historically known for its pathogenic role in developing PAH by pulmonary vasoconstriction, smooth muscle cell proliferation and pulmonary vascular remodeling.

Several studies emphasized a proposed paradigm whereby metabolic syndrome and cardiovascular comorbidities could reinforce PH in patients with LHD by exploiting molecular pathways actively involved in developing PAH, like a deranged interplay between decreased microvascular nitric oxide availability and enhanced endothelin expression[17-20]. Therefore, the close relationship between these two PH phenotypes raised the hypothesis of a potential continuum disease, in which PAH with risk factor for LHD lies in-between. For these reasons, it is possible to assume that the better prognostic outcome observed in NEUi recipients of our study population could also be intrinsically related to an intermediate pathophysiologic standpoint in the spectrum of disease (phenotypically closer to PH due to LHD albeit with a hemodynamic profile comparable with precapillary PH) rather than solely ascribed to the therapeutic properties of neurohormonal axis blockers on cardiovascular comorbidities.

Finally, considering the aforementioned upregulation of the neurohormonal axis in PAH and its deleterious properties on worsening right heart failure in the long-run, a direct favorable implication of NEUi on right ventricular function and pulmonary circulation in this study population may be also taken into account[2,21].

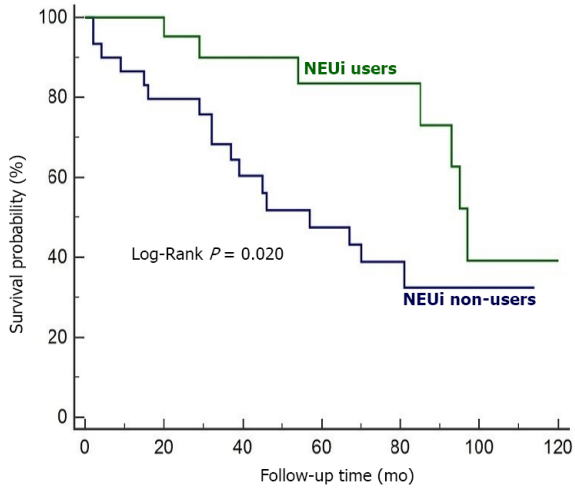

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Figure 1 Survival curves of the study population according to neurohormonal inhibitors users or non-users. NEUi: Neurohormonal inhibitors.

CONCLUSION

In conclusion, our data highlighted a codified subset of patients with PAH and a comorbidity profile for LHD, lying between the extremes of a pathophysiological continuum, in which NEUi use has been shown to be associated with a better prognostic outcome. Further investigation is required to define the proper pharmacological treatment in patients with PAH and hidden LHD.

ARTICLE HIGHLIGHTS

Research background

Despite new insights in pharmacological treatment, patents with pulmonary arterial hypertension (PAH) still have a considerably reduced life expectancy.

Research motivation

Chronic hyperactivity of the neurohormonal axis has been shown to be detrimental in PAH, thus providing novel insights on the role of neurohormonal inhibitors (NEUi) as a new potential therapeutic target.

Research objectives

To assess the use and prognostic impact of NEUi in a single-center cohort of subjects with idiopathic PAH and risk factors for left heart disease.

Research methods

This was a single-center, retrospective observational study, involving 57 subjects with idiopathic PAH, confirmed by right heart catheterization. Patients on beta-blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker or mineralocorticoid receptor antagonist at the time of right heart catheterization were classified as NEUi users and compared to NEUi non-recipients.

Research results

NEUi users were significantly older (67.6 ± 11.9 years *vs* 60.1 ± 14.5 years, $P = 0.039$), had a higher body mass index (25.9 ± 4.4 *vs* 23.5 ± 3.5, $P = 0.025$), a lower estimated glomerular filtration rate (58.7 ± 22.7 mL/min/1.73 m^2 *vs* 73.7 ± 24.7 mL/min/1.73 m^2, $P = 0.022$) and more frequent systemic arterial hypertension (74.1% *vs* 40.0%, $P = 0.020$) and smoking habits (51.9% *vs* 20.0%, $P = 0.025$) compared to non-recipients. Mortality rate was significantly higher among NEUi non-users than in NEUi users (56.7% *vs* 25.9%, $P = 0.038$). NEUi non-users were more likely to die over the course of follow-up (log-rank $P = 0.020$).

Research conclusions

Our analysis highlighted a subset of patients with PAH and cardiovascular comorbidities in which NEUi use has been shown to be associated with improved survival.

Research perspectives

Future prospective studies are needed to identify the most appropriate therapeutic strategies in this subset population.

FOOTNOTES

Author contributions: Scagliola R and Balbi M contributed to the conception and design of the study and acquired and interpreted the data; Brunelli C and Balbi M analyzed the data; Scagliola R drafted the manuscript; All authors contributed equally to the critical revision, editing and approval of the final version of the manuscript.

Institutional review board statement: This study was reviewed and approved by the Institutional Review Board committee at the University of Genoa, Italy.

Informed consent statement: Due to the retrospective design, written informed consent to participate in the study was not applicable.

Conflict-of-interest statement: None to be declared.

Data sharing statement: The present data are anonymized, with no risk of identification.

Country/Territory of origin: Italy

ORCID number: Riccardo Scagliola 0000-0002-5439-3300; Claudio Brunelli 0000-0002-1688-4467; Manrico Balbi 0000-0002-4604-3204.

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REFERENCES

1 **Handoko ML**, de Man FS, Allaart CP, Paulus WJ, Westerhof N, Vonk-Noordegraaf A. Perspectives on novel therapeutic strategies for right heart failure in pulmonary arterial hypertension: lessons from the left heart. *Eur Respir Rev* 2010; **19**: 72-82 [PMID: 20956170 DOI: 10.1183/09059180.00007109]

2 **de Man FS**, Handoko ML, Guignabert C, Bogaard HJ, Vonk-Noordegraaf A. Neurohormonal axis in patients with pulmonary arterial hypertension: friend or foe? *Am J Respir Crit Care Med* 2013; **187**: 14-19 [PMID: 23144327 DOI: 10.1164/rccm.201209-1663PP]

3 **Galiè N**, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016; **37**: 67-119 [PMID: 26320113 DOI: 10.1093/eurheartj/ehv317]

4 **Thenappan T**, Roy SS, Duval S, Glassner-Kolmin C, Gomberg-Maitland M. β-blocker therapy is not associated with adverse outcomes in patients with pulmonary arterial hypertension: a propensity score analysis. *Circ Heart Fail* 2014; **7**: 903-910 [PMID: 25277998 DOI: 10.1161/CIRCHEARTFAILURE.114.001429]

5 **McLaughlin VV**, Vachiery JL, Oudiz RJ, Rosenkranz S, Galiè N, Barberà JA, Frost AE, Ghofrani HA, Peacock AJ, Simonneau G, Rubin LJ, Blair C, Langley J, Hoeper MM; AMBITION Study Group. Patients with pulmonary arterial hypertension with and without cardiovascular risk factors: Results from the AMBITION trial. *J Heart Lung Transplant* 2019; **38**: 1286-1295 [PMID: 31648845 DOI: 10.1016/j.healun.2019.09.010]

6 **Hoeper MM**, Huscher D, Ghofrani HA, Delcroix M, Distler O, Schweiger C, Grunig E, Staehler G, Rosenkranz S, Halank M, Held M, Grohé C, Lange TJ, Behr J, Klose H, Wilkens H, Filusch A, Germann M, Ewert R, Seyfarth HJ, Olsson KM, Opitz CF, Gaine SP, Vizza CD, Vonk-Noordegraaf A, Kaemmerer H, Gibbs JS, Pittrow D. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. *Int J Cardiol* 2013; **168**: 871-880 [PMID: 23164592 DOI: 10.1016/j.ijcard.2012.10.026]

7 **Charalampopoulos A**, Howard LS, Tzoulaki I, Gin-Sing W, Grapsa J, Wilkins MR, Davies RJ, Nihoyannopoulos P, Connolly SB, Gibbs JS. Response to pulmonary arterial hypertension drug therapies in patients with pulmonary arterial

hypertension and cardiovascular risk factors. *Pulm Circ* 2014; **4**: 669-678 [PMID: 25610602 DOI: 10.1086/678512]

8 **Opitz CF**, Hoeper MM, Gibbs JS, Kaemmerer H, Pepke-Zaba J, Coghlan JG, Scelsi L, D'Alto M, Olsson KM, Ulrich S, Scholtz W, Schulz U, Grünig E, Vizza CD, Staehler G, Bruch L, Huscher D, Pittrow D, Rosenkranz S. Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension: A Pathophysiological Continuum. *J Am Coll Cardiol* 2016; **68**: 368-378 [PMID: 27443433 DOI: 10.1016/j.jacc.2016.05.047]

9 **Kovacs G**, Dumitrescu D, Barner A, Greiner S, Grünig E, Hager A, Köhler T, Kozlik-Feldmann R, Kruck I, Lammers AE, Mereles D, Meyer A, Meyer J, Pabst S, Seyfarth HJ, Sinning C, Sorichter S, Stähler G, Wilkens H, Held M. Definition, clinical classification and initial diagnosis of pulmonary hypertension: Updated recommendations from the Cologne Consensus Conference 2018. *Int J Cardiol* 2018; **272S**: 11-19 [PMID: 30219257 DOI: 10.1016/j.ijcard.2018.08.083]

10 **Pieske B**, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2020; **22**: 391-412 [PMID: 32133741 DOI: 10.1002/ejhf.1741]

11 **Robbins IM**, Hemnes AR, Pugh ME, Brittain EL, Zhao DX, Piana RN, Fong PP, Newman JH. High prevalence of occult pulmonary venous hypertension revealed by fluid challenge in pulmonary hypertension. *Circ Heart Fail* 2014; **7**: 116-122 [PMID: 24297689 DOI: 10.1161/CIRCHEARTFAILURE.113.000468]

12 **Fujimoto N**, Borlaug BA, Lewis GD, Hastings JL, Shafer KM, Bhella PS, Carrick-Ranson G, Levine BD. Hemodynamic responses to rapid saline loading: the impact of age, sex, and heart failure. *Circulation* 2013; **127**: 55-62 [PMID: 23172838 DOI: 10.1161/CIRCULATIONAHA.112.111302]

13 **Yaghi S**, Novikov A, Trandafirescu T. Clinical update on pulmonary hypertension. *J Investig Med* 2020; **68**: 821-827 [PMID: 32241822 DOI: 10.1136/jim-2020-001291]

14 **Scagliola R**. Pulmonary arterial hypertension and pulmonary hypertension due to left heart disease: so near and yet so far. *Pol Arch Intern Med* 2020; **130**: 349-350 [PMID: 32383838 DOI: 10.20452/pamw.15328]

15 **Paulus WJ**, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013; **62**: 263-271 [PMID: 23684677 DOI: 10.1016/j.jacc.2013.02.092]

16 **Obokata M**, Kane GC, Reddy YNV, Melenovsky V, Olson TP, Jarolim P, Borlaug BA. The neurohormonal basis of pulmonary hypertension in heart failure with preserved ejection fraction. *Eur Heart J* 2019; **40**: 3707-3717 [PMID: 31513270 DOI: 10.1093/eurheartj/ehz626]

17 **Franssen C**, Paulus WJ. Normal resting pulmonary artery wedge pressure: a diagnostic trap for heart failure with preserved ejection fraction. *Eur J Heart Fail* 2015; **17**: 132-134 [PMID: 25639375 DOI: 10.1002/ejhf.225]

18 **Robbins IM**, Newman JH, Johnson RF, Hemnes AR, Fremont RD, Piana RN, Zhao DX, Byrne DW. Association of the metabolic syndrome with pulmonary venous hypertension. *Chest* 2009; **136**: 31-36 [PMID: 19188551 DOI: 10.1378/chest.08-2008]

19 **Rocha NG**, Templeton DL, Greiner JJ, Stauffer BL, DeSouza CA. Metabolic syndrome and endothelin-1 mediated vasoconstrictor tone in overweight/obese adults. *Metabolism* 2014; **63**: 951-956 [PMID: 24856242 DOI: 10.1016/j.metabol.2014.04.007]

20 **van Heerebeek L**, Hamdani N, Falcão-Pires I, Leite-Moreira AF, Begieneman MP, Bronzwaer JG, van der Velden J, Stienen GJ, Laarman GJ, Somsen A, Verheugt FW, Niessen HW, Paulus WJ. Low myocardial protein kinase G activity in heart failure with preserved ejection fraction. *Circulation* 2012; **126**: 830-839 [PMID: 22806632 DOI: 10.1161/CIRCULATIONAHA.111.076075]

21 **Emanuel R**, Chichra A, Patel N, Le Jemtel TH, Jaiswal A. Neurohormonal modulation as therapeutic avenue for right ventricular dysfunction in pulmonary artery hypertension: till the dawn, waiting. *Ann Transl Med* 2018; **6**: 301 [PMID: 30211189 DOI: 10.21037/atm.2018.06.04]

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Retrospective Study

Retrospective analysis of aspirin's role in the severity of COVID-19 pneumonia

Maya Gogtay, Yuvaraj Singh, Asha Bullappa, Jeffrey Scott

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Maya Gogtay, Yuvaraj Singh, Department of Internal Medicine, Saint Vincent Hospital, Worcester, MA 01604, United States

Asha Bullappa, Community Medicine and Biostatistics, SS Institute of Medical Sciences, Davangere 577003, Karnataka, India

Jeffrey Scott, Department of Critical Care Medicine and Pulmonology, Reliant medical group-Saint Vincent Hospital, Worcester, MA 01604, United States

Corresponding author: Maya Gogtay, MD, Doctor, Department of Internal Medicine, Saint Vincent Hospital, 123 Summer street, Worcester, MA 01604, United States.
drgogtay@gmail.com

Abstract

BACKGROUND

Since December 2019, an outbreak of pneumonia caused by severe acute respiratory syndrome - coronavirus-2 (SARS-CoV-2) has led to a life-threatening ongoing pandemic worldwide. A retrospective study by Chow *et al* showed aspirin use was associated with decreased intensive care unit (ICU) admissions in hospitalized coronavirus disease 2019 (COVID-19) patients. Recently, the RECOVERY TRIAL showed no associated reductions in the 28-d mortality or the progression to mechanical ventilation of such patients. With these conflicting findings, our study was aimed at evaluating the impact of daily aspirin intake on the outcome of COVID-19 patients.

AIM

To study was aimed at evaluating the impact of daily aspirin intake on the outcome of COVID-19 patients.

METHODS

This retrospective cohort study was conducted on 125 COVID-19 positive patients. Subgroup analysis to evaluate the association of demographics and comorbidities was undertaken. The impact of chronic aspirin use was assessed on the survival outcomes, need for mechanical ventilation, and progression to ICU. Variables were evaluated using the chi-square test and multinomial logistic regression analysis.

RESULTS

125 patients were studied, 30.40% were on daily aspirin, and 69.60% were not. Cross-tabulation of the clinical parameters showed that hypertension (P = 0.004), hyperlipidemia (0.016), and diabetes mellitus (P = 0.022) were significantly associated with aspirin intake. Regression analysis for progression to the ICU, need for mechanical ventilation and survival outcomes against daily aspirin intake showed no statistical significance.

CONCLUSION

Our study suggests that daily aspirin intake has no protective impact on COVID-19 illness-associated survival outcomes, mechanical ventilation, or progression to ICU level of care.

Key Words: COVID-19; Aspirin; Intensive care unit progression; Antiplatelet; Hyper-coagulability; Anti-inflammatory

Core Tip: Our study suggests that aspirin has no beneficial effects with regards to progression to intensive care unit (ICU) from the medical floors in coronavirus disease 2019 (COVID-19) positive patients. This study was conducted on the patients presenting during the early phase of the pandemic when there was little evidence on the most beneficial modality of treatment. Over the last 2 years we have learned about the pro-thrombotic nature of COVID-19. Since aspirin is a widely dispensed medication in our adult population, we questioned if its chronic use could have a preventive effect on ICU progression of patients admitted to the medical floors. However, our data analysis suggests that there was no such protective effect.

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INTRODUCTION

Since December 2019, an outbreak of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a life-threatening ongoing pandemic worldwide[1]. Several nonsteroidal anti-inflammatory drugs (NSAIDs) have been used in patients with SARS-CoV-2 infection, but many remain controversial effects on the disease[2]. Aspirin (acetylsalicylic acid), a popular medicine, exhibits a variety of effects, including alleviating anti-inflammatory response, reducing fever and pain, and blocking viral propagation of RNA viruses (*e.g.*, influenza virus and hepatic C virus)[3]. Moreover, coagulopathy plays a central role in the patho-mechanism of coronavirus disease 2019 (COVID-19), which leads to end-organ complications and death[4-6]. COVID-19 has been linked with increased thromboembolic complications such as venous thro-mboembolism, stroke, and myocardial infarction[7-10]. Aspirin is potentially beneficial in patients with COVID-19 due to its antithrombotic nature[11]. Aspirin primarily acts by inhibiting platelet function through irreversible inhibition of cyclo-oxygenase (COX) activity. Low-dose aspirin inhibits COX-1, resulting in reduced thromboxane A2 synthesis which prevents platelet activation and aggregation[12,13]. In a retrospective study by Chow *et al*[14], it was found that aspirin use may be associated with improved outcomes, reduced rates of mechanical ventilation, and decreased intensive care unit (ICU) admissions in hospitalized COVID-19 patients. Given the encouraging findings, the world's largest randomized controlled open-label trial was performed using approximately 15000 patients in the UK (RECOVERY TRIAL)[15]. The patients in the study were allocated to receive aspirin after diagnosis of COVID-19 during in-hospital admission, and the results showed no associated reductions in the 28-d mortality or the progression to mechanical ventilation of such patients. With the above conflicting findings, the present study was designed to evaluate the impact of daily aspirin intake prior to hospitalization on the rate of COVID-19 positive patients' progression to the ICU.

MATERIALS AND METHODS

This single-center retrospective cohort study was conducted on patients that tested COVID-19 positive and were admitted between March and April 2020. IRB approval was obtained before initiating the

study. Patient data including demographic information, history of comorbidities like hypertension, hyperlipidemia and diabetes mellitus, medication use like aspirin, P2Y12 inhibitor, warfarin and NOACs, clinical characteristics, and clinical outcomes were retrieved from the hospital database based on the following inclusion and exclusion criteria.

Inclusion criteria

COVID-19 positive in-patients. Adults aged 18 years and older.

Exclusion criteria

Patients with incomplete medical records. Pregnant women and patients aged 17 years and younger.

All the collected data were stored securely in a password-protected computer, and any paper records were securely stored. Only the approved study team had access to data.

Based on intensive retrospective chart review and recording the baseline characteristics of the patients, they were divided into two cohorts. The first cohort consisted of patients taking daily aspirin of at least 81 mg, and those who were not taking daily aspirin were placed in the second cohort. The patients were on chronic daily aspirin prior to contracting COVID-19 and hospitalization. Aspirin intake was recorded as per their pre-admission medication history. For both the cohorts, we calculated various outcomes, which included the percentage of patients progressing to the ICU, percentage of patients requiring oxygen supplementation, and percentage of patients requiring mechanical ventilation. We also calculated survival outcomes for the two groups. Additionally, subgroup analysis was undertaken by comparing various age groups and gender. All the statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows, Version 21.0; IBM Corp, Armonk, NY, United States). Categorical variables were analyzed using the chi-square test; $P < 0.05$ was considered statistically significant. A multinomial logistic regression analysis was done to study the relationship between various outcomes (ICU admission, intubation rate, and survival rate) and multiple independent variables like the use of aspirin, warfarin, NOACs, P2Y12 inhibitors, and comorbidities like hypertension and diabetes mellitus.

RESULTS

One hundred and twenty-five patients met our inclusion criteria and were stratified for further analysis. Out of them, 38 (30.40%) patients were on daily aspirin, and 87 (69.60%) were not. The majority of the 125 study subjects, *i.e*, 25.6% of the study subjects, belonged to the age group of 76-85 years, followed by 20.8% in the 56-65 age group. 19.2%, 15.2%, 12%, 4%, and 3.2% of study subjects belonged to above 85, 66-75, 46-55, 36-45, and 24-35 years of age respectively. The chi-square test showed a significant (P = 0.016) difference in age groups of study subjects taking daily aspirin as shown in Figure 1.

Amongst the 125 patients, we found that 41.6% were males not taking daily aspirin, 28% were females not taking aspirin, 17.6% were women taking daily aspirin, 12.8% were males on daily aspirin (P = 0.068), as depicted in Figure 2.

For those on daily aspirin, 32 (84.21%), 30 (78.94%), and 18 (47.36%) subjects had significant comorbidities like hypertension, hyperlipidemia and diabetes mellitus, respectively. Cross-tabulation of the clinical parameters of study subjects showed that hypertension (P = 0.004), hyperlipidemia (P = 0.016), diabetes mellitus (P = 0.022), were significantly associated with aspirin intake (Table 1).

In terms of outcomes, 9 (23.68%) patients were on aspirin *vs* 38 (43.6%) not on aspirin progressed to requiring ICU level of care (P = 0.034) as depicted in Figure 3. 5 (13.15%) on aspirin required mechanical ventilation contrary to 21 (24.13%) not on aspirin (P = 0.16). 36 (94.73%) of aspirin users required supplemental oxygen *vs* 73 (83.9%) not on aspirin (P = 0.096). 26 (68.5%) on aspirin survived *vs* 66 (75.8%), not on aspirin (P = 0.38) as depicted in Table 1.

A multinomial logistic regression analysis was further used to predict the categorical placement of each independent variable (aspirin, warfarin, NOACs, P2Y12 inhibitors, hypertension and diabetes mellitus) against the dependent variables: (1) Progression to ICU (Table 2); (2) Need for mechanical ventilation (Table 3); and (3) Survival outcomes (Table 4).

The analysis showed that aspirin users had an odds ratio of 0.367 (P = 0.03, CI: 0.378-2.26), predicting the odds of a patient taking aspirin progressing to the ICU is 0.3677 higher than those not being on aspirin if all the other predictor variables were held constant as represented in Table 2, though not significant.

The odds ratio of warfarin was 1.466 (P = 0.60, CI: 0.179-3.701) higher risk of ICU transfer than those not on warfarin. NOACs users had an odds ratio of 0.8522 (P = 0.79, CI: 0.229-2.520) and P2Y12 inhibitors were 2.998 (P = 0.22, CI: 0.141-5.144). Similarly, comorbidities (hypertension and diabetes mellitus) showed no significant impact on ICU admissions.

Other dependent variables like the need for mechanical ventilation and survival outcomes of the patients were also analyzed using the same independent variables with no significant association as in Table 3 and Table 4, respectively.

Table 1 Distribution of clinical parameters based on aspirin intake

Patient characteristics		Aspirin		Total (n = 125)	χ^2 value	P value
		Taking (n = 38)	Not taking aspirin (n = 87)			
Warfarin	Yes	4	5	9	0.90	0.34
	Percentage (%)	3.2	4.0	7.2		
	No	34	82	116		
	Percentage (%)	27.2	65.6	92.8		
Direct oral anticoagulants (NOAC)	Yes	6	9	15	0.74	0.38
	Percentage (%)	4.8	7.2	12.0		
	No	32	78	110		
	Percentage (%)	25.6	62.4	88.0		
P2Y12 inhibitors	Yes	1	5	6	0.56	0.45
	Percentage (%)	0.8	4.0	4.8		
	No	37	82	119		
	Percentage (%)	29.6	65.6	95.2		
Hypertension	Present	32	50	82	8.38	0.004[a]
	Percentage (%)	84.2	57.4	65.6		
	Absent	6	37	43		
	Percentage (%)	15.78	42.5	34.4		
Hyperlipidemia	Present	30	49	79	5.82	0.016[a]
	Percentage (%)	78.9	56.32	63.2		
	Absent	8	38	46		
	Percentage (%)	21	43.6	36.8		
Diabetes Mellitus	Present	18	23	41	5.25	0.022[a]
	Percentage (%)	47.36	26.4	32.8		
	Absent	20	64	84		
	Percentage (%)	52.6	73.5	67.2		
Immunosuppression	Yes	3	4	7	0.54	0.46
	Percentage (%)	7.8	4.5	5.6		
	No	35	83	118		
	Percentage (%)	92.1	95.4	94.4		
ICU admission	Admitted to ICU	9	38	47	4.50	0.034[a]
	Percentage (%)	23.6	43.67	37.6		
	Remained on medical floors	29	49	78		
	Percentage (%)	90.6	56.3	62.4		
Intubation	Yes	5	21	26	1.93	0.16
	Percentage (%)	13.1	24.1	20.8		
	No	33	66	99		
	Percentage (%)	86.8	75.8	79.2		
Outcome (survival)	Survived	26	66	92	0.75	0.38
	Percentage (%)	68.4	75.8	73.6		
	Died	12	21	33		
	Percentage (%)	31.5	24.1	26.4		

PE/DVT	Present	2	1	3	1.91	0.16
	Percentage (%)	5.2	1.1	2.4		
	Absent	36	86	122		
	Percentage (%)	94.7	98.8	97.6		
Oxygen use	Present	36	73	109	2.77	0.096
	Percentage (%)	94.7	83.9	87.2		
	Absent	2	14	16		
	Percentage (%)	5.2	16	12.8		

[a]$P \leq 0.05$.

Table 2 Logistic regression result for progression to the intensive care unit

Characteristics	Regression coefficients	Standard error	χ^2 (wald)	*P* value	Odds ratio	95%CI
Intercept	-0.45044	0.332171	1.838826	0.175089	0.637351	
Aspirin	-1.00047	0.46281	4.67307	0.030639	0.367707	0.365575-2.269164
Warfarin	0.382791	0.733339	0.272467	0.601681	1.466372	0.179321-3.701697
NOAC's	-0.15984	0.616872	0.067143	0.795543	0.852277	0.22984-2.520831
P2Y12 inhibitors	1.098044	0.908435	1.461005	0.22677	2.998296	0.142169-5.14458
HTN	0.213851	0.424561	0.253712	0.614473	1.238438	0.259028-1.790559
DM	0.018183	0.432623	0.001767	0.966474	1.01835	0.187667-1.05208

NOAC's: Novel oral anticoagulants; HTN: Hypertension; DM: Diabetes mellitus.

Table 3 Logistic regression results for need for mechanical ventilation

Characteristics	Regression coefficients	Standard error	χ^2 (wald)	*P* value	Odds ratio	95%CI
Intercept	-1.22056	0.389142	9.83799	0.001709	0.295063	
Aspirin	-0.83593	0.566163	2.179995	0.139815	0.433472	0.142903-1.31486
Warfarin	0.1583	0.859459	0.033924	0.853868	1.171517	0.217358-6.314246
NOACs	-0.54597	0.812938	0.451048	0.501838	0.57928	0.117737-2.850114
P2Y12 inhibitors	-0.42413	1.139528	0.138534	0.709742	0.654336	0.070118-6.106168
HTN	0.22629	0.500756	0.20421	0.651344	1.253939	0.469929-3.345963
DM	0.020291	0.510762	0.001578	0.968312	1.020498	0.375017-2.776985

NOAC's: Novel oral anticoagulants; HTN: Hypertension; DM: Diabetes mellitus.

DISCUSSION

In a multi-center cohort study on COVID-19 patients by Chow *et al*[14], aspirin use was independently associated with a lower risk of mechanical ventilation, ICU admission, and in-hospital mortality. Given aspirin's wide inexpensive use, it could be the answer we are looking for especially in low-income countries where expensive immunomodulators aren't readily available[14]. But a recent randomized controlled, open-label trial - RECOVERY, compared multiple treatments, including 150 mg aspirin once daily. They found that in hospitalized COVID-19 patients, aspirin was not associated with reductions in 28-d mortality or the risk of progressing to invasive mechanical ventilation or death but was associated with a slight increase in the rate of being discharged alive within 28 d[15]. Given the conflicting nature of recent studies, we sought to evaluate the effect of daily aspirin intake on clinical outcomes in hospitalized patients with COVID-19 and its impact on the rate of COVID-19 positive patient's progression to ICU.

Table 4 Logistic regression results for survival outcomes

Characteristics	Regression coefficients	Standard error	χ^2 (wald)	*P* value	Odds ratio	95%CI
Intercept	1.689138	0.422469	15.98599	6.38E-05	5.41481	
Aspirin	-0.07596	0.456833	0.027651	0.867932	0.926849	0.378575-2.269164
Warfarin	-0.20489	0.772302	0.070384	0.790778	0.814735	0.179321-3.701697
NOACs	-0.27293	0.610988	0.199538	0.655094	0.761148	0.229824-2.520831
P2Y12 inhibitors	-0.1564	0.915497	0.029184	0.864355	0.855219	0.142169-5.14458
HTN	-0.38415	0.49321	0.606636	0.436057	0.681032	01.790559
DM	-0.81116	0.439766	3.402248	0.065108	0.444344	1.05208

NOAC's: Novel oral anticoagulants; HTN: Hypertension; DM: Diabetes mellitus.

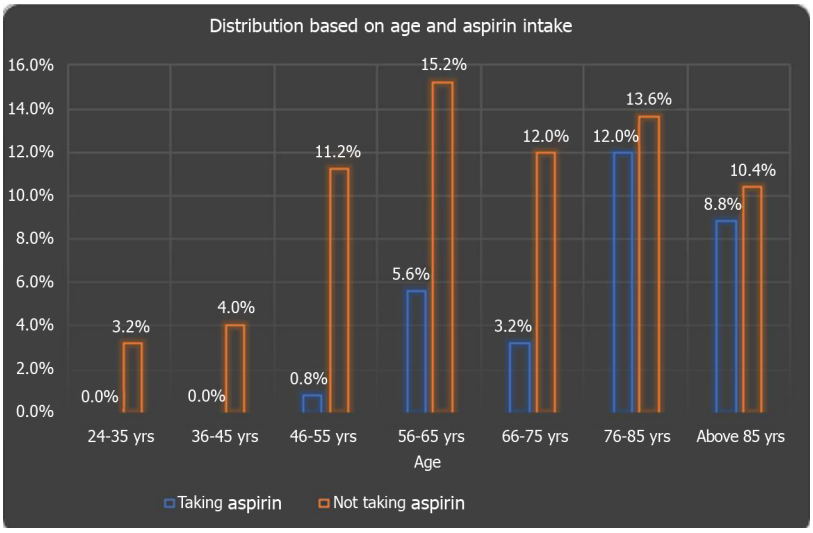

Figure 1 Distribution of study population based on age and aspirin intake (chi-square value of 15.66, *P* value = 0.016).

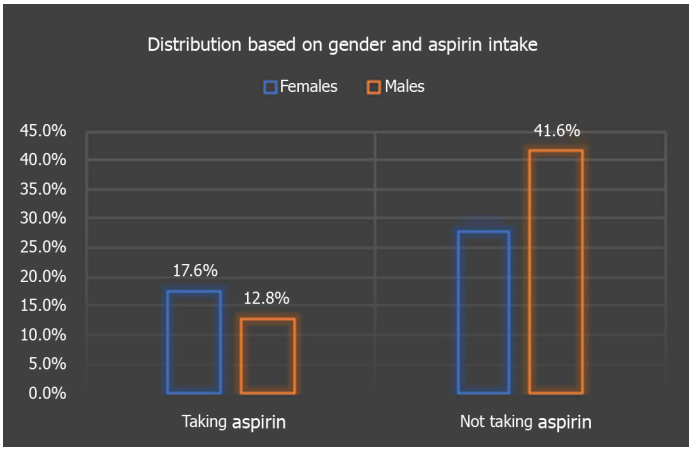

Figure 2 Distribution of study subjects based on gender and aspirin intake (χ^2 value = 3.32, *P* value = 0.068).

Our study analyzed 125 patients, of which 38 patients were on daily aspirin use, with a minimum dose of 81 mg. The study showed a significant association in variables such as age groups, hypertension, hyperlipidemia, and diabetes mellitus. This insinuated that our aspirin patients were older, and most of them had significant comorbidities, putting them at risk of severe COVID-19 illness.

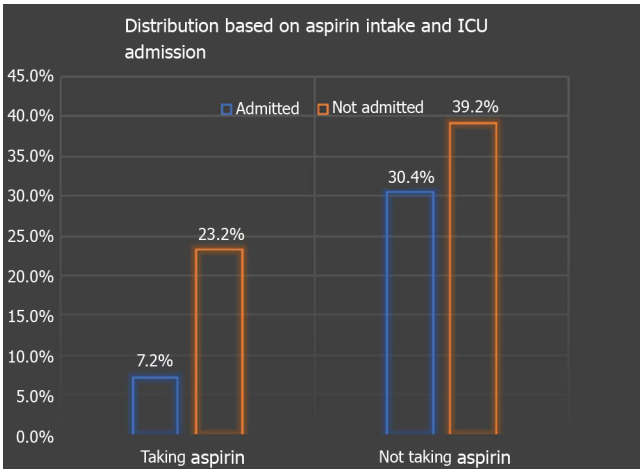

Figure 3 Distribution of study subjects based on aspirin and intensive care unit admission (χ^2 = 4.50, *P* value = 0.034). ICU: Intensive care unit.

At first glance, aspirin showed a possible protective role in progression to ICU on chi-square analysis. It failed to reach significance in multinomial logistic regression analysis. Furthermore, in terms of mortality, patients on aspirin had a higher mortality rate of 32% as compared to only 25% for non-aspirin users. This could be explained by the fact that patients on aspirin were older and had more comorbidities.

Hence, we conclude that aspirin shows no protective role for COVID-19 patients in terms of progression to ICU, survival outcome, and use of mechanical ventilation. Our findings concurred with the results of the RECOVERY trial[15].

Furthermore, bleeding risk is a potential adverse event while on aspirin. In the RECOVERY TRIAL, the incidence of major bleeding events was higher in the aspirin group (1.6% *vs* 1.0%; absolute difference 0.6%, SE: 0.2%). There were 18 reports of serious adverse events believed related to aspirin, all due to hemorrhagic in nature[15]. Even though we did not assess bleeding risk, this is a serious adverse event to bear in mind.

The advantage of our study is that it was conducted on the cohort of patients that presented at our hospital during the initial phase of the COVID-19 pandemic back in March of 2020. At that time, the use of corticosteroids and remdesivir were not established as the standard of care, and hence our study is not confounded by the effects of these medications.

The limitations of our study include a modest sample size and a retrospective - observational analysis, which limits generalizability and adjustment for confounding variables. We did not collect data on other concomitant medications - like statins or ACEI/ARBs, as most patients on aspirin are usually on the above, due to guideline-directed medical therapy for cardiovascular diseases, which could confound results. Some of our patients had their daily aspirin use discontinued after admission due to inability to tolerate enteral feeds, new bleeding complications, or being started on other anticoagulants owing to COVID-19 complications.

CONCLUSION

Our study suggests that aspirin does not have beneficial effects regarding progression to ICU from the medical floors in COVID-19 positive patients. Furthermore, it showed no statistically significant impact in reducing rates of mechanical ventilation, oxygen requirement, or decreasing mortality in patients.

ARTICLE HIGHLIGHTS

Research background

In a retrospective study by Chow *et al*, it was found that aspirin use may be associated with improved outcomes, reduced rates of mechanical ventilation, and decreased intensive care unit (ICU) admissions in hospitalized coronavirus disease 2019 (COVID-19) patients. Given the encouraging findings, the world's largest randomized controlled open-label trial was performed using approximately 15000 patients in the UK (RECOVERY TRIAL). The patients in the study were allocated to receive aspirin after diagnosis of COVID-19 during in-hospital admission, and the results showed no associated reductions in the 28-d mortality or the progression to mechanical ventilation of such patients. With the above

conflicting findings, the present study was designed to evaluate the impact of daily aspirin intake prior to hospitalization on the rate of COVID-19 positive patients' progression to the ICU.

Research motivation

With the never ending COVID-19 pandemic, it is imperative we find ways to keep patients out of the ICU. We have learnt that COVID-19 illness has major thrombotic and inflammatory effects. Aspirin would seem like an ideal choice to curb these effects. With this in mind, we conducted our study. But surprisingly we found that aspirin has no beneficial effects when it comes to preventing severe COVID-19 illness like ICU admissions. We postulate that patients taking aspirin were also older and had significant comorbidities, putting them at high risk for severe COVID-19. Furthermore, this study was carried out back when the most effective treatment modalities like steroids and remdesivir were not used. Hence, we conclude that aspirin's antiviral, anti-inflammatory and anti-thrombotic properties may not be strong enough to combat the COVID-19 illness.

Research objectives

Present study was designed to evaluate the impact of daily aspirin intake prior to hospitalization on the rate of COVID-19 positive patients' progression to the ICU.

Research methods

The idea of using the below methods were modeled after the study by Chow *et al* and the recovery trial on Aspirin in patients admitted to the hospital with COVID-19. Research methods adopted were the following: (1) Categorical variables, such as demographic information, comorbidities, receipt of investigational therapeutics, type of oxygen support, mechanical ventilation need, and outcomes, were reported as the number and percentage of patients and were compared between groups using the χ^2 test. P values < 0.05 were considered statistically significant; and (2) Multinomial logistic regression analysis to control for interplay of confounding from other anti-coagulation agents.

Research results

Our study analyzed 125 patients, of which 38 patients were on daily aspirin use, with a minimum dose of 81 mg. The study showed a significant association of aspirin with variables such as age groups, hypertension, hyperlipidemia, and diabetes mellitus. This insinuated that our aspirin patients were older, and most of them had significant comorbidities, putting them at risk of severe COVID-19 illness. At first glance, aspirin showed a possible protective role in progression to ICU on chi-square analysis. It failed to reach significance in multinomial logistic regression analysis. Furthermore, in terms of mortality, patients on aspirin had a higher mortality rate of 32% as compared to only 25% for non-aspirin users. This could be explained by the fact that patients on aspirin were older and had more comorbidities.

Research conclusions

We conclude that aspirin shows no protective role for COVID-19 patients in terms of progression to ICU, survival outcome, and use of mechanical ventilation. Our findings concurred with the results of the RECOVERY trial**.** The advantage of our study is that it was conducted on the cohort of patients that presented at our hospital during the initial phase of the COVID-19 pandemic back in March of 2020. At that time, the use of corticosteroids and remdesivir were not established as the standard of care, and hence our study is not confounded by the effects of these medications.

Research perspectives

Given the conflicting results of recent studies on aspirin and COVID-19 illness, it would seem beneficial for future studies to study the effect of chronic daily aspirin use on COVID-19 outcomes. Since our N-126, larger studies with N-1000s may be able to show definitive significance between aspirin and COVID-19. In theory, aspirin is an over the counter, cheap medication with a wide range of properties to battle the ill effects of the virus.

FOOTNOTES

Author contributions: Gogtay M contributed to inception of study idea, data collection, statistical interpretations, and manuscript editing and final submission; Singh Y drafting manuscript, assisting with statistics, proof reading and abstract creation; Bullappa A statistical analysis of data; Scott J inception of study idea, proof reading of manuscript and mentor for the study.

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Informed consent statement: Requirement of informed consent was waived by the Saint Vincent- MetroWest Medical

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ORCID number: Maya Gogtay 0000-0001-9955-7121; Yuvaraj Singh 0000-0003-4970-8870; Asha Bullappa 0000-0002-1567-5241; Jeffrey Scott 0000-0002-1416-508X.

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REFERENCES

1 **Wang Y**, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *J Med Virol* 2020; **92**: 568-576 [PMID: 32134116 DOI: 10.1002/jmv.25748]
2 **Russell B**, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? *Ecancermedicalscience* 2020; **14**: 1023 [PMID: 32256706 DOI: 10.3332/ecancer.2020.1023]
3 **Ornelas A**, Zacharias-Millward N, Menter DG, Davis JS, Lichtenberger L, Hawke D, Hawk E, Vilar E, Bhattacharya P, Millward S. Beyond COX-1: the effects of aspirin on platelet biology and potential mechanisms of chemoprevention. *Cancer Metastasis Rev* 2017; **36**: 289-303 [PMID: 28762014 DOI: 10.1007/s10555-017-9675-z]
4 **Huang I**, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. *Ther Adv Respir Dis* 2020; **14**: 1753466620937175 [PMID: 32615866 DOI: 10.1177/1753466620937175]
5 **Lim MA**, Pranata R, Huang I, Yonas E, Soeroto AY, Supriyadi R. Multiorgan Failure With Emphasis on Acute Kidney Injury and Severity of COVID-19: Systematic Review and Meta-Analysis. *Can J Kidney Health Dis* 2020; **7**: 2054358120938573 [PMID: 32685180 DOI: 10.1177/2054358120938573]
6 **Pranata R**, Lim MA, Yonas E, Huang I, Nasution SA, Setiati S, Alwi I, Kuswardhani RAT. Thrombocytopenia as a prognostic marker in COVID-19 patients: diagnostic test accuracy meta-analysis. *Epidemiol Infect* 2021; **149**: e40 [PMID: 33509306 DOI: 10.1017/S0950268821000236]
7 **Barnes GD**, Burnett A, Allen A, Blumenstein M, Clark NP, Cuker A, Dager WE, Deitelzweig SB, Ellsworth S, Garcia D, Kaatz S, Minichiello T. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis* 2020; **50**: 72-81 [PMID: 32440883 DOI: 10.1007/s11239-020-02138-z]
8 **Nishiga M**, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol* 2020; **17**: 543-558 [PMID: 32690910 DOI: 10.1038/s41569-020-0413-9]
9 **Porfidia A**, Pola R. Venous thromboembolism in COVID-19 patients. *J Thromb Haemost* 2020; **18**: 1516-1517 [PMID: 32294289 DOI: 10.1111/jth.14842]
10 **Wichmann D**, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, Heinrich F, Mushumba H, Kniep I, Schröder AS, Burdelski C, de Heer G, Nierhaus A, Frings D, Pfefferle S, Becker H, Bredereke-Wiedling H, de Weerth A, Paschen HR, Sheikhzadeh-Eggers S, Stang A, Schmiedel S, Bokemeyer C, Addo MM, Aepfelbacher M, Püschel K, Kluge S. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med* 2020; **173**: 268-277 [PMID: 32374815 DOI: 10.7326/M20-2003]
11 **Abdelwahab HW**, Shaltout SW, Sayed Ahmed HA, Fouad AM, Merrell E, Riley JB, Salama R, Abdelrahman AG, Darling E, Fadel G, Elfar MSA, Sabry K, Shah J, Amin H, Nieman GF, Mishriky A, Aiash H. Acetylsalicylic Acid Compared with Enoxaparin for the Prevention of Thrombosis and Mechanical Ventilation in COVID-19 Patients: A Retrospective Cohort Study. *Clin Drug Investig* 2021; **41**: 723-732 [PMID: 34328635 DOI: 10.1007/s40261-021-01061-2]
12 **Bianconi V**, Violi F, Fallarino F, Pignatelli P, Sahebkar A, Pirro M. Is Acetylsalicylic Acid a Safe and Potentially Useful Choice for Adult Patients with COVID-19 ? *Drugs* 2020; **80**: 1383-1396 [PMID: 32705604 DOI: 10.1007/s40265-020-01365-1]
13 **Mohamed-Hussein AAR**, Aly KME, Ibrahim MAA. Should aspirin be used for prophylaxis of COVID-19-induced coagulopathy? *Med Hypotheses* 2020; **144**: 109975 [PMID: 32531536 DOI: 10.1016/j.mehy.2020.109975]
14 **Chow JH**, Khanna AK, Kethireddy S, Yamane D, Levine A, Jackson AM, McCurdy MT, Tabatabai A, Kumar G, Park P, Benjenk I, Menaker J, Ahmed N, Glidewell E, Presutto E, Cain S, Haridasa N, Field W, Fowler JG, Trinh D, Johnson KN, Kaur A, Lee A, Sebastian K, Ulrich A, Peña S, Carpenter R, Sudhakar S, Uppal P, Fedeles BT, Sachs A, Dahbour L, Teeter

W, Tanaka K, Galvagno SM, Herr DL, Scalea TM, Mazzeffi MA. Aspirin Use Is Associated With Decreased Mechanical Ventilation, Intensive Care Unit Admission, and In-Hospital Mortality in Hospitalized Patients With Coronavirus Disease 2019. *Anesth Analg* 2021; **132**: 930-941 [PMID: 33093359 DOI: 10.1213/ANE.0000000000005292]

15 **Group RC**, Horby PW, Pessoa-Amorim G, Staplin N, Emberson JR, Campbell M, Spata E, Peto L, Brunskill NJ, Tiberi S, Chew V, Brown T, Tahir H, Ebert B, Chadwick D, Whitehouse T, Sarkar R, Graham C, Baillie JK, Basnyat B, Buch MH, Chappell LC, Day J, Faust SN, Hamers RL, Jaki T, Juszczak E, Jeffery K, Lim WS, Montgomery A, Mumford A, Rowan K, Thwaites G, Mafham M, Haynes R, Landray MJ. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. 2021 [DOI: 10.1101/2021.06.08.21258132]

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ORIGINAL ARTICLE

Observational Study

Association of latitude and altitude with adverse outcomes in patients with COVID-19: The VIRUS registry

Aysun Tekin, Shahraz Qamar, Romil Singh, Vikas Bansal, Mayank Sharma, Allison M LeMahieu, Andrew C Hanson, Phillip J Schulte, Marija Bogojevic, Neha Deo, Simon Zec, Diana J Valencia Morales, Katherine A Belden, Smith F Heavner, Margit Kaufman, Sreekanth Cheruku, Valerie C Danesh, Valerie M Banner-Goodspeed, Catherine A St Hill, Amy B Christie, Syed A Khan, Lynn Retford, Karen Boman, Vishakha K Kumar, John C O'Horo, Juan Pablo Domecq, Allan J Walkey, Ognjen Gajic, Rahul Kashyap, Salim Surani, The Society of Critical Care Medicine (SCCM) Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 Registry Investigator Group

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Aysun Tekin, Romil Singh, Mayank Sharma, Diana J Valencia Morales, Rahul Kashyap, Salim Surani, Department of Anesthesiology, Mayo Clinic, Rochester, MN 55905, United States

Shahraz Qamar, Post-baccalaureate Research Education Program, Mayo Clinic College of Medicine and Science, Rochester, MN 55905, United States

Vikas Bansal, Marija Bogojevic, Simon Zec, John C O'Horo, Ognjen Gajic, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Mayo Clinic, Rochester, MN 55905, United States

Allison M LeMahieu, Andrew C Hanson, Phillip J Schulte, Division of Clinical Trials and Biostatistics, Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN 55905, United States

Neha Deo, Alix School of Medicine, Mayo Clinic, Rochester, MN 55905, United States

Katherine A Belden, Division of Infectious Diseases, Thomas Jefferson University Hospital, Philadelphia, PA 19107, United States

Smith F Heavner, Prisma Health, Greenville, SC 29605, United States

Margit Kaufman, Englewood Health, Englewood, NJ 07631, United States

Sreekanth Cheruku, Divisions of Cardiothoracic Anesthesiology and Critical Care Medicine, Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX 75390, United States

Valerie C Danesh, Center for Applied Health Research, Baylor Scott and White Health, Dallas, TX 75246, United States

Valerie M Banner-Goodspeed, Department of Anesthesiology, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Boston, MA 02215, United States

Catherine A St Hill, Allina Health, Minneapolis, MN 55407, United States

Amy B Christie, Department of Critical Care, Atrium Health Navicent, Macon, GA 31201, United States

Syed A Khan, Division of Critical Care Medicine, Mayo Clinic Health System, Mankato, MN 56001, United States

Lynn Retford, Karen Boman, Vishakha K Kumar, Society of Critical Care Medicine, Mount Prospect, IL 60056, United States

John C O'Horo, Division of Infectious Diseases, Mayo Clinic, Rochester, MN 55905, United States

Juan Pablo Domecq, Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, MN 55905, United States

Allan J Walkey, Pulmonary Center, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Department of Medicine, Evans Center of Implementation and Improvement Sciences, Boston University School of Medicine, Boston, MA 02118, United States

Salim Surani, Department of Pulmonary and Critical Care Medicine, Texas A&M University, Bryan, TX 77807, United States

Corresponding author: Salim Surani, FACP, FCCP, MD, MPH, Doctor, Professor, Department of Pulmonary and Critical Care Medicine, Texas A&M University, 8447 Riverside Pkwy, Bryan, TX 77807, United States. srsurani@hotmail.com

Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) course may be affected by environmental factors. Ecological studies previously suggested a link between climatological factors and COVID-19 fatality rates. However, individual-level impact of these factors has not been thoroughly evaluated yet.

AIM

To study the association of climatological factors related to patient location with unfavorable outcomes in patients.

METHODS

In this observational analysis of the Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study: COVID-19 Registry cohort, the latitudes and altitudes of hospitals were examined as a covariate for mortality within 28 d of admission and the length of hospital stay. Adjusting for baseline parameters and admission date, multivariable regression modeling was utilized. Generalized estimating equations were used to fit the models.

RESULTS

Twenty-two thousand one hundred eight patients from over 20 countries were evaluated. The median age was 62 (interquartile range: 49-74) years, and 54% of the included patients were males. The median age increased with increasing latitude as well as the frequency of comorbidities. Contrarily, the percentage of comorbidities was lower in elevated altitudes. Mortality within 28 d of hospital admission was found to be 25%. The median hospital-free days among all included patients was 20 d. Despite the significant linear relationship between mortality and hospital-free days (adjusted odds ratio (aOR) = 1.39 (1.04, 1.86), P = 0.025 for mortality within 28 d of admission; aOR = -1.47 (-2.60, -0.33), P = 0.011 for hospital-free days), suggesting that adverse patient outcomes were more common in locations further away from the Equator; the results were no longer significant when adjusted for baseline differences (aOR = 1.32 (1.00, 1.74), P = 0.051 for 28-day mortality; aOR = -1.07 (-2.13, -0.01), P = 0.050 for hospital-free days). When we looked at the altitude's effect, we discovered that it demonstrated a non-linear association with mortality within 28 d of hospital admission (aOR =

0.96 (0.62, 1.47), 1.04 (0.92, 1.19), 0.49 (0.22, 0.90), and 0.51 (0.27, 0.98), for the altitude points of 75 MASL, 125 MASL, 400 MASL, and 600 MASL, in comparison to the reference altitude of 148 m.a.s.l, respectively. $P = 0.001$). We detected an association between latitude and 28-day mortality as well as hospital-free days in this worldwide study. When the baseline features were taken into account, however, this did not stay significant.

CONCLUSION

Our findings suggest that differences observed in previous epidemiological studies may be due to ecological fallacy rather than implying a causal relationship at the patient level.

Key Words: 28 d mortality; Altitude; COVID-19; Hospital-free days; Latitude; Outcomes

Core Tip: We detected an association between latitude and mortality within 28 d of admission and hospital-free days in this worldwide study. When the baseline features were taken into account, however, this did not stay significant. Our findings suggest that differences observed in previous epidemiological studies may be due to ecological fallacy rather than implying a causal relationship at the patient level.

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INTRODUCTION

After being identified at the end of 2019, Coronavirus disease 2019 (COVID-19) rapidly disseminated worldwide and affected millions[1,2]. Although studies have shown the efficacy of some medications or the impact of certain conditions on the disease process[3-8], there are still unknown factors that affect the patient outcomes. The investigation of the relationship of disease severity with different environmental settings might provide better insight into the pathogenesis of COVID-19.

A link between climatological factors and Coronavirus Disease 2019 (COVID-19) fatality rates was previously suggested by ecological studies[9-13]. Geographic factors were also demonstrated to impact other respiratory infection processes[14,15]. However, these studies may be subject to the ecological fallacy, in which grouped population-level associations are not observed at the individual level[16]. Large-scale, patient-level cohort studies have thus far not evaluated associations between factors such as altitude and latitude with COVID-19 severity.

The Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 registry[17-19] is a global collaboration of partners from 27 countries that provides a novel resource for the investigation of associations between altitude and latitude, with outcomes of individuals with COVID-19, allowing adjustment for baseline factors to evaluate the relationship between COVID-19 disease severity and geographical factors. Using this large cohort, we targeted to assess the relationship of altitude and latitude with unfavorable patient outcomes.

MATERIALS AND METHODS

This study was conducted on the data collected within the scope of the VIRUS: COVID-19 registry. The project was approved as exempt by the institutional review board at Mayo Clinic (IRB:20-002610). Clinical Trials Database registration number for the registry is NCT04323787.

Study population and data collection

All subjects hospitalized with a COVID-19 associated indication (laboratory-confirmed or clinically diagnosed infection) at participating institutions were eligible for inclusion in the VIRUS: COVID-19

registry[20]. The exclusion criteria for the VIRUS Registry study are non-COVID-19 related admissions, Minnesota patients who have not provided research authorization, and readmissions of already included patients. De-identified data were collected through Research Electronic Data Capture software (REDCap, version 8.11.11, Vanderbilt University, Nashville, Tennessee) and stored in a central database hosted by Mayo Clinic[21].

Regarding the analysis for this particular study, all adult subjects admitted between March 15, 2020, and January 15, 2021, were screened for inclusion. Although enrolled in the VIRUS: COVID-19 registry, we excluded pediatric patients (< 18 years old) from this project. Another exclusion criterion was patients enrolled from institutions reporting fewer than 65% of subjects with hospital discharge status. Since those participating centers were unlikely to represent a realistic distribution of outcomes, they were omitted as non-participating. After the application of exclusion criteria, patients of 143 participating hospitals in 21 countries were found to be eligible for inclusion. Detailed inclusion and exclusion criteria for the VIRUS Registry and this project is provided in Supplementary Figure 1.

The patients' residential addresses at the time of diagnosis were not accessible due to the de-identified database. As a surrogate, the location of the participating institutions, which was available for all enrolled patients, was used to determine geographical variables. Latitude and altitude information was retrieved from the Google Earth software[22]. Based on their locations, subjects were grouped according to the elevation above the sea level and the distance from the Equator, regardless of the hemisphere of location[23,24]. Baseline information and disease-related specifics were gathered from the VIRUS Registry.

Outcome of interest

The primary outcome was mortality within 28 d of admission, and the secondary outcome was length of hospital stay. The variable "hospital-free days" (HFD) was used to analyze the impact on hospital length of stay[25], calculated by subtracting the number of admission days from 28; which was 0 for patients who died in the hospital or stayed in the hospital for longer than 28 d. Both outcomes were evaluated independently.

Statistical analyses

The statistical methodology was reviewed by our co-authors from the Division of Clinical Trials and Biostatistics, Department of Quantitative Health Sciences, Mayo Clinic, Rochester.

The median and interquartile range (IQR) were used to summarize continuous data. Categorical variables were reported as numbers and percentages. Unadjusted and multivariable-adjusted logistic regression assessed the association with outcomes. To account for the clustering of patients within sites, models were fitted using generalized estimating equations using an exchangeable working correlation for individual hospitals. When the results indicated a non-linear functional structure, they were graphically summarized using the restricted cubic spline fit; otherwise, the linear relationship was defined. Age, gender, race, body mass index, number of days with symptoms prior to admission, symptom groups, the timing of admission with regards to the start of the pandemic, and comorbidities were factored into the models. Unadjusted and multivariable linear regression models assessed the association with HFD using a similar approach. Odds ratios (OR) and 95% confidence intervals for the mortality endpoint were determined per 10-degrees of latitude and 250-meters of altitude in relation to the median reference points, *i.e.*, 39° and 148 meters above sea-level (MASL), respectively. For HFD, the estimate is the expected difference in mean days, similarly displayed per 10 degrees of latitude and 250 meters of altitude.

For missing data among included institutions and patients, multiple imputations assuming data were missing at random using fully conditional specification with 100 imputations was used to impute missing covariates or outcomes. Analyses were performed on each dataset, and results combined to reflect uncertainty due to missingness. Without correcting for multiplicity related to testing the outcomes or testing both altitude and latitude in regression models, statistical significance was specified as $P < 0.05$.

RESULTS

After exclusion of "non-participating sites," 23210 patients with complete data enrolled in the VIRUS registry were evaluated. Among those, 22108 met eligibility criteria after excluding pediatric patients (Supplementary Figure 2, Supplementary Table 1). The median age was 62 (IQR 49-74) years, with 54% males. Among the subjects, 51% of the included were White, 26% were Black, and 65% of the patients were non-Hispanic; 86% had at least one comorbid condition, hypertension (46%) being the most prevalent. When baseline data were analyzed within latitude and altitude groups, patients were more often older on high-latitude locations (locations farther from the Equator). The frequency of patients with comorbidities and the proportion of females also increased with latitude. At higher altitudes, however, females and patients with comorbidities were less prevalent (Table 1).

Table 1 Baseline characteristics and their distribution to latitude and altitudes

Variables	Total (*n* = 22108)	Latitude				Altitude		
		0-15° (*n* = 589)	16-30° (*n* = 1961)	31-45° (*n* = 19163)	46-60° (*n* = 395)	< 500 MASL (*n* = 21122)	500 - 1000 MASL (*n* = 765)	> 1000 MASL (*n* = 221)
Age, median, IQR	62 (49-74)	50 (36-62)	59 (47-70)	62 (49-74)	72 (59-83)	62 (59-74)	58 (46-69)	60 (49-71)
Gender								
Female	9804 (44%)	198 (34%)	797 (41%)	8626 (46%)	183 (46%)	9476 (45%)	255 (33%)	73 (33%)
Male	12025 (54%)	391 (66%)	1163 (59%)	10259 (54%)	212 (54%)	11367 (55%)	510 (67%)	148 (67%)
Race								
White	11210 (51%)	2 (0%)	471 (24%)	10449 (55%)	288 (73%)	10928 (52%)	227 (30%)	55 (25%)
African American	5757 (26%)	74 (13%)	505 (26%)	5145 (27%)	33 (8%)	5738 (27%)	17 (2%)	2 (1%)
Mixed race	785 (4%)	164 (28%)	119 (6%)	501 (3%)	1 (0%)	524 (2%)	129 (17%)	132 (60%)
Asian American	416 (2%)	-	9 (0%)	398 (2%)	9 (2%)	412 (2%)	4 (1%)	0 (0%)
Others	3940 (18%)	349 (59%)	857 (44%)	2670 (14%)	61 (15%)	3122 (15%)	371 (48%)	32 (1%)
Ethnicity								
Hispanic	4592 (21%)	88 (15%)	313 (16%)	4185 (22%)	6 (2%)	4322 (20%)	197 (26%)	73 (33%)
Non-Hispanic	14411 (65%)	354 (60%)	1250 (64%)	12571 (66%)	236 (60%)	14073 (67%)	281 (37%)	57 (26%)
BMI	29.0 (25, 35)	26.7 (24, 28)	28.0 (25, 34)	29.3 (25, 35)	26.7 (23, 32)	29.0 (25, 35)	28.6 (26, 33)	28 (26, 32)
Comorbidities (any)	18991 (86%)	295 (50%)	1580 (81%)	16753 (87%)	363 (92%)	18262 (86%)	578 (76%)	151 (68%)
Hypertension	10267 (46%)	191 (32%)	1050 (54%)	8785 (46%)	241 (61%)	9865 (47%)	322 (42%)	80 (36%)
Diabetes	6473 (29%)	134 (23%)	738 (38%)	5474 (29%)	127 (32%)	6163 (29%)	256 (33%)	54 (24%)
Coronary artery disease	4124 (19%)	29 (5%)	338 (17%)	3678 (19%)	79 (20%)	4017 (19%)	87 (11%)	20 (9%)
Obesity	3794 (17%)	34 (6%)	394 (20%)	3304 (17%)	62 (16%)	3640 (17%)	125 (16%)	29 (13%)
Dyslipidemia	3521 (16%)	7 (1%)	315 (16%)	3168 (17%)	31 (8%)	3422 (16%)	87 (11%)	12 (5%)
Chronic kidney disease	2609 (12%)	5 (1%)	233 (12%)	2295 (12%)	76 (19%)	2543 (12%)	56 (7%)	10 (5%)

BMI: Body mass index; IQR: Interquartile range; MASL: Meters above sea level.

A total of 3451 patients (25% of 13,959 patients with mortality data available) died within 28 d following admission. The median HFD for the general study population was 20 (IQR 3.0-24.0) days. The 28-day mortality rate was higher in higher-latitude locations. Mortality rates were also higher for patients hospitalized in higher altitudes. Additionally, the median HFD was lower for higher latitude and altitude levels (Figure 1).

The unadjusted analysis showed a significant linear association of higher latitude locations associated with increased mortality (OR = 1.39, 95%CI = 1.04, 1.86, P = 0.025) and lower number of HFD (Estimate = -1.47, 95%CI = -2.60, -0.33, P = 0.011) per 10 (degree) latitude. However, after adjustment to the baseline characteristics, there was insufficient evidence to indicate a significant association with both outcomes (adjusted OR (aOR) = 1.32, 95%CI = 1.00, 1.74, P = 0.051 for mortality, and adjusted Estimate = -1.07, 95%CI = -2.13, -0.01, P = 0.050 for HFD) (Table 2).

When evaluating the impact of higher altitudes on adverse outcomes, there was a non-linear association with mortality, which remained significant after adjustment (aOR and 95%CIs for the altitude points of 400 MASL and 600 MASL, compared to the reference altitude of 148 MASL were 0.49 (0.22, 0.90), and 0.51 (0.27,0.98), respectively, P = 0.017) (Table 2). The odds of fatal disease course slightly increased at altitude levels between 125 and 145 MASL; decreased to the lowest around the altitude of 350 MASL, and gradually increased after that point with the increasing altitude (Figure 1C). No association was present with HFD and altitude levels either before or after adjustment.

Table 2 Comparison of outcomes according to latitude and altitudes

Study outcomes	Latitude						Altitude					
	Unadjusted			Adjusted			Unadjusted			Adjusted		
	Estimate	95%CI	*P* value	Estimate	95%CI	*P* value	Estimate	95%CI	*P* value	Estimate	95%CI	*P* value
28 d mortality	1.39	(1.04, 1.86)	0.025	1.32	(1.00, 1.74)	0.051	RCS, *P* value non-linearity ≤ 0.001, *P* value overall association = 0.001			RCS, *P* value non-linearity = 0.049, *P* value overall association = 0.017		
Hospital-free days	-1.47	(-2.60, -0.33)	0.011	-1.07	(-2.13, -0.01)	0.050	0.14	(-0.37, 0.64)	0.587	0.10	(0.37, 0.56)	0.683

For the altitude points of 75 MASL, 125 MASL, 400 MASL, and 600 MASL, compared to the reference altitude of 148 MASL; the adjusted odds ratios and 95%CIs regarding 28 d mortality were 0.96 (0.62,1.47), 1.04 (0.92,1.19), 0.49 (0.22, 0.90), and 0.51 (0.27, 0.98), respectively. CI: Confidence interval; ICU: Intensive care unit; MASL: Meters above sea level; RCS: Restricted cubic spline.

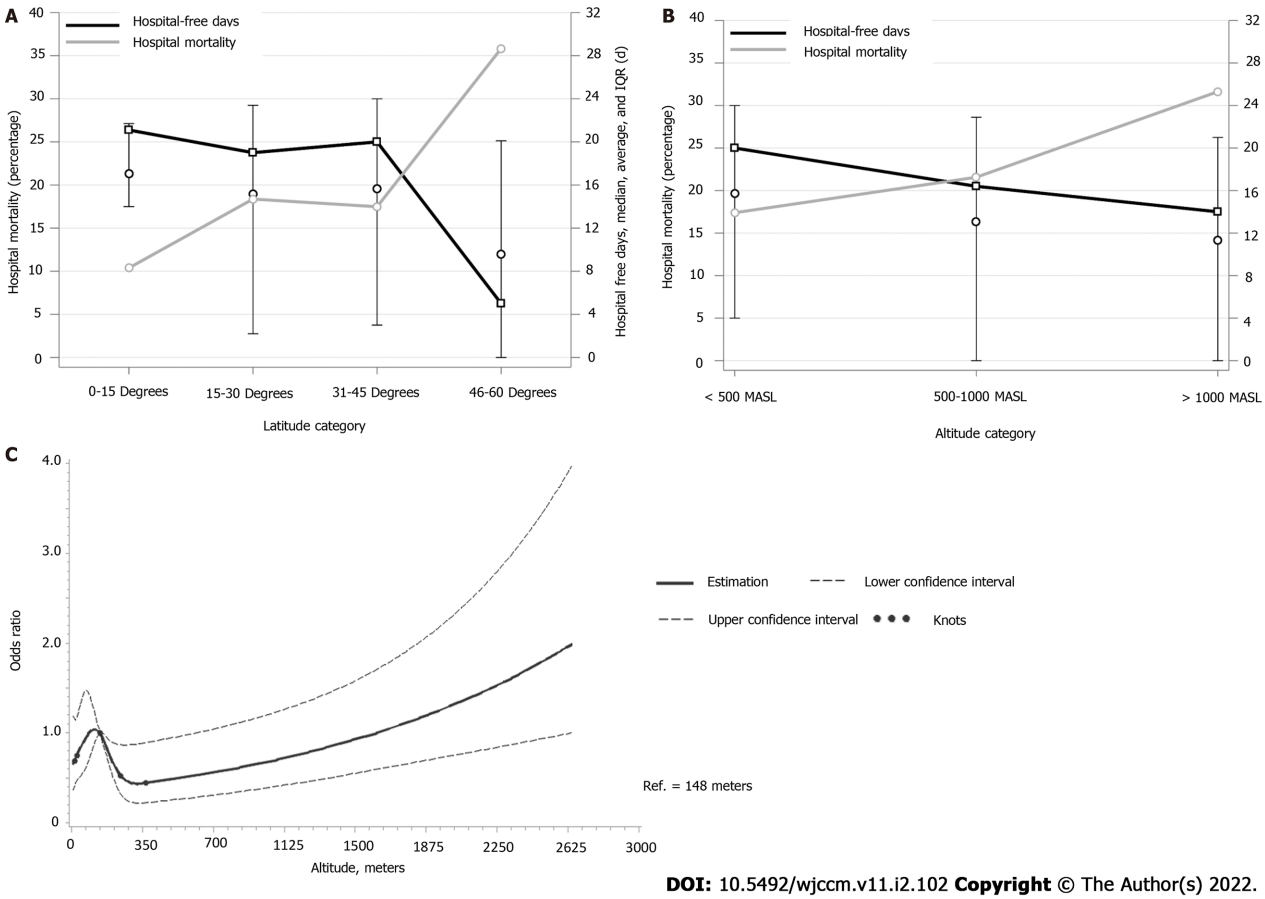

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Figure 1 Distribution of outcomes and adjusted associations to different altitude and latitude levels. A: Outcomes and latitude; B: Outcomes and altitude; C: Adjusted associations between 28 d mortality with altitude, shown using restricted cubic spline with 5 knots. IQR: Interquartile range; MASL: Meters above sea level.

DISCUSSION

We reported the distribution of patient outcomes to different altitudes and latitudes within an international COVID-19 registry. In our study, even though 28-day mortality increased and the number of HFD decreased in high-latitude locations on unadjusted estimates, the associations were not significant after adjustment for patients' characteristics. In the adjusted model, the odds of mortality were associated with altitude, gradually increasing after 350 MASL.

Older age and certain comorbidities were shown to be associated with unfavorable disease outcomes for COVID-19 patients[26,27]. Populations living in higher latitudes were shown to have a higher median age and more frequent comorbid conditions[28]. Furthermore, individuals living at higher elevations from the sea level were shown to have less comorbidity burdens[12]. Our study sample also noted a similar distribution of median age and comorbidities to different latitude and altitude levels.

Prior studies suggested that the variation of mortality rates in different latitude settings was partly attributable to baseline characteristics of populations[32,33]. However, others detected a relationship between humidity or sunlight exposure and case rates, which was thought to be related to viral dynamics[11,34]. In this study, the association of mortality within 28 d of admission and HFD with latitude, although statistically significant in the unadjusted analysis, was not statistically significant after case-mix adjustment. Our findings indicate that differences observed in previous epidemiological studies may be due to ecological fallacy rather than implying a causal relationship with environmental factors at the individual level[16].

Studies evaluating the impact of altitude on case and fatality rates of COVID-19 illustrated that higher altitude had a protective effect, possibly due to physiological and habitual characteristics of the individuals and environmental factors impacting virus survival[12,35]. Conversely, in our study, mortality gradually increased with increasing altitude after 350 MASL, suggesting the impact of environmental hypoxia resulting in the fragility of pulmonary functions or coagulation disorders. Although our results might suggest an impact of different elevation levels on disease outcomes, not having enough variation in altitude to test the impact of atmospheric oxygen pressure impedes our ability to conclude the actual effect of higher altitudes. Thus, our analysis results should be interpreted with caution.

Studies that evaluated the effects of latitude and altitude in patients with COVID-19 were epidemiological investigations that were conducted on populations rather than on individual patients. Thus, they are subject to the bias of aggregated variables rather than providing insight for a causal relationship[16]. This is the first study to evade ecological fallacy by considering individual baseline characteristics to the best of our knowledge. Thus, it might provide a better insight into the causal effect of environmental factors on adverse outcomes.

The most important limitation was the small sample variety in lower latitude and higher altitude environments. Especially not having patients from a wide range of altitude levels precluded drawing definitive conclusions about the impact of higher altitudes. Another limitation is being conducted exclusively on hospitalized patients, which might subject our results to collider bias[36]. Although our outcomes of interest might have ameliorated this limitation's impact, it still hampers the generalizability of our results. Additionally, variations in patient management among different regions might have an impact on our results. Another weakness of our analysis is the lack of information about patients' home location (exempt IRB only allowed de-identified data use) and institutions' geographical locations as a surrogate. However, travel restrictions imposed during the study period might have kept patients confined to their primary residence and resultant nearby hospital admissions. Furthermore, although it was suggested as a contributor to disease severity, especially in higher latitudes, vitamin D levels were not incorporated in the analysis due to the unavailability. However, the timing of the study encompassing enough sunlight hours for the Northern Hemisphere might mitigate this limitation's impact. Also, the number of patients included from the countries outside of the United States was limited. Moreover, to increase the accuracy of the frequency measurement, several institutions were not included in the study due to incomplete data variables.

CONCLUSION

Although 28 d mortality and HFD seemed to be associated with latitude, the association did not remain significant after adjustment. Our results might indicate that reported variations in COVID-19 in different environmental conditions might be based on individual patient characteristics rather than geographic factors.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) has taken the world by storm. Several factors were attributed to the spread of the virus including altitude and latitude. We studied the relationship of location with unfavorable patient outcomes in COVID-19.

Research motivation

There were variations in the case and fatality rates in different regions of the world. Using a large cohort, we aimed to assess if latitude or altitude had an impact on the disease course of the COVID-19

on the individual patient level.

Research objectives

To study the association of certain aspects of location with unfavorable outcomes in COVID-19.

Research methods

An observational study using the Virus COVID-19 Registry was used to analyze for mortality within 28 d of admission and hospital length of stay. Adjusting for baseline parameters and admission date, multivariable regression modeling was utilized.

Research results

Twenty-two thousand one hundred eight patients from 21 countries were included. Mortality within 28 d of hospital admission was found to be 25%. The median number of hospital-free days among all included patients was 20 days. Despite the linear association between mortality within 28 d of hospital admission and hospital-free days and increasing latitude being significant, indicating that adverse disease outcomes were more frequent in locations further away from the Equator, the association was not significant after adjusting for baseline characteristics. A non-linear association between altitude and 28-day mortality was seen.

Research conclusions

There seemed to be an association of latitude with mortality within 28 d of admission and hospital-free days, which was nonsignificant when adjusted for baseline characteristics.

Research perspectives

The differences observed in previous epidemiological studies may be due to ecological fallacy rather than implying a causal relationship with environmental factors at the individual level.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Aysun Tekin 0000-0002-1891-2118; Shahraz Qamar 0000-0002-9097-0443; Romil Singh 0000-0003-3777-5670; Vikas Bansal 0000-0001-6047-5559; Mayank Sharma 0000-0001-7808-9912; Allison LeMahieu 0000-0003-1554-795X; Andrew C Hanson 0000-0003-4673-5486; Phillip J Schulte 0000-0001-6575-4741; Marija Bogojevic 0000-0001-5460-3753; Neha Deo 0000-0002-0583-8916; Simon Zec 0000-0002-4353-8535; Diana J Valencia Morales 0000-0001-8835-9541; Katherine A Belden 0000-0002-2556-3083; Smith F Heavner 0000-0003-0912-0407; Margit Kaufman 0000-0003-4535-6214; Sreekanth Cheruku 0000-0003-3185-0000; Valerie C Danesh 0000-0002-2078-2578; Valerie M Banner-Goodspeed 0000-0002-7644-2521; Catherine A St Hill 0000-0002-6113-5705; Amy B Christie 0000-0001-9100-7045; Syed A Khan 0000-0002-2452-2079; Lynn Retford 0000-0002-1618-7063; Karen Boman 0000-0001-6864-2569; Vishakha K Kumar 0000-0003-4998-5114; John C O'Horo 0000-0002-0880-4498; Juan Pablo Domecq 0000-0002-8540-9862; Allan J Walkey 0000-0003-4685-6894; Ognjen Gajic 0000-0003-4218-0890; Rahul Kashyap 0000-0002-4383-3411; Salim Surani 0000-0001-7105-4266; The Society of Critical Care Medicine (SCCM) Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 Registry Investigator Group 0000-0000-0000-0000.

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REFERENCES

1 **WHO**. Novel coronavirus china: World Health Organization; 2020. [cited 29 November 2020]. Available from: https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/
2 **WHO**. Who director-general's opening remarks at the media briefing on COVID-19. [cited 11 March 2020]. World Health Organization; 2020 [DOI: 10.1093/ww/9780199540884.013.u23682]
3 **Bansal V**, Mahapure KS, Bhurwal A, Gupta I, Hassanain S, Makadia J, Madas N, Armaly P, Singh R, Mehra I, O'Horo JC, Kashyap R. Mortality Benefit of Remdesivir in COVID-19: A Systematic Review and Meta-Analysis. *Front Med (Lausanne)* 2020; **7**: 606429 [PMID: 33585508 DOI: 10.3389/fmed.2020.606429]
4 **Menon T**, Sharma R, Kataria S, Sardar S, Adhikari R, Tousif S, Khan H, Rathore SS, Singh R, Ahmed Z. The Association of Acute Kidney Injury With Disease Severity and Mortality in COVID-19: A Systematic Review and Meta-Analysis. *Cureus* 2021; **13**: e13894 [PMID: 33880250 DOI: 10.7759/cureus.13894]
5 **Bansal V**, Mahapure KS, Mehra I, Bhurwal A, Tekin A, Singh R, Gupta I, Rathore SS, Khan H, Deshpande S, Gulati S, Armaly P, Sheraton M, Kashyap R. Mortality Benefit of Convalescent Plasma in COVID-19: A Systematic Review and Meta-Analysis. *Front Med (Lausanne)* 2021; **8**: 624924 [PMID: 33898477 DOI: 10.3389/fmed.2021.624924]
6 **Singh R**, Shaik L, Mehra I, Kashyap R, Surani S. Novel and Controversial Therapies in COVID-19. *Open Respir Med J* 2020; **14**: 79-86 [PMID: 33717367 DOI: 10.2174/1874306402014010079]
7 **Singh R**, Rathore SS, Khan H, Bhurwal A, Sheraton M, Ghosh P, Anand S, Makadia J, Ayesha F, Mahapure KS, Mehra I, Tekin A, Kashyap R, Bansal V. Mortality and Severity in COVID-19 Patients on ACEIs and ARBs-A Systematic Review, Meta-Analysis, and Meta-Regression Analysis. *Front Med (Lausanne)* 2021; **8**: 703661 [PMID: 35083229 DOI: 10.3389/fmed.2021.703661]
8 **Singh R**, Rathore SS, Khan H, Karale S, Bhurwal A, Tekin A, Jain N, Mehra I, Anand S, Reddy S, Sidhu GS, Panagopoulos A, Pattan V, Kashyap R, Bansal V. Association of obesity with covid-19 severity and mortality: A systemic review and meta-regression [DOI: 10.1101/2021.05.08.21256845]
9 **Rhodes JM**, Subramanian S, Laird E, Kenny RA. Editorial: Low population mortality from covid-19 in countries south of latitude 35 degrees north supports vitamin d as a factor determining severity. *Alimentary Pharmacology & Therapeutics* 2020; **51**: 1434 [DOI: 10.1111/apt.15777]
10 **Sajadi MM**, Habibzadeh P, Vintzileos A, Shokouhi S, Miralles-Wilhelm F, Amoroso A. Temperature, Humidity, and Latitude Analysis to Estimate Potential Spread and Seasonality of Coronavirus Disease 2019 (COVID-19). *JAMA Netw Open* 2020; **3**: e2011834 [PMID: 32525550 DOI: 10.1001/jamanetworkopen.2020.11834]
11 **Sehra ST**, Salciccioli JD, Wiebe DJ, Fundin S, Baker JF. Maximum Daily Temperature, Precipitation, Ultraviolet Light, and Rates of Transmission of Severe Acute Respiratory Syndrome Coronavirus 2 in the United States. *Clin Infect Dis* 2020; **71**: 2482-2487 [PMID: 32472936 DOI: 10.1093/cid/ciaa681]
12 **Srivastava S**, Garg I, Bansal A, Kumar B. SARS-CoV-2 infection: physiological and environmental gift factors at high altitude. *Virusdisease* 2020; 1-3 [PMID: 32953947 DOI: 10.1007/s13337-020-00626-7]
13 **Liu N**, Li H. Letter: population mortality from COVID-19 and latitude-data from China. *Aliment Pharmacol Ther* 2020; **52**: 1259-1260 [PMID: 33016550 DOI: 10.1111/apt.16048]
14 **Choudhuri JA**, Ogden LG, Ruttenber AJ, Thomas DS, Todd JK, Simoes EA. Effect of altitude on hospitalizations for respiratory syncytial virus infection. *Pediatrics* 2006; **117**: 349-356 [PMID: 16452353 DOI: 10.1542/peds.2004-2795]
15 **Bloom-Feshbach K**, Alonso WJ, Charu V, Tamerius J, Simonsen L, Miller MA, Viboud C. Latitudinal variations in seasonal activity of influenza and respiratory syncytial virus (RSV): a global comparative review. *PLoS One* 2013; **8**: e54445 [PMID: 23457451 DOI: 10.1371/journal.pone.0054445]
16 **Loney T**, Nagelkerke NJ. The individualistic fallacy, ecological studies and instrumental variables: a causal interpretation. *Emerg Themes Epidemiol* 2014; **11**: 18 [PMID: 25745504 DOI: 10.1186/1742-7622-11-18]
17 **Domecq JP**, Lal A, Sheldrick CR, Kumar VK, Boman K, Bolesta S, Bansal V, Harhay MO, Garcia MA, Kaufman M, Danesh V, Cheruku S, Banner-Goodspeed VM, Anderson HLI, Milligan PS, Denson JL, St. Hill CA, Dodd KW, Martin GS, Gajic O, Walkey AJ, Kashyap R. Outcomes of patients with coronavirus disease 2019 receiving organ support therapies: The international viral infection and respiratory illness universal study registry. *Critical Care Medicine* 2021; **49**: 437 [DOI: 10.1097/ccm.0000000000004879]
18 **Walkey AJ**, Kumar VK, Harhay MO, Bolesta S, Bansal V, Gajic O, Kashyap R. The Viral Infection and Respiratory Illness Universal Study (VIRUS): An International Registry of Coronavirus 2019-Related Critical Illness. *Crit Care Explor* 2020; **2**: e0113 [PMID: 32426754 DOI: 10.1097/CCE.0000000000000113]
19 **Walkey AJ**, Sheldrick RC, Kashyap R, Kumar VK, Boman K, Bolesta S, Zampieri FG, Bansal V, Harhay MO, Gajic O. Guiding Principles for the Conduct of Observational Critical Care Research for Coronavirus Disease 2019 Pandemics and Beyond: The Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study Registry. *Crit Care Med* 2020; **48**: e1038-e1044 [PMID: 32932348 DOI: 10.1097/CCM.0000000000004572]
20 **Turek J**, Bansal V, Tekin A, Sharma M, Bogojevic M, Deo N, Qamar S, Singh R, Kashyap R. Rapid project management in a time of covid-19 crisis: Lessons learned from a global virus: Covid-19 registry (preprint) 2021 [DOI: 10.2196/preprints.27921]
21 **Harris PA**, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;

42: 377-381 [PMID: 18929686 DOI: 10.1016/j.jbi.2008.08.010]
22 **Keyhole I**. Artographer Google earth: Google, 2001 [DOI: 10.5040/9781501300325.ch-002]
23 **Lu C**, Yu Y, Li L, Yu C, Xu P. Systematic review of the relationship of Helicobacter pylori infection with geographical latitude, average annual temperature and average daily sunshine. *BMC Gastroenterol* 2018; **18**: 50 [PMID: 29665777 DOI: 10.1186/s12876-018-0779-x]
24 **Arias-Reyes C**, Zubieta-DeUrioste N, Poma-Machicao L, Aliaga-Raduan F, Carvajal-Rodriguez F, Dutschmann M, Schneider-Gasser EM, Zubieta-Calleja G, Soliz J. Does the pathogenesis of SARS-CoV-2 virus decrease at high-altitude? *Respir Physiol Neurobiol* 2020; **277**: 103443 [PMID: 32333993 DOI: 10.1016/j.resp.2020.103443]
25 **Ely EW**, Angus DC, Williams MD, Bates B, Qualy R, Bernard GR. Drotrecogin alfa (activated) treatment of older patients with severe sepsis. *Clin Infect Dis* 2003; **37**: 187-195 [PMID: 12856210 DOI: 10.1086/375775]
26 **Clift AK**, Coupland CAC, Keogh RH, Diaz-Ordaz K, Williamson E, Harrison EM, Hayward A, Hemingway H, Horby P, Mehta N, Benger J, Khunti K, Spiegelhalter D, Sheikh A, Valabhji J, Lyons RA, Robson J, Semple MG, Kee F, Johnson P, Jebb S, Williams T, Hippisley-Cox J. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. *BMJ* 2020; **371**: m3731 [PMID: 33082154 DOI: 10.1136/bmj.m3731]
27 **Chow DS**, Glavis-Bloom J, Soun JE, Weinberg B, Loveless TB, Xie X, Mutasa S, Monuki E, Park JI, Bota D, Wu J, Thompson L, Boden-Albala B, Khan S, Amin AN, Chang PD. Development and external validation of a prognostic tool for COVID-19 critical disease. *PLoS One* 2020; **15**: e0242953 [PMID: 33296357 DOI: 10.1371/journal.pone.0242953]
28 **Ouchetto O**, Bourhanbour AD. Risk factors for mortality of covid-19 patients [DOI: 10.1101/2020.07.02.20145375]
29 **Holtgrave DR**, Barranco MA, Tesoriero JM, Blog DS, Rosenberg ES. Assessing racial and ethnic disparities using a COVID-19 outcomes continuum for New York State. *Ann Epidemiol* 2020; **48**: 9-14 [PMID: 32723697 DOI: 10.1016/j.annepidem.2020.06.010]
30 **Sili U**, Ay P, Topuzoglu A, Bilgin H, Tigen ET, Sengel BE, Caglayik DY, Balcan B, Kocakaya D, Yildizeli SO, Gul F, Bilgili B, Sarinoglu RC, Yagci AK, Durmusoglu LM, Eryuksel E, Odabasi Z, Direskeneli H, Karakurt S, Cinel I, Korten V. Factors associated with progression to critical illness in 28 d among covid-19 patients: Results from a tertiary care hospital in Istanbul, Turkey [DOI: 10.1101/2020.10.09.20209775]
31 **Petrilli CM**, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, Tobin KA, Cerfolio RJ, Francois F, Horwitz LI. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020; **369**: m1966 [PMID: 32444366 DOI: 10.1136/bmj.m1966]
32 **Ouchetto O**, Drissi Bourhanbour A. Risk Factors of COVID-19 Patients. *Disaster Med Public Health Prep* 2021; 1-3 [DOI: 10.1017/dmp.2021.7]
33 **Endailalu TB**, Hadgu FW. Trends of sars-cov-2 infection worldwide: Role of population density, age structure, and climate on transmission and case fatality [DOI: 10.1101/2020.05.20.20104257]
34 **Herman J**, Biegel B, Huang L. Inactivation times from 290 to 315 nm uvb in sunlight for sars coronaviruses cov and cov-2 using omi satellite data for the sunlit earth. Air Quality, Atmosphere & Health, 2020 [DOI: 10.1007/s11869-020-00927-2]
35 **Arias-Reyes C**, Carvajal-Rodriguez F, Poma-Machicao L, Aliaga-Raduán F, Marques DA, Zubieta-DeUrioste N, Accinelli RA, Schneider-Gasser EM, Zubieta-Calleja G, Dutschmann M, Soliz J. Decreased incidence, virus transmission capacity, and severity of COVID-19 at altitude on the American continent. *PLoS One* 2021; **16**: e0237294 [PMID: 33780470 DOI: 10.1371/journal.pone.0237294]
36 **Griffith GJ**, Morris TT, Tudball MJ, Herbert A, Mancano G, Pike L, Sharp GC, Sterne J, Palmer TM, Davey Smith G, Tilling K, Zuccolo L, Davies NM, Hemani G. Collider bias undermines our understanding of COVID-19 disease risk and severity. *Nat Commun* 2020; **11**: 5749 [PMID: 33184277 DOI: 10.1038/s41467-020-19478-2]

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LETTER TO THE EDITOR

Potential role of vitamin D in patients with diabetes, dyslipidaemia, and COVID-19

Ming-Ke Wang, Xue-Lu Yu, Li-Yun Zhou, Hong-Mei Si, Ju-Fen Hui, Ji-Shun Yang

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Ming-Ke Wang, Xue-Lu Yu, Li-Yun Zhou, Hong-Mei Si, Ju-Fen Hui, Department of Disease Control and Prevention, Naval Medical Center of PLA, Naval Medical University, Shanghai 200052, China

Ji-Shun Yang, Medical Care Center, Naval Medical Center of PLA, Naval Medical University, Shanghai 200052, China

Corresponding author: Ji-Shun Yang, MD, PhD, Director, Medical Care Center, Naval Medical Center of PLA, Naval Medical University, No. 338 Huaihai West Road, Shanghai 200052, China. jasunyang@foxmail.com

Abstract

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 has become a worldwide public health crisis. Studies have demonstrated that diabetes and dyslipidaemia are common comorbidities and could be high-risk factors for severe COVID-19. Vitamin D, a group of fat-soluble compounds responsible for intestinal absorption of calcium, magnesium, and phosphate, has been widely used as a dietary supplement for the prevention and treatment of numerous diseases, including infectious and non-infectious diseases, due to its high cost-effectiveness; safety; tolerability; and anti-thrombotic, anti-inflammatory, antiviral, and immunomodulatory properties. In this letter to the editor, we mainly discuss the potential role of vitamin D in patients with diabetes, dyslipidaemia, and COVID-19.

Key Words: Coronavirus disease 2019; Severe acute respiratory syndrome coronavirus-2; Vitamin D; Diabetes; Dyslipidaemia

Core Tip: Diabetes and dyslipidaemia are common comorbidities in patients with coronavirus disease 2019 (COVID-19), and these comorbidities are often associated with worse clinical outcome. In this letter to the editor, we hypothesize that vitamin D may be a prognostic factor and could be a promising preventive measure and treatment for patients with diabetes, dyslipidaemia, and COVID-19.

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TO THE EDITOR

We read with great interest the recent article by Iglesias *et al*[1] entitled "Retrospective analysis of anti-inflammatory therapies during the first wave of coronavirus disease 2019 (COVID-19) at a community hospital", which demonstrated the survival benefit associated with anti-inflammatory therapy with glucocorticoids and revealed that combination treatment with tocilizumab and glucocorticoids could provide the most benefit in critically ill patients with COVID-19 caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). However, monotherapy with tocilizumab as an interleukin 6 (IL-6) antagonist was not associated with an increase in survival among critically ill patients with COVID-19, which could be explained by the fact that tocilizumab non-selectively blocks both anti-inflammatory and pro-inflammatory actions of IL-6[2]. Meanwhile, vitamin D, a group of fat-soluble compounds, may have advantages over tocilizumab as an IL-6 immunomodulator by potentially reducing the pro-inflammatory effects, but avoiding the deleterious effects on the anti-inflammatory actions of IL-6 in patients with COVID-19[2]. Additionally, vitamin D could modulate the innate and adaptive immune responses, and its deficiency is associated with increased morbidity and mortality in SARS-CoV-2 infection[3]. Vitamin D status may be a potential predictor of COVID-19 outcomes, and vitamin D supplementation could be a promising therapeutic and preventive method against COVID-19, due to its high cost-effectiveness; safety; tolerability; and anti-thrombotic, anti-inflammatory, antiviral, and immunomodulatory properties[3,4].

Another published article in your journal by Gkoufa *et al*[5] entitled "Elderly adults with COVID-19 admitted to intensive care unit: A narrative review" found that diabetes and hypercholesterolemia were common comorbidities in older patients with COVID-19 and these comorbidities were often associated with worse clinical outcome. Previous studies also showed that vitamin D deficiency was associated with diabetes and dyslipidaemia[6,7]. Unfortunately, about 30%-50% of people in the world have vitamin D deficiency or insufficiency, and vitamin D deficiency has been a global health problem[8]. Singh *et al*[3] reviewed the evidence of vitamin D deficiency in patients with diabetes and COVID-19, and they proposed that diabetes increased the tendency for infection and COVID-19, vitamin D deficiency was linked to both diabetes and an increased risk of infections, including COVID-19, and vitamin D supplementation may be a safe, cheap, and simple adjuvant therapy in patients with diabetes and COVID-19. Verdoia *et al*[4] reviewed the mechanisms of action of vitamin D and its potential interaction with SARS-CoV-2 infection, and they reported that vitamin D plays an important protective role in the cardiovascular system, immune system, respiratory system, and glucose-lipid metabolism. Therefore, we hypothesize that vitamin D status has prognostic significance in diabetes and dyslipidaemia, and vitamin D supplementation could exert a triple preventive and therapeutic effect in patients with diabetes, dyslipidaemia, and COVID-19.

In summary, diabetes and dyslipidaemia are common comorbidities in patients with COVID-19. Patients with diabetes and dyslipidaemia are more prone to SARS-CoV-2 infection, and they have poor clinical outcomes. Vitamin D may be a potential prognostic factor and could be a promising preventive measure and treatment for patients with diabetes, dyslipidaemia, and COVID-19. Notably, hypervitaminosis D is a rare but potentially serious condition, and it should be avoided when recommending fat-soluble vitamin D supplementation in the era of COVID-19[9]. Certainly, more robust studies are still required to ascertain the prognostic significance and one-arrow three-vulture effect of vitamin D in patients with diabetes, dyslipidaemia, and COVID-19.

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Country/Territory of origin: China

ORCID number: Ming-Ke Wang 0000-0001-9918-0491; Xue-Lu Yu 0000-0002-8527-2093; Li-Yun Zhou 0000-0003-1413-8679; Hong-Mei Si 0000-0003-1175-6594; Ju-Fen Hui 0000-0001-7816-0635; Ji-Shun Yang 0000-0001-7160-706X.

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REFERENCES

1 **Iglesias JI**, Vassallo AV, Sullivan JB, Elbaga Y, Patel VV, Patel N, Ayad L, Benson P, Pittiglio M, Gobran E, Clark A, Khan W, Damalas K, Mohan R, Singh SP. Retrospective analysis of anti-inflammatory therapies during the first wave of COVID-19 at a community hospital. *World J Crit Care Med* 2021; **10**: 244-259 [PMID: 34616660 DOI: 10.5492/wjccm.v10.i5.244]
2 **Silberstein M**. COVID-19 and IL-6: Why vitamin D (probably) helps but tocilizumab might not. *Eur J Pharmacol* 2021; **899**: 174031 [PMID: 33722593 DOI: 10.1016/j.ejphar.2021.174031]
3 **Singh SK**, Jain R, Singh S. Vitamin D deficiency in patients with diabetes and COVID- 19 infection. *Diabetes Metab Syndr* 2020; **14**: 1033-1035 [PMID: 32640414 DOI: 10.1016/j.dsx.2020.06.071]
4 **Verdoia M**, De Luca G. Potential role of hypovitaminosis D and vitamin D supplementation during COVID-19 pandemic. *QJM* 2021; **114**: 3-10 [PMID: 32735326 DOI: 10.1093/qjmed/hcaa234]
5 **Gkoufa A**, Maneta E, Ntoumas GN, Georgakopoulou VE, Mantelou A, Kokkoris S, Routsi C. Elderly adults with COVID-19 admitted to intensive care unit: A narrative review. *World J Crit Care Med* 2021; **10**: 278-289 [PMID: 34616662 DOI: 10.5492/wjccm.v10.i5.278]
6 **Maddaloni E**, Cavallari I, Napoli N, Conte C. Vitamin D and Diabetes Mellitus. *Front Horm Res* 2018; **50**: 161-176 [PMID: 29597238 DOI: 10.1159/000486083]
7 **Arif MA**, Niazi R, Arif SA. Association of dyslipidaemia in patients with varying degrees of Vitamin D deficiency in the Asian population. *J Pak Med Assoc* 2017; **67**: 1843-1847 [PMID: 29256527]
8 **Nakashima A**, Yokoyama K, Yokoo T, Urashima M. Role of vitamin D in diabetes mellitus and chronic kidney disease. *World J Diabetes* 2016; **7**: 89-100 [PMID: 26981182 DOI: 10.4239/wjd.v7.i5.89]
9 **Jovic TH**, Ali SR, Ibrahim N, Jessop ZM, Tarassoli SP, Dobbs TD, Holford P, Thornton CA, Whitaker IS. Could Vitamins Help in the Fight Against COVID-19? *Nutrients* 2020; **12** [PMID: 32842513 DOI: 10.3390/nu12092550]

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ABOUT COVER

Peer Reviewer of *World Journal of Critical Care Medicine*, Athanasia Papazafiropoulou, MD, MSc, PhD, Attending Doctor, Research Scientist, 1st Department of Internal Medicine and Diabetes Center, Tzaneio General Hospital of Piraeus, Piraeus 18536, Greece. pathan@ath.forthnet.gr

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EDITORIAL

Cough as a neurological sign: What a clinician should know

Mohammed Al-Biltagi, Adel Salah Bediwy, Nermin Kamal Saeed

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Mohammed Al-Biltagi, Department of Pediatrics, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Manama 26671, Bahrain

Mohammed Al-Biltagi, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31512, Al Gharbia, Egypt

Mohammed Al-Biltagi, Department of Pediatrics, University Medical Center, Dr. Sulaiman Al Habib Medical Group, Manama 26671, Bahrain

Adel Salah Bediwy, Department of Chest Disease, Faculty of Medicine, Tanta University, Tanta 31512, Alghrabia, Egypt

Adel Salah Bediwy, Department of Chest Disease, University Medical Center, King Abdullah Medical City, Arabian Gulf University, Manama 26671, Bahrain

Adel Salah Bediwy, Department of Chest Diseases, University Medical Center, Dr. Sulaiman Al Habib Medical Group, Manama 26671, Bahrain

Nermin Kamal Saeed, Department of Pathology, Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain, Manama 26671, Bahrain

Nermin Kamal Saeed, Department of Pathology, Irish Royal College of Surgeon, Busaiteen 15503, Almuharraq, Bahrain

Corresponding author: Mohammed Al-Biltagi, MBChB, MD, MSc, Chairman, Professor, Department of Pediatrics, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Building 61, King Abdelaziz Avenue, Manama 26671, Bahrain.
mbelrem@hotmail.com

Abstract

Cough is a common respiratory complaint driving patients to seek medical advice. Besides being a fundamental respiratory sign, it is also a crucial neurological sign. There are three main types of coughs: Reflex cough (type I), voluntary cough (type II), and evoked cough (type III). Cough is a reflex predominantly mediated by control centers in the respiratory areas of the brainstem, modulated by the cerebral cortex. Cough reflex sensitivity could be increased in many neurological disorders such as brainstem space-occupying lesions, medullary lesions secondary to Chiari type I malformations, tics disorders such as Tourette's syndrome, somatic cough, cerebellar neurodegenerative diseases, and chronic vagal neuropathy due to allergic and non-allergic conditions. Meanwhile, cough sensitivity decreases in multiple sclerosis, brain hypoxia, cerebral hemispheric stroke with a brainstem shock, Parkinson's disease, dementia due to

Lewy body disease, amyotrophic lateral sclerosis, and peripheral neuropathy as diabetic neuropathy, hereditary sensory and autonomic neuropathy type IV, vitamin B12, and folate deficiency. Arnold's nerve ear-cough reflex, syncopal cough, cough headache, opioids-associated cough, and cough-anal reflex are signs that could help diagnose underlying neurological conditions. Cough reflex testing is a quick, easy, and cheap test performed during the cranial nerve examination. In this article, we reviewed the role of cough in various neurological disorders that increase or decrease cough sensitivity.

Key Words: Cough reflex; Neurological disorders; Cerebral disorders; Cerebellar disorder; Vagal neuropathy; Parkinsonism

Core Tip: The article aimed to define the role of cough as a crucial symptom and sign for various neurological disorders. It sheds some light on the cough reflex and when its sensitivity is exaggerated or depressed and related to multiple neurological diseases. Cough reflexes can help diagnose some acute and chronic neurologic disorders, both in children and adults.

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INTRODUCTION

Cough is a forced expiratory effort against a closed glottis that opens suddenly with the expulsion of secretion and foreign particles out of the airways, producing a distinctive sound. Cough is one of the most common complaints driving patients to seek medical advice. It is one of the essential respiratory protective mechanisms, alerting to the presence of a potential or actual respiratory tract lesion, and helps to clear secretions and foreign particles from the airways[1]. There are three main types of coughs according to the central control mechanisms: Reflex cough (type I), voluntary cough (type II), and evoked cough (type III), which follows the urge to cough[1,2].

Both reflex and voluntary cough initiate similar mechanisms of cough motor behavior. Cough is a reflex predominantly mediated by control centers in the respiratory areas of the brainstem, modulated by the cerebral cortex (Figure 1). Cough production passes through three harmonized phases: Inspiratory, compression, and expiratory. It starts with contraction of the inspiratory muscles (drawing air into the lungs), closure of the glottis (which generates a subglottic pressure), and abduction of the vocal folds with a forced expiration (enforcing the glottis to open) with expelling of the secretions out. However, the cough reflex is under the voluntary control of the higher neurologic centers, such as the cerebral cortex, which has a vital role in initiating and inhibiting cough[3]. The reflex has afferent sensory nerve fibers (mainly branches of the vagus nerve), which carry the afferent impulses diffusely to the medulla to reach the upper brain stem and pons. Other brain parts are integrated with the proper function of the cough center in the medulla as the pontine respiratory group, the lateral tegmental field, and deep cerebellar nuclei, which play a role in the pattern of cough generation, and regulation. The efferent fibers carry the signals from the cough center *via* the vagus, phrenic, and spinal motor nerves to the diaphragm, abdominal wall, and muscles[4]. As the cough reflex is a reflex, it could affect or be affected by different neurological disorders (Table 1). Both reflex and volitional coughs could be tested in various neurological and otolaryngological conditions. Other methods can test the sensitivity and efficiency of the cough reflex. The sensitivity can be assessed by the concentration or the duration at which the cough can be evoked when exposed to variable concentrations and/or durations of nebulized aerosols of a tussive substance (such as citric acid, L-tartaric acid, or capsaicin). However, considerable variabilities in the used methods are present while performing the test[5-7]. A group of Japanese scientists developed a device to measure cough strength while testing the cough reflex to assess cough efficiency and strength. They added an electronic spirometer to an ultrasonic nebulizer through a special pipe with a double lumen. The spirometer measures the peak cough flow of the provoked involuntary cough[8].

Table 1 Neurological conditions associated with increased cough reflex sensitivity and its mechanism

Disorder		Mechanism
Cerebral disorders	Psychogenic causes: Somatic or "tic" cough, Tourette's syndrome	(1) Peer and familial psychosocial stress; and (2) Mediated in part by the dopaminergic activity
	Primary central reasons: (1) Medullary lesion: Chiari I malformations; (2) Space-occupying lesion; and (3) Neuromyelitis Optica spectrum disorder	(1) Lesions in the dorsal medullary region of the brainstem; (2) Irritation of the cough center; and (3) Autonomic dysregulation secondary to loss of parasympathetic innervation
Cerebellar disorders	Cerebellar neurodegenerative disorders *e.g.*, autosomal dominant cerebellar ataxia	Lesions in deep cerebellar nuclei which are engaged in neural activities necessary for breathing and coughing causing laryngeal hyperreactivity and vagal dysfunction
Vagal neuropathy	Viral infections	Induction of persistent plasticity in the neural pathways mediating cough with activation of the cough-evoking sensory nerves that innervate the airway wall
	Irritant exposure	Irritation of the rapidly adapting irritant receptors, located mainly on the posterior wall and the carina of the trachea, and pharynx
	Chronic conditions such as asthma	Due to Airway vagal hypertonia
	Vitamin B12 deficiency	Damages the myelin sheath and axonal degeneration

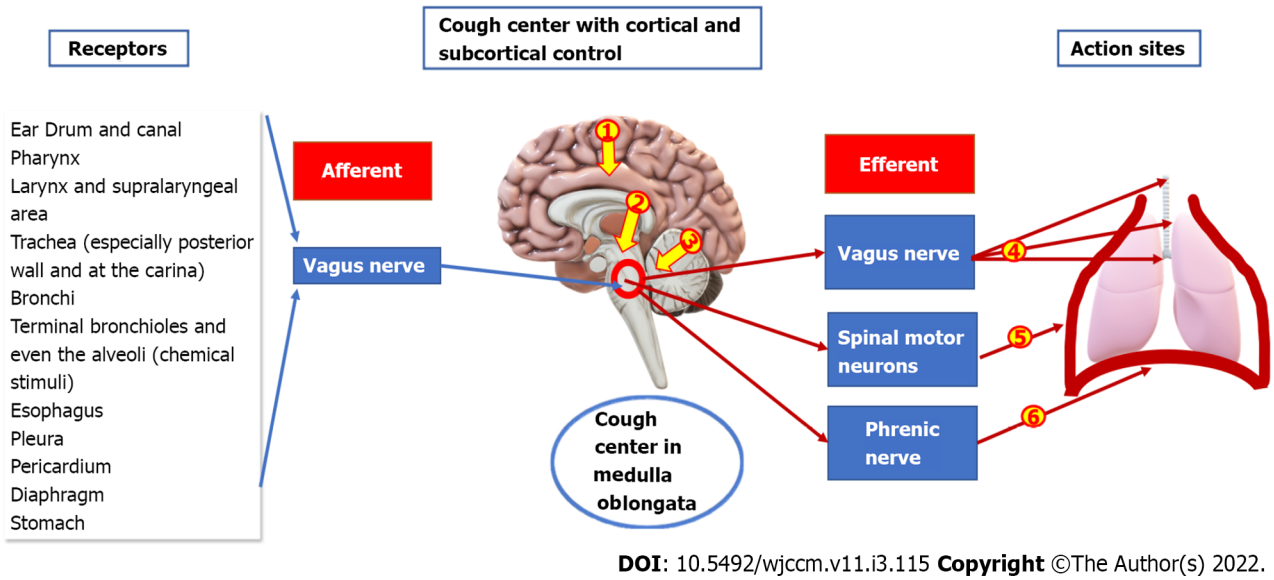

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Figure 1 Cough reflex. The cough center lies in the medulla oblongata in the brainstem. Cough receptors project through the vagus nerve to relay neurons in the solitary nucleus, which project to other parts of the respiratory network, especially the pre-Bötzinger complex. Higher brain centers (cerebral cortex[1]) provide voluntary control over cough, *e.g.*, cough inhibition. However, voluntary coughing does not seem to activate medullary systems. Subcortical centers[2] receive signals from other receptors and other emotional stimuli acting through the hypothalamus. Cerebellum[3] also has control over the cough center. The cough center starts the cough by signaling to the effector organs through the vagus nerve to the larynx, trachea, and bronchi[4], spinal motor neurons[5] to the expiratory muscles, and the phrenic nerve[6] to the diaphragm.

NEUROLOGICAL CONDITIONS ASSOCIATED WITH INCREASED COUGH REFLEX SENSITIVITY

Various neurological diseases could associate with increased cough reflex sensitivity, including cerebral and cerebellar disorders, neuromyelitis optica spectrum disorder (NMOSD), and vagal neuropathy (Table 1).

Cerebral disorders

The urge-to-cough (UTC) is a cognitive sensation needed to initiate and inhibit the reflexive cough stimuli lower than what is usually required to evoke a motor cough. Cough is mediated by the cerebral cortical or subcortical regions and activates multiple brain regions such as the insula, anterior midcingulate cortex, primary sensory cortex, orbitofrontal cortex, supplementary motor area, and cerebellum [9]. Cough, without an apparent medical etiology, is refractory to medical management, underlying a possible psychiatric or psychological basis was previously called psychogenic, habit, or tic cough.

Nowadays, the term "psychogenic" is replaced by "somatic" cough, and the term "habit" was replaced by "tic" cough, according to the Diagnostic and Statistical Manual of Mental Disorders, fifth (DSM-5) edition[10]. The exact prevalence of somatic cough syndrome is not well known due to scarcity and discrepancies in studies. However, it affects about 3% to 10% of children suffering from a chronic cough with unknown causes and about 3.02% of Chinese in-patients with chronic cough[11].

The differentiation between somatic and non-somatic chronic cough is occasionally challenging because patients with chronic cough are more prone to psychomorbidities such as anxiety and depression, which can trigger a chronic cough. Diagnosis of somatic cough syndrome should only be made if the patient meets the DSM-5 criteria, independent of the presence or absence of the nocturnal cough or a cough with a barking/honking quality. Some categories of patients with somatic cough disorders (as children) may benefit from non-pharmacological trials of hypnosis or suggestion therapy or combinations of reassurance, counseling, or referral to a psychologist and/or psychiatrist[12]. Tic cough is a form of vocal or phonic tics characterized by sudden, brief, intermittent, involuntary, or semi-voluntary cough. It may be associated with other motor or vocal tics such as throat clearing, sniffing, grunting, squeaking, screaming, barking, blowing, and sucking sounds[13]. To diagnose the cough as a tic, we depend on core tic criteria such as suppressibility, distractibility, suggestibility, variability, presence of a premonitory sensation, and whether the cough is single or a part of many tics[14]. Tourette's syndrome is a well-described neuropsychiatric disorder characterized by involuntary motor and phonics tics such as coughing, grunting, and wheezing. These phonic tics can be misdiagnosed as respiratory tract disorders such as asthma and upper and lower respiratory system infections. A careful history and thorough neurologic assessment are needed to reach a proper diagnosis. Behavior therapy, psychotherapy, deep brain stimulation, botulinum (Botox) injections, antiepileptics, and antidepressants are possible therapeutic options[15]. When the chronic cough is associated with cerebral manifestations such as truncal ataxia, nystagmus, or incoordination, a central cause in the cough center or higher controlling area should be suspected. Primary central reasons for chronic cough are scarce. A cough may be the initial symptom in patients with Chiari I malformations due to lesions in the dorsal medullary region of the brainstem. A space-occupying brainstem lesion involving the cough center or compressing on the efferent fibers can be a rare cause of chronic cough[16].

NMOSD

NMOSD is a rare autoimmune disease of the central nervous system with inflammation of the long segments of the spinal cord inflammation (myelitis) and optic nerve (severe optic neuritis) with attacks of intractable vomiting and hiccoughs due to autoimmune-mediated lesion affecting the postrema area and medullary floor of the fourth ventricle[17]. An uncontrollable cough may be an added key manifestation aiding the diagnosis of NMOSD, as described in many case reports. The cough is caused by autonomic dysregulation secondary to loss of parasympathetic innervation, which originates predominantly in the nucleus ambiguous of the medulla oblongata[18].

Cerebellar disorders

The neurons in the ventrolateral medulla that create cough and respiratory patterns interact with neural networks in the cerebellum-rostral interposed nucleus, rostral fastigial nucleus, and infra-cerebellar nucleus. The deep cerebellar nuclei are engaged in neural activities necessary for breathing and coughing. For this reason, a dramatic reduction in the cough frequency is observed after cerebellectomy or lesion of the interposed nucleus[19]. In neurodegenerative disorders associated with cerebellar degeneration, there is a reduction in the frequency of coughing episodes that coincides with cerebellar atrophy. However, in a rare type of autosomal dominant cerebellar ataxia (Spinocerebellar ataxia type 5), episodes of spasmodic cough begin 10 to 30 years earlier than the onset of ataxia. It could also be associated with spasmodic dysphonia and tremor. A study from Portugal showed that the prevalence of spasmodic cough is about 2.7% in all the families with documented autosomal dominant cerebellar ataxia. Both spasmodic cough and dysphonia can be caused by laryngeal hyperreactivity and vagal dysfunction. These cough bursts could be considered reliable markers for familial neurodegenerative disease if a previously diagnosed case exists in the family[20].

Vagal neuropathy

The prevalence of chronic cough in vagal neuropathy differs according to the underlying pathology. It is prevalent with laryngeal disorders such as laryngeal sensory neuropathy, postviral vagal neuropathy, and irritable larynx. On the other hand, it is rare with hereditary sensory neuropathy and Vitamin B_{12} deficiency[21]. Cough reflex hypersensitivity manifests by coughing spells, frequently triggered by low threshold stimuli which the patient faces during his usual daily activities such as exposure to a changing temperature, aerosols, perfumes, odors, or during talking or laughing. Cough reflex hypersensitivity is observed in all respiratory diseases (either acute or chronic) when the cough is a predominant feature. At the same time, neuroinflammation is one of the important underlying reasons for cough reflex hypersensitivity[22]. Cranial nerves, including the vagus nerve, can be affected by neuropathic inflammatory processes. The vagus nerve extensively innervates the respiratory and digestive tracts. Vagus nerve dysfunction can trigger cough[23].

Chronic neuropathy of the laryngopharyngeal nerve, a branch of the vagus nerve, presents with symptoms of laryngeal irritation such as chronic cough, stridor, throat irritation, dysphonia, and foreign body sensation in the throat. There is increased cough reflex sensitization with abnormal neuropathic responses to the receptor stimuli in patients suffering from laryngeal neuropathy. Laryngopharyngeal neuropathy can result in changes in the afferent branches of the laryngeal and digestive reflex arch. Consequently, various stimuli like acids can trigger the symptoms. This laryngopharyngeal neuropathy may be associated with paradoxical vocal fold movement as a part of an irritable larynx syndrome where afferent reflex hypersensitivity is a common mechanism[24]. A vagal nerve neuropathy can also impair other motor branches of the vagus nerve, causing paresis or even paralysis of the vocal folds, paradoxical vocal fold movement, or other sensory branches inducing chronic cough and other symptoms such as throat tickling sensation, sore throat, laryngeal paraesthesia, and laryngospasm. These symptoms may be exacerbated and provoked by talking, laughter, irritating inhalants, and laryngeal palpation[25].

Vagus nerve dysfunction can follow viral infections, irritant exposure, or complicated chronic conditions such as asthma. In asthma, elevated substance P and neurokinin A levels in the induced sputum samples reflect airway neuronal activation. Furthermore, neuropeptide calcitonin-gene-related peptide (NCRP) levels in bronchoalveolar lavage from children with chronic cough are positively correlated with capsaicin cough reflex sensitivity. There is an increased expression of NCRP in the nerves supplying the airways in patients with chronic cough[26]. In conditions with intractable coughs, such as idiopathic pulmonary fibrosis, there are high levels of the nerve growth factor in the patients' airways which has significant neuroinflammatory consequences and is one of the factors responsible for cough chronicity[27]. Vitamin B12 deficiency can cause sensory neuropathy resulting in pharyngeal and laryngeal dysfunction, triggering a chronic cough. Vitamin B12 supplementation can improve the histamine threshold and significantly increase the cough threshold in patients with chronic cough due to vitamin B12 deficiency but has no significant effect on subjects without deficiency[28]. Vitamin B12 deficiency-related cough should be in mind in patients treated with proton pump inhibitors or cytotoxic medications.

Behavioral therapy and medical management are needed to treat the hypersensitive cough reflex. Practicing respiratory retraining and learning how to do cough suppression strategies and techniques could help the patients cut the vicious circle of cough by loop suppression of the reflex. A superior laryngeal nerve (SLN) block is another method to help relieve chronic cough due to hypersensitive cough reflex. SLN block can be done as an outpatient service, where a combination of triamcinolone acetonide, lidocaine, and epinephrine is injected into the SLN internal branch at the level of the thyroid membrane. If injection of both sides is needed, we should do one side at a time[29]. Gabapentin, a well-known antiepileptic drug, showed efficacy in controlling epilepsy and various painful conditions such as pruritus, diabetic neuropathy, fibromyalgia syndrome, hiccups, hot flashes, neuropathic pain, and restless leg syndrome. It was also successful in treating some cases of chronic refractory cough. It works by modulating the release of excitatory neurotransmitters, which act by interacting with gamma-aminobutyric acid (GABA) receptors or N-methyl-D-aspartate receptors. Gabapentin is a valuable and safe drug in treating sensory neuropathic cough. Successful control of the cough by Gabapentin can help to confirm the diagnosis of sensory neuropathic cough. Tricyclic antidepressants, amitriptyline, and desipramine can also be used to treat this type of cough, but they are not as safe as Gabapentin, especially in old age[30]. Considering chronic cough as a neuropathic disorder, just like chronic neuropathic pain, will significantly change the potential strategies for diagnosing and managing chronic cough[31].

NEUROLOGICAL CONDITIONS ASSOCIATED WITH DIMINISHED COUGH REFLEX SENSITIVITY

Being a reflex predominantly involves the brainstem and is modulated by the cerebral cortex; cough can be diminished in several neurological disorders affecting the peripheral and central nervous systems. Diminishing cough reflex (dystussia) is associated with a high risk of developing pneumonia and increased morbidity and mortality rates in these diseases (Table 2).

Brain hypoxia and cerebrovascular events

The central nervous system (CNS) is significantly affected by hypoxia, which can depress cough through different mechanisms and decrease the sensitivity of the peripheral cough receptors and the rostral and caudal parts of the solitary nucleus. This nucleus is the recipient of all visceral afferents and an essential part of the regulatory centers of internal homeostasis through its multiple projections with cardiorespiratory and gastrointestinal regulatory centers[32]. The depressive effect of the hypoxia on the solitary nucleus is mediated by the GABA–mediated pathway. GABA is the chief inhibitory neurotransmitter and can down-regulate the cough reflex sensitivity. Therefore, Baclofen, a GABA agonist, can decrease the cough sensitivity to capsaicin in healthy individuals[33]. In addition, hypoxia can increase CNS levels of endogenous opioids, thus reducing the cough sensitivity by inhibiting the central

Table 2 Neurological conditions associated with diminished cough reflex sensitivity

Category	
Cerebral disorders	Brain hypoxia
	Cerebrovascular events
	Dementia
	Parkinson's disease
	Drugs: *e.g.*, antipsychotic drugs, anaesthetics
Amyotrophic lateral sclerosis and multiple sclerosis	
Neuromuscular diseases: *e.g.*, myasthenia gravis	
Peripheral neuropathy	Hereditary sensory autonomic neuropathies
	Phrenic nerve palsy or injury
	Diabetic autonomic neuropathy
	Vitamin B12 and folate deficiency

component of the cough. Hypoxia can occur in many cardiovascular diseases. The hypoxia-related impairment of the cough increases the morbidity and mortality rates in these diseases[34]. Cough reflex can be assessed in a comatose patient as a part of the Brainstem Responses Assessment Sedation Score in the intensive care unit by observing the patient's response to a tracheal suctioning. It is considered positive if any contraction of abdominal muscles is observed[35].

Cortex has control over the cough. The ability to voluntarily produce and suppress a cough is an example of the cortical control of the cough. Reduced strength of the voluntary cough may increase the risk of aspiration and other pulmonary consequences due to inadequate clearing of the aspirated material from the airway, as seen in patients with brainstem or cerebral stroke associated with an abnormal laryngeal cough reflex[36]. Many patients with cerebral hemispheric stroke showed a temporary or long-lasting malfunction of the laryngeal cough reflex (Known as "brainstem shock"). This shock is characterized by a generalized transient or permanent neurological malfunction of one or more vital neurological functions, including the respiratory drive, reticular activating system, or the laryngeal cough reflex.

Consequently, many patients with significant or minor hemispheric strokes may develop impaired consciousness and need intubation due to reduced respiratory drive. Addington *et al*[37] showed the importance of the stroke location in determining the effect of stroke on the laryngeal cough reflex and consequently on the pneumonia risk. They showed that the brainstem and cerebral hemispheric infarcts are more liable to affect the laryngeal cough reflex than basal ganglionic or cerebellar infarcts[37]. Daniels *et al*[38] showed that 67% of their patients with stroke did not show cough response, and 38% had suffered from aspiration[38]. Therefore, adding cough sensitivity testing to the clinical evaluation of the swallowing function will significantly reduce the aspiration pneumonia risk in patients with cerebral or brainstem stroke[7]. It also helps in monitoring the recovery from stroke and evaluating the postsurgical recovery of the laryngeal cough reflex after extubation and following general anesthesia [39].

Patients with Lewy body disease-related dementia have decreased cough reflex sensitivity and central respiratory chemosensitivity, with decreased insula activation associated with UTC[9]. Patients with Parkinson's disease also have reduced intensity of voluntary and reflex cough efforts with a slightly higher cough threshold. Fontana *et al*[39] found that a motor rather than a sensory component of the cough reflex is primarily involved, especially in the early stages, primarily due to impairment in the central activation of motor units and reduced neural drive to expiratory muscles. The impaired central activation reflects the presence of bradykinesia which is one of the critical functional disorders in these patients[36]. Parkinsonism is associated with decreased Dopamine and other neurotransmitters production in substantia nigra, impairing substance P production in vagal sensory nerve C-fibers in the cervical ganglia. The low level of substance P weakens the swallowing reflex and suppresses the cough reflex causing frequent aspiration[40]. About 20% of deaths in patients with Parkinsonism were related to pneumonia, probably because of the impaired cough reflex and upper airway muscle dysfunction [41]. In the same way, multiple sclerosis, with its characteristic disseminated demyelination patches in both the brain and spinal cord, can affect the voluntary cough efficiency and respiratory muscle power due to bulbar dysfunction and corticospinal tract damage in the spinal cord. The degree of impairment of cough reflex has an inverse correlation with the patients' degree of disability[42].

Motor neuron diseases

Motor neuron disease is a chronic degenerative neurological disorder affecting the corticospinal tracts,

motor nuclei in the brainstem, and the anterior horn cells of the spinal cord. It reduces the capacity of efficient cough. There is a hyperactive cough reflex in its early stages due to inflammatory mediators such as bradykinin and prostaglandins. As the disease progresses, there is continuous damage-causing cough desensitization. Various combinations of upper and lower motor neuron dysfunction may increase the need to cough but, unfortunately, impair the efficiency of both the voluntary and reflex types of coughs[43]. Amyotrophic lateral sclerosis is characterized by upper (UMN) and lower motor neuron (LMN) degeneration which negatively impacts the ability of respiratory and laryngeal musculature to work in harmony during the cough phases. The rigidity due to UMN degeneration and weakness due to LMN degeneration led to abnormal cough flow and impaired airway clearance abilities, causing different pulmonary sequelae, such as poor secretion management, recurrent pneumonia, and even respiratory failure[44]. Voluntary cough testing detects the presence of dysphagia and impaired airway defense physiologic capacity and secretion management. Constant assessment of voluntary cough function provides rapid detection of respiratory deterioration, permitting appropriate implementation of cough assist, non-invasive ventilation, and respiratory training before significant function degradation[45].

Neuromuscular diseases

Neuromuscular diseases are associated with increasing breathing disorders, including swallowing dysfunction, cough impairment, and frequent choking. In myasthenia gravis, cranial nerves impairment and bulbar weakness could be the initial symptoms causing frequent aspiration and, consequently, increasing the coughing frequency. However, if the patient develops a respiratory failure, the associated hypoxia causes peripheral and central impairment of the cough reflex sensitivity[46]. Phrenic nerve palsy or injury is associated with decreased cough reflex[47].

Peripheral neuropathy

Since cough is a defensive reflex, it could be affected by diseases targeting the peripheral nerves. Consequently, vagotomy or anesthesia-induced vagal block abolishes cough[48]. Hereditary Sensory Autonomic Neuropathies (HSAN) are rare hereditary peripheral neuropathies characterized by the loss of large myelinated and unmyelinated fibers resulting in decreased pain sensation and its associated consequences. Congenital insensitivity to pain with anhidrosis (CIPA) is HSAN type-IV; it occurs due to a mutation in the gene encoding for the neurotrophic tyrosine kinase receptor type I, called the *NTRK1* gene[49]. Both pain and cough can be evoked experimentally by stimulating nociceptive C-fibers and faster-conducting A-δ-fibers. Consequently, CIPA can impair both pain and cough. Few cases reports described this association[50,51].

Diabetes-related autonomic neuropathy is one of the most typical complications of diabetes mellitus (DM). Meanwhile, the vagus nerve is one of the first nerves damaged in DM. Different studies showed a significant increase in the cough threshold with cough reflex impairment. Ciljakova *et al*[52] found a robust negative correlation between cough reflex sensitivity and heart rate variability as an indicator of diabetic autonomic neuropathy[52]. Down-regulation of the cough reflex may start very early in the pathogenesis of diabetes. Varechova *et al*[53] found decreased cough reflex sensitivity in children with Type-I DM with subclinical autonomic neuropathy. Testing those children for reduced cough reflex could reflect the presence of autonomic dysfunction and its impact on respiratory and general health [53]. Cough reflex sensitivity could also decrease with aging, during sleep, cranial nerve conduction abnormalities due to vitamin B12 and folate deficiency, and inhibition of dopamine receptors by antipsychotic drugs[40].

HOW CAN COUGH HELP TO DIAGNOSE NEUROLOGIC DISORDERS?

When a chronic cough is present, the underlying lesion should be investigated.

Arnold's nerve ear-cough reflex

In Arnold's nerve ear-cough reflex, the cough is triggered by mechanical stimulation of the external auditory meatus through the auricular branch of the vagus nerve (Arnold's nerve), which supplies the external auditory canal, middle ear, and auditory tube. The test is done using a cotton swab on a stick to stimulate the ear by placing the swab 3 to 5 mm into the external auditory canal and rotating for 2 to 3 s. We consider the test positive if the patient coughs within 10 s. The test should be performed on both sides, as many persons may only have one affected side. The test is positive in 2% of healthy children and adults, 3% of children, and 25% of adults with chronic cough. A positive reflex is more common in women than men and is unilateral in over 90% of patients[54].

Interestingly, hair within the ear canal can stimulate Arnold's nerve and trigger the urge to cough (Oto-tricho-tussia). Such patients can be easily treated by removing the hair[55]. This effect can be applied to any foreign body or earwax impaction in the auditory canal. Consequently, examining the external auditory canal should be a routine in patients with chronic cough, especially in old age[56]. The high prevalence of positive Arnold's nerve reflex in patients with chronic cough suggests that chronic

cough is a neuropathic condition due to a disorder or alteration in the vagus (vagal hypersensitivity) that could be secondary to sensory nerve damage caused by the inflammatory, infective, or allergic factors. It is usually accompanied by other neuropathic features such as throat irritation (laryngeal paraesthesia). Cough is triggered upon exposure to non-tussive triggers such as cold air and eating (allotussia or UTC). The low prevalence of positive reflex in children with chronic cough (3%) compared to the adults (25%) indicates that the hypersensitivity of this reflex may be acquired, possibly by a viral infection[57]. A positive Arnold's nerve reflex can be reversed after successful therapy of chronic cough. However, a positive Arnold's nerve reflex is not a valid predictor of the cause of chronic cough but can trigger the need to investigate it[58].

Holmes-Adie syndrome

Holmes-Adie syndrome is another rare cause of tendon areflexia, unilateral or bilateral tonic pupils with slow reaction to near direct light, and chronic cough; due to autonomic dysfunction affecting some cranial nerves, including the vagus nerve. Autonomic dysfunction is a frequent finding for this condition; attributed to lesions in both afferent and efferent sympathetic and parasympathetic neurons. Airways reflux secondary to vagal dysfunction is a possible etiology of cough in these patients. The patients present with anisocoria, abnormal deep tendon reflexes, patchy hyperhidrosis or anhidrosis, and chronic cough[59]. Many patients with sensory neuropathic cough were relieved by neuralgia-neuromodulator drugs, such as amitriptyline, desipramine, Gabapentin, pregabalin, oxcarbazepine, and others, when other potential causes of chronic cough have been ruled out. These medications may help reduce or abolish cough by diminishing the nerve-ending "misfires" caused by sensory neuropathic cough[60].

Cough syncope

Cough syncope is a temporary impairment or loss of consciousness with facial congestion and cyanosis; it typically occurs within seconds of a coughing paroxysm, followed by a rapid recovery. Cough syncope originally can mimic epilepsy. It was previously considered a form of epilepsy "known as laryngeal epilepsy" because of the associated jerking movements. However, many studies showed regular brain electrical activity during the episodes. It typically occurs in middle-aged and older, overweight, or muscularly built male smokers with a history of chronic obstructive lung disease. These persons are more prone to create a very high intrathoracic pressure associated with cough-induced syncope and fainting[61]. As it is mainly an adult disease, cough syncope was rarely reported in children, particularly under ten years[62]. The exact mechanism of cough syncope is debatable. Cough markedly elevates the intrathoracic pressures, diminishes the cardiac output, and decreases the systemic blood pressure and cerebral perfusion. At the same time, cerebrospinal fluid (CSF) pressure increases causing reduced brain perfusion; or a cerebral concussion-like effect due to rapid CSF pressure elevation. Another theory suggests that the cough initiates a neurally-mediated reflex vasodepressor-bradycardia. Elimination of cough eliminates the resultant syncopal episodes[63].

The patient may have a fixed upward deviation of the eyes during the syncopal episode, which should not be confused with epilepsy. EEG shows temporary slowing during the attack but no seizure discharges. It is always accompanied by a coughing paroxysm. During the attack, the face becomes plethoric rather than cyanotic, and the entire episode lasts less than a minute. An aura never precedes it and is very rarely followed by post-ictal confusion/headache. Cough syncope frequently occurs at night while prone, whereas epilepsy can develop in any position[64]. Cough syncope is associated with a high incidence of pulmonary, cardiac, and neurologic disorders. Numerous CNS disorders were reported to be associated with cough syncope, including cerebral tumors (meningioma, glioblastoma), herniation of cerebellar tonsils (Type 1 Arnold-Chiari malformation), hydrocephalus, carotid and vertebral arterial occlusive disease, basilar invagination, autosomal dominant hereditary sensory neuropathy, and medullary infarction[65].

Cough headache

Cough-triggered headaches are uncommon, with a lifetime prevalence of 1%. Headache can be triggered by a rapid increase in the intra-abdominal, intra-thoracic, and intracranial pressure, caused by coughing, sneezing or straining in patients with low pain threshold[66]. It is either primary or symptomatic. Primary cough headache (previously known as benign cough headache or Valsalva maneuver headache) is currently defined as a headache with sudden onset, occurring only in association with coughing, straining, and/or Valsalva maneuver. It lasts from one second to 30 min and is unrelated to other disorders[67]. It is more frequent in males over 40 years, and usually bilateral, but sometimes unilateral. Pain is of moderate-to-severe intensity and is usually located in the fronto-temporal regions, but sometimes presents with different patterns such as toothache. The pain can be triggered by Valsalva maneuvers but never by physical exercise. Nausea, vomiting, photo- and phonophobia are uncommon[68].

Underlying disorders can be detected in 40% of cases with symptomatic cough headaches. These lesions may involve but are not limited to Chiari type I malformation, obstructive hydrocephalus, posterior fossa structural lesions (as arachnoid cysts, dermoid tumors, meningiomas, or Os

odontoideum), spontaneous low CSF pressure or leak, subdural hematoma, multiple brain metastases, acute sphenoid sinusitis, pneumocephalus, pneumococcal meningitis, or non-ruptured cerebral aneurysm[69]. Symptoms are more common than those observed with the primary type, depending on the underlying abnormality. The headache is increasing in intensity with variable durations and locations. The pain may be pressing, explosive, bursting, stabbing, dull, electrical, lancinating, or having a mixed nature. Headache duration ranges from seconds to several weeks[65]. Headache can be triggered by a cough and other factors such as laughing, exertion, weightlifting, defecation, or rapid body or head postural changes. Posterior fossa symptoms are common, such as dizziness, unsteadiness, facial and upper limb numbness, vertigo, and syncope. The mechanism of headache is due to raised intracranial pressure, evidenced by the disappearance of the headache after surgical correction of the lesion[70].

Opioids-associated cough

Opioids are well known to have a central antitussive action. However, some opioids such as Alfentanil, Fentanyl, and Sufentanil can elicit a brief tussive effect in about 50% of the patients (especially smokers) within a few seconds from the rapid bolus intravenous injection. This tussive effect is due to the chemical stimulation of opioid receptors in the smooth muscles in the trachea, bronchi, and bronchioles. This pulmonary chemoreflex is unlikely to be mediated by the vagus nerve, as it is not affected by atropine pretreatment. Instead, pretreatment with inhaled β-2 adrenergic agonists considerably decreases the rate of cough related to the intravenous opioid injection. This opioid-associated cough is usually self-limited. It is also related to circulation time and could serve as a clinical landmark for vein-to-brain time or cardiac output[71].

Cough-anal reflex

The anal wink in response to cough or sniff is a significant clinical sign during a neurological examination. It could be elicited by asking the patient to voluntarily cough or sniff while observing the anus. This reflex is not affected by transection of the spinal cord while being lost in cauda equina lesions. It is easier to be done and more convenient to the patient than the classic anal reflex. It is a promising tool and is better to be included in the neurological examination[72].

OTHER RESPIRATORY SYMPTOMS THAT COULD HAVE NEUROLOGICAL PATHOLOGY

Many other respiratory symptoms and signs could have underlying neuropathologies. Intractable sneezing and hiccup could be seen in patients with NMOSD[73]. However, a diminished sneezing reflex or difficulty initiating sneezing or the urge to sneeze is an uncommon neurological symptom. A runny nose and hypo or hyper-reflexive rhinopathy could indicate autonomic nervous system dysfunction [74]. Nasal discharge may be observed in Parkinson's disease, dementia, and Alzheimer's disease or arise from their treatment[75]. CSF rhinorrhea is observed in head trauma and can be easily distinguished by a simple glucose dipstick test[76]. Throat clearing, dysphonia, and vocal fatigue can be observed in many patients with postviral vagal neuropathy[77]. However, a detailed discussion of these symptoms is out of the scope of this review.

TREATMENT OF NEUROLOGICAL DISEASE-RELATED COUGH

Treatment of cough secondary to neurogenic disorder is mainly directed to treat the cause. A suggested guideline for managing chronic neuropathic cough is demonstrated in Figure 2. Different modalities could be used to treat these coughs after trying to treat the original neurogenic disorder. Speech and language therapy, behavior modification, biofeedback, self-hypnosis, bed-sheet technique, and differential reinforcement can help treat somatic cough[21]. We can also try combined codeine and guaifenesin or empiric therapy with Gabapentin, Pregabalin, Nortriptyline, or Amitriptyline[78]. Botulinum toxin injection into the thyroarytenoid muscles or vocal cords may help to relieve chronic cough secondary to a neuropathic disorder[79]. Referral to a Specialist cough clinic could be an excellent choice to reach a definitive treatment for chronic cough not responding to the previous management. Enrolment in ongoing clinical trials could also be a valid option. Transcutaneous electrical nerve stimulation is a relatively new electroanalgesia method that helps relieve neuropathic pain disorders, including refractory chronic neuropathic cough, which is physiologically like other neuropathic pain conditions. Michalowski *et al*[80] studied the tolerability and feasibility of using Transcutaneous electrical nerve stimulation to treat neuropathic cough[80]. Other new modalities and novel therapeutic agents are under trial, especially those working on the brainstem and cerebral cortex.

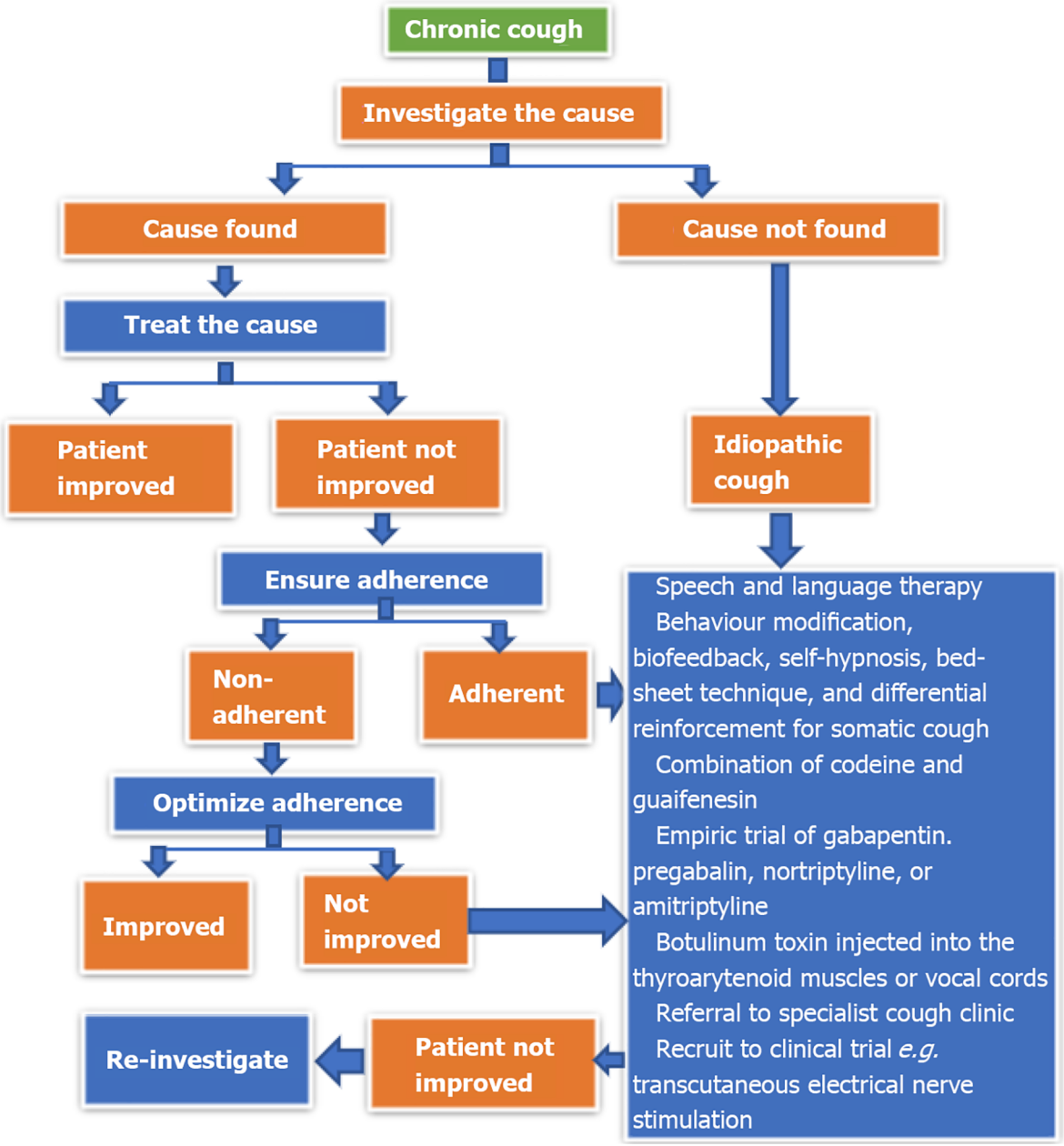

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Figure 2 Proposed guidelines for the treatment of chronic cough.

CONCLUSION

A cough is a crucial neurological sign, the same as a critical respiratory sign. Cough reflex sensitivity could be increased or decreased in many neurological disorders. Cough reflex testing is quick, easy, and cheap tests can be performed during the cranial nerve examination.

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Country/Territory of origin: Bahrain

ORCID number: Mohammed Al-Biltagi 0000-0002-7761-9536; Adel Salah Bediwy 0000-0002-0281-0010; Nermin Kamal Saeed 0000-0001-7875-8207.

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REFERENCES

1 **Canning BJ**, Mori N, Mazzone SB. Vagal afferent nerves regulating the cough reflex. *Respir Physiol Neurobiol* 2006; **152**: 223-242 [PMID: 16740418 DOI: 10.1016/j.resp.2006.03.001]
2 **Hegland KW**, Bolser DC, Davenport PW. Volitional control of reflex cough. *J Appl Physiol (1985)* 2012; **113**: 39-46 [PMID: 22492938 DOI: 10.1152/japplphysiol.01299.2011]
3 **Niimi A**, Matsumoto H, Ueda T, Takemura M, Suzuki K, Tanaka E, Chin K, Mishima M, Amitani R. Impaired cough reflex in patients with recurrent pneumonia. *Thorax* 2003; **58**: 152-153 [PMID: 12554900 DOI: 10.1136/thorax.58.2.152]
4 **Polverino M**, Polverino F, Fasolino M, Andò F, Alfieri A, De Blasio F. Anatomy and neuro-pathophysiology of the cough reflex arc. *Multidiscip Respir Med* 2012; **7**: 5 [PMID: 22958367 DOI: 10.1186/2049-6958-7-5]
5 **Monroe MD**, Manco K, Bennett R, Huckabee M. Citric acid cough reflex test: stablishing normative data. *Speech Lang Hear* **17**: 216-224 [DOI: 10.1179/2050572814Y.0000000041]
6 **Mills C**, Jones R, Huckabee ML. Measuring voluntary and reflexive cough strength in healthy individuals. *Respir Med* 2017; **132**: 95-101 [PMID: 29229113 DOI: 10.1016/j.rmed.2017.09.013]
7 **Miles A**, Zeng IS, McLauchlan H, Huckabee ML. Cough reflex testing in Dysphagia following stroke: a randomized controlled trial. *J Clin Med Res* 2013; **5**: 222-233 [PMID: 23671548 DOI: 10.4021/jocmr1340w]
8 **Fujiwara K**, Kawamoto K, Shimizu Y, Fukuhara T, Koyama S, Kataoka H, Kitano H, Takeuchi H. A novel reflex cough testing device. *BMC Pulm Med* 2017; **17**: 19 [PMID: 28100202 DOI: 10.1186/s12890-017-0365-y]
9 **Ebihara T**, Gui P, Ooyama C, Kozaki K, Ebihara S. Cough reflex sensitivity and urge-to-cough deterioration in dementia with Lewy bodies. *ERJ Open Res* 2020; **6** [PMID: 32166090 DOI: 10.1183/23120541.00108-2019]
10 **Vertigan AE**, Murad MH, Pringsheim T, Feinstein A, Chang AB, Newcombe PA, Rubin BK, McGarvey LP, Weir K, Altman KW, Weinberger M, Irwin RS, Adams TM, Barker AF, Birring SS, Blackhall F, Bolser DC, Boulet LP, Braman SS, Brightling C, Callahan-Lyon P, Canning BJ, Coeytaux R, Cowley T, Davenport P, Diekemper RL, Ebihara S, El Solh AA, Escalante P, Field SK, Fisher D, French CT, Gibson P, Gold P, Gould MK, Grant C, Harding SM, Harnden A, Hill AT, Kahrilas PJ, Keogh KA, Lane AP, Lim K, Malesker MA, Mazzone P, Mazzone S, McCrory DC, McGarvey L, Molasiotis A, Newcombe P, Nguyen HQ, Oppenheimer J, Prezant D, Restrepo MI, Rosen M, Rubin B, Ryu JH, Smith J, Tarlo SM, Vertigan AE, Wang G, Wiener RS; CHEST Expert Cough Panel. Somatic Cough Syndrome (Previously Referred to as Psychogenic Cough) and Tic Cough (Previously Referred to as Habit Cough) in Adults and Children: CHEST Guideline and Expert Panel Report. *Chest* 2015; **148**: 24-31 [PMID: 25856777 DOI: 10.1378/chest.15-0423]
11 **Wei WZY**, Li H, Hou J, Lv H, Li C. Detection rate of psychogenic cough in patients with chronic cough in Chinese hospital: a meta-analysis. *Int J Clin Exp Med* 2016; **9**: 504-514
12 **Vertigan AE**. Somatic cough syndrome or psychogenic cough-what is the difference? *J Thorac Dis* 2017; **9**: 831-838 [PMID: 28449492 DOI: 10.21037/jtd.2017.03.119]
13 **Duncan KL**, Faust RA. Tourette syndrome manifests as chronic cough. *Int J Pediatr Otorhinolaryngol* 2002; **65**: 65-68 [PMID: 12127225 DOI: 10.1016/s0165-5876(02)00122-2]
14 **Tan H**, Büyükavci M, Arik A. Tourette's syndrome manifests as chronic persistent cough. *Yonsei Med J* 2004; **45**: 145-149 [PMID: 15004882 DOI: 10.3349/ymj.2004.45.1.145]
15 **Perotin JM**, Launois C, Dewolf M, Dumazet A, Dury S, Lebargy F, Dormoy V, Deslee G. Managing patients with chronic cough: challenges and solutions. *Ther Clin Risk Manag* 2018; **14**: 1041-1051 [PMID: 29922064 DOI: 10.2147/TCRM.S136036]
16 **Huda S**, Whittam D, Bhojak M, Chamberlain J, Noonan C, Jacob A. Neuromyelitis optica spectrum disorders. *Clin Med (Lond)* 2019; **19**: 169-176 [PMID: 30872305 DOI: 10.7861/clinmedicine.19-2-169]
17 **Fujita-Nakata M**, Tomioka R, Tanaka K, Nakanishi M, Nagayama S, Takahashi R, Machiya T, Hamada T, Matsui M. Intractable cough as characteristic symptom of neuromyelitis optica and neuromyelitis optica spectrum disorder. *Mult Scler* 2016; **22**: 576-577 [PMID: 26199354 DOI: 10.1177/1352458515596602]
18 **Williams SP**, Bhutta MF. Chronic cough as a presenting feature of cerebral lymphoma. *J Surg Case Rep* 2014; **2014** [PMID: 25344556 DOI: 10.1093/jscr/rju109]
19 **Xu F**, Frazier DT. Role of the cerebellar deep nuclei in respiratory modulation. *Cerebellum* 2002; **1**: 35-40 [PMID:

12879972 DOI: 10.1080/147342202753203078]
20 **Coutinho P**, Cruz VT, Tuna A, Silva SE, Guimarães J. Cerebellar ataxia with spasmodic cough: a new form of dominant ataxia. *Arch Neurol* 2006; **63**: 553-555 [PMID: 16606768 DOI: 10.1001/archneur.63.4.553]
21 **Chung KF**, McGarvey L, Mazzone SB. Chronic cough as a neuropathic disorder. *Lancet Respir Med* 2013; **1**: 414-422 [PMID: 24429206 DOI: 10.1016/S2213-2600(13)70043-2]
22 **Sacre-Hazouri JA**, Sacre L. [Chronic cough. Cough reflex hypersensitivity syndrome]. *Rev Alerg Mex* 2019; **66**: 217-231 [PMID: 31200420 DOI: 10.29262/ram.v66i2.565]
23 **Amin MR**, Koufman JA. Vagal neuropathy after upper respiratory infection: a viral etiology? *Am J Otolaryngol* 2001; **22**: 251-256 [PMID: 11464321 DOI: 10.1053/ajot.2001.24823]
24 **Benninger MS**, Campagnolo A. Chronic laryngopharyngeal vagal neuropathy. *Braz J Otorhinolaryngol* 2018; **84**: 401-403 [PMID: 29853310 DOI: 10.1016/j.bjorl.2018.04.001]
25 **Pacheco A**, Cobeta I. Refractory chronic cough, or the need to focus on the relationship between the larynx and the esophagus. *Cough* 2013; **9**: 10 [PMID: 23552099 DOI: 10.1186/1745-9974-9-10]
26 **Morice AH**, Millqvist E, Belvisi MG, Bieksiene K, Birring SS, Chung KF, Dal Negro RW, Dicpinigaitis P, Kantar A, McGarvey LP, Pacheco A, Sakalauskas R, Smith JA. Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. *Eur Respir J* 2014; **44**: 1132-1148 [PMID: 25142479 DOI: 10.1183/09031936.00218613]
27 **Hope-Gill BD**, Hilldrup S, Davies C, Newton RP, Harrison NK. A study of the cough reflex in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003; **168**: 995-1002 [PMID: 12917229 DOI: 10.1164/rccm.200304-597OC]
28 **Bucca CB**, Culla B, Guida G, Sciascia S, Bellone G, Moretto A, Heffler E, Bugiani M, Rolla G, Brussino L. Unexplained chronic cough and vitamin B-12 deficiency. *Am J Clin Nutr* 2011; **93**: 542-548 [PMID: 21248188 DOI: 10.3945/ajcn.110.000802]
29 **Dhillon VK**. Superior laryngeal nerve block for neurogenic cough: A case series. *Laryngoscope Investig Otolaryngol* 2019; **4**: 410-413 [PMID: 31453350 DOI: 10.1002/lio2.292]
30 **Giliberto JP**, Cohen SM, Misono S. Are neuromodulating medications effective for the treatment of chronic neurogenic cough? *Laryngoscope* 2017; **127**: 1007-1008 [PMID: 27861928 DOI: 10.1002/lary.26393]
31 **Cho YS**. Now is the Right Time to Establish a New Strategy for Managing Chronic Cough as a Neuropathic Disorder. *Allergy Asthma Immunol Res* 2014; **6**: 373-375 [PMID: 25228993 DOI: 10.4168/aair.2014.6.5.373]
32 **Baker E**, Lui F. Neuroanatomy, Vagal Nerve Nuclei. 2021 Jul 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan- [PMID: 31424793]
33 **Tabata M**, Kurosawa H, Kikuchi Y, Hida W, Ogawa H, Okabe S, Tun Y, Hattori T, Shirato K. Role of GABA within the nucleus tractus solitarii in the hypoxic ventilatory decline of awake rats. *Am J Physiol Regul Integr Comp Physiol* 2001; **281**: R1411-R1419 [PMID: 11641110 DOI: 10.1152/ajpregu.2001.281.5.R1411]
34 **Eckert DJ**, Catcheside PG, Stadler DL, McDonald R, Hlavac MC, McEvoy RD. Acute sustained hypoxia suppresses the cough reflex in healthy subjects. *Am J Respir Crit Care Med* 2006; **173**: 506-511 [PMID: 16322644 DOI: 10.1164/rccm.200509-1455OC]
35 **Rohaut B**, Porcher R, Hissem T, Heming N, Chillet P, Djedaini K, Moneger G, Kandelman S, Allary J, Cariou A, Sonneville R, Polito A, Antona M, Azabou E, Annane D, Siami S, Chrétien F, Mantz J, Sharshar T; Groupe d'Exploration Neurologique en Réanimation (GENER). Brainstem response patterns in deeply-sedated critically-ill patients predict 28-day mortality. *PLoS One* 2017; **12**: e0176012 [PMID: 28441453 DOI: 10.1371/journal.pone.0176012]
36 **Addington WR**, Stephens RE, Gilliland K, Rodriguez M. Assessing the laryngeal cough reflex and the risk of developing pneumonia after stroke. *Arch Phys Med Rehabil* 1999; **80**: 150-154 [PMID: 10025488 DOI: 10.1016/s0003-9993(99)90112-0]
37 **Addington WR**, Stephens RE, Widdicombe JG, Rekab K. Effect of stroke location on the laryngeal cough reflex and pneumonia risk. *Cough* 2005; **1**: 4 [PMID: 16270928 DOI: 10.1186/1745-9974-1-4]
38 **Daniels SK**, Brailey K, Priestly DH, Herrington LR, Weisberg LA, Foundas AL. Aspiration in patients with acute stroke. *Arch Phys Med Rehabil* 1998; **79**: 14-19 [PMID: 9440410 DOI: 10.1016/s0003-9993(98)90200-3]
39 **Fontana GA**, Pantaleo T, Lavorini F, Benvenuti F, Gangemi S. Defective motor control of coughing in Parkinson's disease. *Am J Respir Crit Care Med* 1998; **158**: 458-464 [PMID: 9700121 DOI: 10.1164/ajrccm.158.2.9705094]
40 **The committee for The Japanese Respiratory Society guidelines for management of cough**. Mechanism of cough. *Respirology***11**: S4, S137-S139 [DOI: 10.1111/j.1440-1843.2006.00920_2.x]
41 **Mangera Z**, Panesar G, Makker H. Practical approach to management of respiratory complications in neurological disorders. *Int J Gen Med* 2012; **5**: 255-263 [PMID: 22505823 DOI: 10.2147/IJGM.S26333]
42 **Aiello M**, Rampello A, Granella F, Maestrelli M, Tzani P, Immovilli P, Franceschini M, Olivieri D, Chetta A. Cough efficacy is related to the disability status in patients with multiple sclerosis. *Respiration* 2008; **76**: 311-316 [PMID: 18319585 DOI: 10.1159/000119641]
43 **Hadjikoutis S**, Wiles CM, Eccles R. Cough in motor neuron disease: a review of mechanisms. *QJM* 1999; **92**: 487-494 [PMID: 10627867 DOI: 10.1093/qjmed/92.9.487]
44 **Kim WH**, Kim JH, Kim EK, Yun SP, Kim KK, Kim WC, Jeong HC. Myasthenia gravis presenting as an isolated respiratory failure: a case report. *Korean J Intern Med* 2010; **25**: 101-104 [PMID: 20195411 DOI: 10.3904/kjim.2010.25.1.101]
45 **Tabor-Gray LC**, Gallestagui A, Vasilopoulos T, Plowman EK. Characteristics of impaired voluntary cough function in individuals with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 2019; **20**: 37-42 [PMID: 30652513 DOI: 10.1080/21678421.2018.1510011]
46 **Rafiq MK**, Bradburn M, Mustfa N, McDermott CJ, Annane D. Mechanical cough augmentation techniques in amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev* 2016; **2016(12)**: CD012482 [DOI: 10.1002/14651858.CD012482]
47 **Prasad S**, Athreya BH. Transient paralysis of the phrenic nerve associated with head injury. *JAMA* 1976; **236**: 2532-2533 [PMID: 1036522]

48 **Woodcock A**, Young EC, Smith JA. New insights in cough. *Br Med Bull* 2010; **96**: 61-73 [PMID: 21030396 DOI: 10.1093/bmb/ldq034]

49 **Sasnur AH**, Sasnur PA, Ghaus-Ul RS. Congenital insensitivity to pain and anhidrosis. *Indian J Orthop* 2011; **45**: 269-271 [PMID: 21559108 DOI: 10.4103/0019-5413.80047]

50 **Gracely RH**, Undem BJ, Banzett RB. Cough, pain and dyspnoea: similarities and differences. *Pulm Pharmacol Ther* 2007; **20**: 433-437 [PMID: 17336558 DOI: 10.1016/j.pupt.2006.12.005]

51 **Al-Biltagi M**, Bediwy AS, Mattar ME. Congenital insensitivity to pain, with impaired pulmonary functions, and diminished cough reflex. *Pediatr Pulmonol* 2021; **56**: 21-22 [PMID: 33174679 DOI: 10.1002/ppul.25148]

52 **Ciljakova M**, Vojtkova J, Durdik P, Turcan T, Petrikova M, Michnova Z, Banovcin P. Cough reflex sensitivity in adolescents with diabetic autonomic neuropathy. *Eur J Med Res* 2009; **14** Suppl 4: 45-48 [PMID: 20156724 DOI: 10.1186/2047-783x-14-s4-45]

53 **Varechova S**, Durdik P, Cervenkova V, Ciljakova M, Banovcin P, Hanacek J. The influence of autonomic neuropathy on cough reflex sensitivity in children with diabetes mellitus type 1. *J Physiol Pharmacol* 2007; **58** Suppl 5: 705-715 [PMID: 18204186]

54 **Dicpinigaitis PV**, Kantar A, Enilari O, Paravati F. Prevalence of Arnold Nerve Reflex in Adults and Children With Chronic Cough. *Chest* 2018; **153**: 675-679 [PMID: 29197546 DOI: 10.1016/j.chest.2017.11.019]

55 **Castro RA**, Zalvan CH, Berzofsky C. Oto-tricho-tussia: An Unexpected Cause of Cough. *Case Rep Otolaryngol* 2020; **2020**: 3527481 [PMID: 32292619 DOI: 10.1155/2020/3527481]

56 **Gold KR**, Wester JL, Gold R. Foreign Body in External Ear Canal: An Unusual Cause of Chronic Cough. *Am J Med* 2017; **130**: e143-e144 [PMID: 28159186 DOI: 10.1016/j.amjmed.2016.11.026]

57 **Ryan NM**, Gibson PG, Birring SS. Arnold's nerve cough reflex: evidence for chronic cough as a sensory vagal neuropathy. *J Thorac Dis* 2014; **6**: S748-S752 [PMID: 25383210 DOI: 10.3978/j.issn.2072-1439.2014.04.22]

58 **Mai Y**, Zhan C, Zhang S, Liu J, Liang W, Cai J, Lai K, Zhong N, Chen R. Arnold Nerve Reflex: Vagal Hypersensitivity in Chronic Cough With Various Causes. *Chest* 2020; **158**: 264-271 [PMID: 31945317 DOI: 10.1016/j.chest.2019.11.041]

59 **Kimber J**, Mitchell D, Mathias CJ. Chronic cough in the Holmes-Adie syndrome: association in five cases with autonomic dysfunction. *J Neurol Neurosurg Psychiatry* 1998; **65**: 583-586 [PMID: 9771793 DOI: 10.1136/jnnp.65.4.583]

60 **Shi G**, Shen Q, Zhang C, Ma J, Mohammed A, Zhao H. Efficacy and Safety of Gabapentin in the Treatment of Chronic Cough: A Systematic Review. *Tuberc Respir Dis (Seoul)* 2018; **81**: 167-174 [PMID: 29926540 DOI: 10.4046/trd.2017.0089]

61 **Waldmann V**, Combes N, Narayanan K, Sharifzadehgan A, Bouzeman A, Beganton F, Combes S, Albenque JP, Boveda S, Marijon E. Cough Syncope. *Am J Med* 2017; **130**: e295-e296 [PMID: 28238688 DOI: 10.1016/j.amjmed.2017.01.050]

62 **Katz RM**. Cough syncope in children with asthma. *J Pediatr* 1970; **77**: 48-51 [PMID: 5430795 DOI: 10.1016/s0022-3476(70)80043-9]

63 **Deshmukh A**, Schulle D. Cough syncope in a patient with severe chronic obstructive pulmonary disease. *Respiratory Medicine CME* 2008; **1**: 120-122 [DOI: 10.1016/j.rmedc.2008.01.004]

64 **Haslam RH**, Freigang B. Cough syncope mimicking epilepsy in asthmatic children. *Can J Neurol Sci* 1985; **12**: 45-47 [PMID: 3978474 DOI: 10.1017/s0317167100046576]

65 **Dicpinigaitis PV**, Lim L, Farmakidis C. Cough syncope. *Respir Med* 2014; **108**: 244-251 [PMID: 24238768 DOI: 10.1016/j.rmed.2013.10.020]

66 **Chen PK**, Fuh JL, Wang SJ. Cough headache: a study of 83 consecutive patients. *Cephalalgia* 2009; **29**: 1079-1085 [PMID: 19438909 DOI: 10.1111/j.1468-2982.2009.01844.x]

67 **Headache Classification Subcommittee of the International Headache Society**. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia* 2004; **24** Suppl 1: 9-160 [PMID: 14979299 DOI: 10.1111/j.1468-2982.2003.00824.x]

68 **Pascual J**, González-Mandly A, Martín R, Oterino A. Headaches precipitated by cough, prolonged exercise or sexual activity: a prospective etiological and clinical study. *J Headache Pain* 2008; **9**: 259-266 [PMID: 18751938 DOI: 10.1007/s10194-008-0063-5]

69 **Cordenier A**, De Hertogh W, De Keyser J, Versijpt J. Headache associated with cough: a review. *J Headache Pain* 2013; **14**: 42 [PMID: 23687906 DOI: 10.1186/1129-2377-14-42]

70 **Sansur CA**, Heiss JD, DeVroom HL, Eskioglu E, Ennis R, Oldfield EH. Pathophysiology of headache associated with cough in patients with Chiari I malformation. *J Neurosurg* 2003; **98**: 453-458 [PMID: 12650413 DOI: 10.3171/jns.2003.98.3.0453]

71 **Bailey PL**. Possible mechanism(s) of opioid-induced coughing. *Anesthesiology* 1999; **90**: 335 [PMID: 9915357 DOI: 10.1097/00000542-199901000-00067]

72 **Strober M**, Freeman R, Rigali J, Schmidt S, Diamond R. The pharmacotherapy of depressive illness in adolescence: II. Effects of lithium augmentation in nonresponders to imipramine. *J Am Acad Child Adolesc Psychiatry* 1992; **31**: 16-20 [PMID: 1537769 DOI: 10.1097/00004583-199201000-00004]

73 **López-Chiriboga AS**, Huang JF, Flanagan EP, Cheshire WP Jr. Paroxysmal sneezing in NMOSD: Further evidence of the localization of the human sneeze center. *Neurol Neuroimmunol Neuroinflamm* 2017; **4**: e303 [PMID: 27844040 DOI: 10.1212/NXI.0000000000000303]

74 **Seijo-Martínez M**, Varela-Freijanes A, Grandes J, Vázquez F. Sneeze related area in the medulla: localisation of the human sneezing centre? *J Neurol Neurosurg Psychiatry* 2006; **77**: 559-561 [PMID: 16354739 DOI: 10.1136/jnnp.2005.068601]

75 **Yao A**, Wilson JA, Ball SL. Autonomic nervous system dysfunction and sinonasal symptoms. *Allergy Rhinol (Providence)* 2018; **9**: 2152656718764233 [PMID: 29977656 DOI: 10.1177/2152656718764233]

76 **Oakley GM**, Alt JA, Schlosser RJ, Harvey RJ, Orlandi RR. Diagnosis of cerebrospinal fluid rhinorrhea: an evidence-based review with recommendations. *Int Forum Allergy Rhinol* 2016; **6**: 8-16 [PMID: 26370330 DOI: 10.1002/alr.21637]

77 **Rees CJ**, Henderson AH, Belafsky PC. Postviral vagal neuropathy. *Ann Otol Rhinol Laryngol* 2009; **118**: 247-252 [PMID: 19462843 DOI: 10.1177/000348940911800402]

78 **Jeyakumar A**, Brickman TM, Haben M. Effectiveness of amitriptyline versus cough suppressants in the treatment of chronic cough resulting from postviral vagal neuropathy. *Laryngoscope* 2006; **116**: 2108-2112 [PMID: 17146380 DOI: 10.1097/01.mlg.0000244377.60334.e3]

79 **Chu MW**, Lieser JD, Sinacori JT. Use of botulinum toxin type A for chronic cough: a neuropathic model. *Arch Otolaryngol Head Neck Surg* 2010; **136**: 447-452 [PMID: 20479373 DOI: 10.1001/archoto.2010.59]

80 **Michalowski A**, Haines A, Shaparin N, Gritsenko K, Kaye AD, Cornett EM, Lerner MZ. Transcutaneous Electrical Nerve Stimulation as a Treatment for Neuropathic Cough: A Tolerability and Feasibility Study. *Neurol Ther* 2021; **10**: 1127-1133 [PMID: 34002358 DOI: 10.1007/s40120-021-00255-2]

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MINIREVIEWS

Presentation and outcome of myocardial infarction with non-obstructive coronary arteries in coronavirus disease 2019

Kevin John, Amos Lal, Nitish Sharma, Amr ElMeligy, Ajay K Mishra

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Kevin John, Department of Critical Care, Believers Church Medical College Hospital, Thiruvalla 689103, Kerala, India

Amos Lal, Division of Pulmonary & Critical Care Medicine, Mayo Clinic, Rochester, MN 55905, United States

Nitish Sharma, Division of Cardiology, Saint Vincent Hospital, Worcester, MA 01608, United States

Amr ElMeligy, Division of Interventional Cardiology, Saint Vincent Hospital, Worcester, MA 01608, United States

Ajay K Mishra, Department of Cardiovascular Medicine, Saint Vincent Hospital, Worcester, MA 01608, United States

Corresponding author: Ajay K Mishra, FACP, MBBS, MD, Assistant Professor, Postdoctoral Fellow, Department of Cardiovascular Medicine, Saint Vincent Hospital, 123 Summer Street, Worcester, MA 01608, United States. ajay.mishra@stvincenthospital.com

Abstract

Among the cardiac complications of coronavirus disease 2019 (COVID-19), one increasingly reported in the literature is myocardial infarction with non-obstructive coronaries (MINOCA). We reviewed all reported cases of MINOCA in COVID-19 patients to summarize its clinical features, evaluation, and treatment. We performed a literature search in Pubmed using the search terms 'COVID-19' and 'MINOCA' or 'non-obstructive coronaries'. Among the reported cases, the mean age was 61.5 years (SD ± 13.4), and 50% were men. Chest pain was the presenting symptom in five patients (62.5%), and hypertension was the most common comorbidity (62.5%). ST-elevation was seen in most patients (87.5%), and the overall mortality rate was 37.5%. MINOCA in COVID-19 is an entity with a broad differential diagnosis. Therefore, a uniform algorithm is needed in its evaluation to ensure timely diagnosis and management.

Key Words: COVID-19; Myocardial infarction with non-obstructive coronary arteries; Outcome

Core Tip: Myocardial infarction with non-obstructive coronary arteries (MINOCA) may be more commonly seen in patients with coronavirus disease 2019 (COVID-19). To ensure that cases of MINOCA are identified and managed appropriately, a well-defined, algorithmic approach should be taken while evaluating COVID-19 patients with evidence of myocardial injury. This review summarizes the clinical characteristics and outcomes of all COVID-19 patients with MINOCA reported to date.

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INTRODUCTION

Myocardial infarction with non-obstructive coronaries (MINOCA) is defined as a rise or fall of cardiac troponin, with at least one value above the 99th percentile of the upper reference limit, corroborative clinical evidence of infarction (classic symptoms, electrocardiogram changes, or new wall motion abnormality), non-obstructive coronary arteries on angiography (< 50% obstruction), and lack of an alternative diagnosis[1]. MINOCA is seen in 5%-6% of patients with acute myocardial infarction (AMI)[2]. However, this number may be as high as 15% in certain subgroups[2]. Compared to patients with AMI due to obstructive coronary artery disease (CAD), patients with MINOCA are younger, consist of more women, and have a lesser prevalence of traditional risk factors such as dyslipidemia, diabetes mellitus, hypertension, tobacco use, and family history of AMI[1].

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to more than 4,250,000 deaths worldwide. Although primarily a respiratory illness, it is becoming increasingly clear that COVID-19 is a multi-system disease. How COVID-19 affects the cardiac system has been well documented. However, as more cases are reported, uncommon presentations and complications of COVID-19 are surfacing. Although there have been many reports of MINOCA in COVID-19 patients, a unified approach to evaluate such patients is lacking. In this paper, we review cases of MINOCA reported in patients with COVID-19 and provide a summary of its clinical features, evaluation, and treatment.

METHODS

In this review, we included articles on COVID-19 and MINOCA published in PubMed until January 2022. We used the search terms 'COVID-19' and 'MINOCA' or 'non-obstructive coronaries'. Case reports, case series, retrospective, and prospective observational studies on adult patients with COVID-19 were eligible to be included. We excluded opinions, recommendations, and reviews that did not have clinical details of patients. Patients whose initial diagnosis of MINOCA was modified after further evaluation were also excluded. Studies in languages other than English were translated using Google Translate. Two independent clinicians were involved in the screening of the articles.

RESULTS

We found five cases and one case series of three patients with MINOCA and COVID-19[3-8] (Table 1). We also found five observational studies of MINOCA in COVID-19 patients, which are discussed seperately[9-13] (Table 2). Among the reported cases, the mean age of patients was 61.5 years (SD ± 13.4), and 50% were men.

Demographic details and presentations

Chest pain was the presenting symptom in five patients (62.5%), two patients (25%) had dyspnea without chest pain, and one patient (12.5%) was found unresponsive at the time of presentation. Hypertension was the most common comorbidity and was present in 62.5% of the patients. Other comorbidities included diabetes mellitus, chronic obstructive pulmonary disease, non-ischemic heart failure with reduced ejection fraction, past ST-elevation myocardial infarction (STEMI), hypercholesterolemia, and motor-neuron disease.

Table 1 Case reports of myocardial infarction with non-obstructive coronary arteries in coronavirus disease 2019

Sl. No	Ref.	Age in yr	Sex	Presenting complaint	Comorbidities	Chest imaging	ECG	Cardiac troponins	Echocardiogram	Angiogram	Other investigations	Management	Outcome
1	[3]	47	M	Shortness of breath for 6 d, angina on day 2 of admittion	Hypertension	CT thorax: Diffuse bilateral infiltrates, ground glass opacities, crazy paving with thickened interlobular septa, and consolidation in lower lobes	Inferior STEMI	0.012 ng/mL (Ref range: < 0.0262 ng/mL)	Not reported	Emergency coronary angiography showed 30%-40% stenosis in the midportion of the left anterior descending artery. In addition to this, the left main coronary artery, left circumflex artery and right coronary artery were normal. ST segment elevation regressed in the ECG of the patient, who had no more ischemic cardiac symptoms after the intervention	CTPA did not reveal any evidence of pulmonary embolism. Cardiogoniometry (a non-invasive medical tool worked with spatiotemporal vectocardiographic advancement), was performed after 24 h of the pain, it revealed septal inferior myocardial ischemia	300 mg po acetylsalicylic acid, 180 mg po ticagrelor, and 4000 IU IV heparin	Discharged on the eleventh day of his hospitalization in a healthy state
2	[4]	48	F	Pain in her chest and left shoulder for 1 day	none	none	Inverted T-waves in II, III, aVF, V4, V5, and V6	Upward of 25000 pg/mL (Ref range: 0.0–51.4 pg/mL)	Hypokinesis in the apical inferior segment of the left ventricle	CTCA was performed to exclude a coronary origin for the complaints and for the laboratory and ECG abnormalities, which revealed no significant coronary obstruction	CMR showed features of myocardial oedema restricted to the mid-ventricular to apical territory of the right coronary artery (RCA). Based on subendocardial to partially transmural late gadolinium enhancement in the mid-ventricular to apical inferior wall, an acute myocardial infarction was diagnosed. Cardiac positron emission tomography–computed tomography showed evidence of reduced metabolic activity in the area affected by the infarction	Acetylsalicylic acid, prophylactic-dose low-molecular-weight heparin, and statin. Later dual anti-platelet therapy and an angiotensin-converting-enzyme inhibitor was started	Discharged. Follow-up echocardiography 2 d after discharge revealed a normal ejection fraction (58%) despite persistent inferior apical akinesia
3	[5]	86	M	Cough and shortness of breath which progressed		Chest X-ray: bilateral infiltrates at the bases with no	3–4 mm ST-segment elevations in leads V2 and	4.82 ng/mL (Ref range: < 0.10	Ejection fraction of 50%–55%, no significant regional wall motion	No significant coronary artery disease		Admitted to the intensive care unit, requiring mechanical ventilation and	Respiratory status worsened and he required increased oxygen and positive

				to acute hypoxemic respiratory failure requiring intubation		other abnormalities	V3	ng/mL	abnormalities, and no signs of cardiac tamponade			vasopressor support	end-expiratory pressure, renal function worsened, as did lymphopenia and inflammatory biomarker abnormalities. Died on day 8
4	[6]	61	M	Shortness of breath, respiratory failure requiring intubation	Hypertension, diabetes mellitus		2 mm of antero-lateral ST-elevation without reciprocal depression	6283 ng/L (Ref range: < 40 ng/L)	Moderate left ventricular systolic dysfunction	No luminal stenosis or thrombosis, with preserved TIMI 3 flows in all coronary arteries	Left ventriculography: Mild apical hypokinesis	Loading dose of ticagrelor and IV heparin	On day 13, he was anuric and CVVH was started. Continued to worsen and died
5	[6]	59	F	Found minimally responsive on the ground. Intubated by paramedics	Hypertension, COPD	CT thorax: Bilateral lower lung lobe infiltrates and pulmonary oedema with moderate calcification in the mid-left anterior descending artery	ST-segment elevations in V1–V4 and reciprocal ST-depressions in leads II, III, and aVF	2390 ng/L	reduced left ventricular ejection fraction of 40% with antero-apical wall hypokinesis	Moderate diffuse atherosclerotic disease was observed in the left system with no significant luminal obstruction elsewhere		Not specified	Extubated on Day 3. Discharged home subsequently
6	[6]	69	F	acute onset chest tightness and dyspnea	Non-ischemic heart failure with reduced ejection. Implantable cardioverter-defibrillator was placed in 2004. Motor neurone disease, diagnosed 4 yr previously	Chest X-ray: Bilateral infiltrates	Left bundle branch block. On day 3 progressive dynamic concordant ST-elevation in V1–V2 and ST-depression in V3–V5	504 ng/L	Impaired left ventricular function which was similar to baseline	No obstructive atheroma or thrombus		Loading dose dual antiplatelets, therapeutic low molecular weight heparin, high-dose IV diuretics, and IV nitrates	The patient died on Day 7 of admission
7	[7]	51	M	Left sided chest pain, diaphoresis, syncope	Hypertension and hypercholesterolemia	Chest X-ray: Bilateral interstitial prominenceCT chest: perihilar ground glass opacities, thickening of interlobular septa, and minimal bilateral	3.5 mm ST elevation in I and avL, 5 mm isolated ST elevation in lead V2, with deep reciprocal depressions in III, avF and avR	Not reported	Preserved left ventricular ejection fraction (LVEF) of 55% and anteroapical hypokinesis on ventriculography	Patent coronary arteries		Admitted to Cardiac Intensive Care Unit and started on supportive measures. Treated with lopinavir/ritonavir 400 mg/100 mg tablet every 12 h for 4 d and hydroxychloroquine 500 mg every 12 h, then hydroxy-	The patient recovered and was discharged home on day 26 on aspirin, statin and metoprolol

						pleural effusions, interpreted as consistent with congestive heart failure						chloroquine alone 400 mg daily	
8	[8]	71	F	Chest-pain	Hypertension, past STEMI	Chest X-ray: No pulmonary opacities	ST-segment elevation in inferior leads, and ST depression, and inverted T waves in V1-3	Negative	Preserved left ventricular ejection fraction of 50% with inferior and septal hypokinesis	Non-obstructive coronary artery disease		Loading dose of ticagrelor and unfractionated heparin	Discharged

M: Male; F: Female; ECG: electrocardiogram; CT: Computed tomography; STEMI: ST-elevation myocardial infarction; CTPA: Computed tomographic pulmonary angiography; CTCA: Computed tomography coronary angiography; CMR: Cardiac Magnetic Resonance Imaging; TIMI: Thrombolysis in myocardial infarction; CVVH: Continuous veno-venous hemofiltration; COPD: Chronic Obstructive Pulmonary Disease.

Investigations

ST-elevation was seen in most patients (87.5%), while one patient (12.5%) had only T-wave inversion. In addition, a new-onset left bundle branch block was seen in one patient (12.5%)[6]. Three-quarters of all patients had elevated troponin levels. On echocardiography, three patients (37.5%) had reduced ejection fraction, and four (50%) had preserved ejection fraction. One case report did not include echocardiography findings. Non-obstructive coronary arteries were demonstrated by invasive angiography in all patients, except one who underwent computed tomography coronary angiography (CTCA)[4]. Cardiac magnetic resonance imaging (CMR) was performed on one patient. It showed myocardial edema restricted to the mid-ventricular to apical territory of the right coronary artery, and subendocardial-to-partially transmural late gadolinium enhancement in the mid-ventricular to apical inferior wall. These findings were suggestive of acute myocardial infarction[4]. The same patient underwent cardiac positron emission tomography-computed tomography (PET-CT), which showed reduced metabolic activity in the area affected by the infarction. Another patient underwent computed tomographic pulmonary angiography, which ruled out pulmonary embolism, and cardiogoniometry, which revealed septal inferior myocardial ischemia[3].

Treatment and outcome

While most patients were treated with supportive care, antiplatelets, statins, and anticoagulation, one patient received anti-viral therapy (lopinavir/ritonavir) with hydroxychloroquine[7]. The overall mortality rate was 37.5%.

Observational studies reporting outcomes of MINOCA in COVID-19

In the five observational studies included in this review, the incidence of MINOCA among COVID-19 patients with an acute coronary syndrome varied from 5.2% to 54.5%[9-13]. Demographic details were only reported in the study by Stefanini *et al*[9]. The mean age of patients with MINOCA in that study was 69.27 years (SD ± 10.6), and 54.5% were male. Hypertension was the most common comorbidity

Table 2 Studies that reported myocardial infarction with non-obstructive coronary arteries in coronavirus disease 2019

Sl. No	Ref.	Total number of patients with MINOCA (%)	Mean age	Male (%)	Comorbidities (%)	Smoking(%)	Prior MI (%)	LVEF	EKG (%)	Mortality (%)
1	[9]	11/28 (39.3)	69.27 ± 10.6	6 (54.5)	Diabetes mellitus: 1/11 (9.1), Hypertension: 9/11 (91.8), Dyslipidemia: 3/11 (27.3), Chronic kidney disease: 5/11 (45.4)	1/11 (9.1)	1/11 (9.1)	43 ± 12.7	ST elevation: 9/11 (81.81), New onset LBBB: 2/11 (18.2)	5/11 (45.4)
2	[10]	6/11 (54.5)	-	-	-	-	-		-	-
3	[11]	3/9 (33.3)	-	-	-	-	--	Low ejection fraction and RWMA in 2 patients (ECHO not done for third)	ST elevation: 3/3 (100)	2/3 (66)
4	[12]	1/19 (5.2)	-	-	-	-		-	-	-
5	[13]	5/29 (17.24)	-	-	-	-	-	-	-	-

MINOCA: Myocardial infarction with non-obstructive coronary arteries; MI: Myocardial infarction; LVEF: Left ventricular ejection fraction; EKG: Electrocardiogram; LBBB: Left bundle branch block: RWMA: Regional Wall Motion Abnormality: ECHO: Echocardiography.

(91.8%), followed by chronic kidney disease (45.4%), dyslipidemia (27.3%) and diabetes mellitus (9.1%). The proportion of patients with ST-elevation on ECG was between 81.8% and 100%, and the mortality rate ranged from 45.4% to 66%.

DISCUSSION

Gross and Sternberg first described MINOCA in 1939[14]. Later, the term MINC or MINCA (myocardial infarction with normal coronary arteries) was coined, which was modified to MINOCA to be more inclusive. Other words that have been used in the literature to describe this pathology include 'acute coronary syndromes with normal or near-normal coronary arteries' (ACS-NNOCA) and ischemic syndromes with non-obstructive coronaries (INOCA). Strictly speaking, MINCA is a subset of MINOCA, which is a subset of ACS-NNOCA. The subtle differences between these terms have been confusing as these terms are often used interchangeably. Nevertheless, the term MINOCA provides a framework for evaluating such patients and is often used as a 'working diagnosis'. Further evaluation may reveal secondary causes such as myocarditis, Takostubo cardiomyopathy, sepsis, cardiac contusion, spontaneous coronary artery dissection, microvascular disease, coronary artery spasm, or missed obstructive coronary artery disease. If a secondary cause is not found, a diagnosis of 'unclassified MINOCA' is made[1].

The proportion of MINOCA seems to be higher in COVID-19 patients. In the study by Popovic *et al* [10], there was a statistically significant increase in the proportion of MINOCA in COVID-19 patients compared to a historical cohort (54.5% *vs* 1.4%, $P < 0.001$). Due to the heterogeneity in case definitions and evaluation protocols between centers, the actual proportion of MINOCA among COVID-19 patients is difficult to estimate. One can gauge the upper limit of this estimate from the proportion of COVID-19 patients with acute cardiac injury (ACI), which is one of the earliest measures of cardiac involvement reported during the COVID-19 pandemic. ACI, defined as cardiac-troponin elevation with values exceeding the 99th percentile of the upper reference limit, was observed in 8%-62% of COVID-19 patients [15]. Also noteworthy was that any amount of cardiac injury was significantly associated with mortality (adjusted HR 1.75, $P < 0.001$)[16].

Some other characteristics of COVID-19 patients with MINOCA can be extrapolated from the results of a systematic review of 161 patients from 42 studies of COVID-19 patients with ST-elevation[17]. The authors observed that patients with non-obstructive CAD had more diffuse ST-segment elevation (13% *vs* 1%, $P = 0.03$) and diffuse left ventricular wall-motion abnormality (23% *vs* 3%, $P = 0.02$) when compared to those with obstructive CAD[17]. In the same review, the proportion of men in the group with obstructive CAD was higher than in the group with non-obstructive CAD (79% *vs* 57%)[17].

Our literature review found that many patients with COVID-19 and MINOCA received alternative diagnoses such as Takotsubo cardiomyopathy, coronary vasospasm, myocarditis, and coronary vasculitis on further evaluation. This is consistent with the concept that MINOCA is a dynamic diagnosis, and patients who were initially diagnosed with MINOCA may receive a revised diagnosis on

further evaluation. However, some patients were presumed to have myocarditis without objective evidence for the same[18-21]. A diagnosis of MINOCA or MINOCA under evaluation would better suit such patients. It must also be noted that the cases of MINOCA with COVID-19 that were included in this review are cases of 'unclassified MINOCA.'

Specific causes for MINOCA in COVID-19 patients

Myocarditis: Myocarditis is defined as an inflammatory disease of the myocardium diagnosed by histological, immunological, immunohistochemical, and molecular criteria[22]. There have only been a handful of COVID-19 patients with endomyocardial biopsy-proven myocarditis[23,24]. Even in these patients, the SARS-CoV-2 genome could not be isolated from the biopsy sample. Thus, there is no conclusive proof that SARS-CoV-2 infects the myocardium resulting in myocarditis. Instead, the mechanism is probably one of immune-mediated damage and would justify steroids for treatment. However, many COVID-19 patients who were diagnosed with myocarditis do not meet the strict diagnostic criteria for the same, and giving steroids to such patients may be harmful[18-21].

Takotsubo cardiomyopathy: Takotsubo cardiomyopathy is an intriguing disorder, and its mechanism is yet to be elucidated fully. Takotsubo cardiomyopathy has been well documented in COVID-19 patients and can be due to the infection or the emotional stress associated with the pandemic[25]. Whether Takotsubo cardiomyopathy should be included as a cause of MINOCA is debatable. This is because the 'Fourth Universal Definition of Myocardial Infarction' does not consider Takotsubo cardiomyopathy a form of myocardial infarction[26]. On the other hand, the elevation of cardiac troponins is well documented in Takotsubo cardiomyopathy[27]. In our opinion, Takotsubo cardiomyopathy must be included in the diagnostic algorithm of MINOCA as there seems to be an increased incidence in COVID-19. Such a diagnosis carries certain therapeutic and prognostic implications as well.

Coronary vasculitis: Although coronary vasculitis is a rare cause of MINOCA, it has been reported in patients with COVID-19. Feuchtner *et al*[27] described an interesting case of a 48-year-old COVID-19 patient who was evaluated for chest pain and was found to have non-obstructive coronaries suggestive of MINOCA. However, further evaluation with CMR confirmed subendocardial inferior zonal late enhancement, and CTCA showed diffuse irregular vessel wall thickening and perivascular edema suggestive of vasculitis. The patient was managed with acetylsalicylic acid and clopidogrel and was discharged after cardiac enzyme levels declined. Postmortem studies showed COVID-19 viral inclusion bodies in endothelial cells, supporting the possibility of endothelial cell infection and endarteritis[28]. Hence, COVID-19 induced coronary vasculitis may be more common than currently reported. This case also underscores the importance of identifying patients with MINOCA and evaluating them further, rather than giving a presumptive diagnosis of myocarditis.

Spontaneous coronary artery dissection: Multiple case reports in COVID-19 patients have documented spontaneous coronary artery dissection[29-32]. The obstruction is caused by the separation of the medial and adventitial walls, with an intramural hematoma protruding into the lumen. It is hypothesized that there is an intrinsic underlying vasculopathy, and the dissection is precipitated by stress, catecholamine surge, physical activity, or sympathetic stimulation[33]. The underlying endothelial dysfunction and thrombo-inflammation may be the reason for coronary artery dissection occurring in COVID-19.

Coronary vasospasm: Diagnosis of coronary vasospasm in COVID-19 patients with MINOCA is challenging, but possible, if a systematic approach is followed. This was demonstrated by Rivero *et al* [34] in their case report of a 66-year-old man who presented with bilateral COVID-19 pneumonia and chest pain. After angiography, optical coherence tomography showed a stable, mainly fibrotic atheromatous plaque. The diagnosis of coronary vasospasm was clinched by administering intracoronary ergonovine at increasing doses which led to severe chest pain and universal ST-segment elevation. Coronary angiography done at this time revealed nearly occlusive coronary vasospasm involving both the left anterior descending coronary artery and left circumflex coronary artery. Given how challenging it is to diagnose coronary vasospasm, it may be another under-reported cause of MINOCA in COVID-19.

Miscellaneous causes: Type 2 myocardial infarction refers to events that occur due to a mismatch between myocardial oxygen supply and demand[26]. This is a heterogeneous class that can include various causes such as sepsis, anemia, arrhythmia, and pulmonary embolism-all of which can be seen in the setting of COVID-19 infection.

Evaluation of MINOCA

The differential diagnosis for MINOCA is broad, and therefore, a complete history and physical examination must remain at the core of its evaluation. It is also vital to re-take history and re-examine the patient multiple times at various stages of the evaluation process. This will ensure that investigations are directed appropriately and a 'fishing-expedition' approach is avoided. The initial set of investigations may give clues to the underlying diagnosis before more invasive tests are undertaken. In a prospective cohort of STEMI patients who underwent primary percutaneous coronary intervention

(PPCI) during the COVID-19 outbreak, patients with COVID-19 and MINOCA had elevated markers of inflammation and abnormal coagulation parameters[10]. Moreover, anti-phospholipid antibodies were observed in three of these patients.

Once obstructive coronary artery disease has been ruled out, the most important investigation for evaluating the cause of MINOCA is CMR[35]. A large prospective multicenter observational study conducted from 2007 to 2011 included 152 patients with MINOCA. In this study, CMR showed that 19% of the patients had signs of myocardial necrosis, 7% had signs of myocarditis, and 7% had unrecognized hypertrophic cardiomyopathy or could not be classified[36]. A meta-analysis of 34 studies with 199 COVID-19 patients for whom CMR was performed showed abnormal results in 79% and myocarditis in 40.2%[37]. A caveat is that the absence of myocardial necrosis on CMR does not exclude MINOCA as they may have other findings that support the diagnosis[38].

Prognosis

While the prognosis of MINOCA depends on the underlying disease, most studies to date indicate a better prognosis for MINOCA when compared to patients with AMI due to obstructive CAD[2]. A review of ST-elevation in COVID-19 patients observed an overall in-hospital mortality of 30%, with no significant difference between obstructive and non-obstructive CAD[17]. This is comparable with the mortality rate of 37.5% in our review. The effect of anti-viral therapy for MINOCA on COVID-19 is debatable. While none of the patients who died received anti-viral therapy, the small sample size and study designs preclude us from drawing definite conclusions[39,40]. As more cases of MINOCA are reported, it may be feasible to conduct well-designed prospective studies to explore these questions further.

LIMITATIONS

There are several limitations to this review. Many cases of MINOCA may have been treated along the lines of COVID-19 associated myocarditis. Therefore, it is likely that MINOCA is grossly under-reported in the literature. The small sample size of this review, due to the under-reporting of cases and the rarity of this condition, limits the generalizability of our findings. The publication of challenging cases with a positive outcome may have led to publication bias. There is also a lack of uniformity in the evaluation and diagnosis of MINOCA in COVID-19[41].

CONCLUSION

This review highlights that MINOCA in COVID-19 has a broad differential diagnosis that must be evaluated with a systematic diagnostic algorithm. COVID-19 patients with MINOCA had a mean age of 61.5 years, and 50% of them were men. The most common presenting symptom was chest pain (62.5%), and ST-elevation was present in most patients (87.5%). The overall mortality rate was 37.5%. More studies are required to arrive at a reliable estimate of the true prevalence and prognostic relevance of MINOCA.

FOOTNOTES

Author contributions: John K and Mishra AK contributed to the conceptual design of the study; John K and Mishra AK independently screened the articles and extracted the data; John K, Mishra AK, and Lal A contributed to the write-up and submission of the study; Mishra AK and Lal A reviewed the final manuscript; All authors reviewed and agreed with the final content of the article.

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Country/Territory of origin: United States

ORCID number: Kevin John 0000-0003-3382-0294; Amos Lal 0000-0002-0021-2033; Nitish Sharma 0000-0002-6221-3197; Amr ElMeligy 0000-0002-3053-0024; Ajay K Mishra 0000-0003-4862-5053.

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REFERENCES

1 **Tamis-Holland JE**, Jneid H, Reynolds HR, Agewall S, Brilakis ES, Brown TM, Lerman A, Cushman M, Kumbhani DJ, Arslanian-Engoren C, Bolger AF, Beltrame JF; American Heart Association Interventional Cardiovascular Care Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; and Council on Quality of Care and Outcomes Research. Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease: A Scientific Statement From the American Heart Association. *Circulation* 2019; **139**: e891-e908 [PMID: 30913893 DOI: 10.1161/CIR.0000000000000670]

2 **Pasupathy S**, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation* 2015; **131**: 861-870 [PMID: 25587100 DOI: 10.1161/CIRCULATIONAHA.114.011201]

3 **Eroglu SE**, Ademoglu E, Bayram S, Aksel G. A Rare Cause of ST-Segment Elevation Myocardial Infarction in COVID-19: MINOCA Syndrome. *Medeni Med J* 2021; **36**: 63-68 [PMID: 33828892 DOI: 10.5222/MMJ.2021.25478]

4 **Burkert FR**, Niederreiter L, Dichtl W, Mayr A, Virgolini I, Klauser A, Weiss G, Bellmann-Weiler R. Case report of a COVID-19-associated myocardial infarction with no obstructive coronary arteries: the mystery of the phantom embolus or local endothelitis. *Eur Heart J Case Rep* 2021; **5**: ytaa521 [PMID: 33598613 DOI: 10.1093/ehjcr/ytaa521]

5 **Meizinger C**, Klugherz B. Focal ST-segment elevation without coronary occlusion: myocardial infarction with no obstructive coronary atherosclerosis associated with COVID-19-a case report. *Eur Heart J Case Rep* 2021; **5**: ytaa532 [PMID: 33768195 DOI: 10.1093/ehjcr/ytaa532]

6 **Saririan M**, Armstrong R, George JC, Olechowski B, O'Connor S, Byrd JB, Chapman AR. ST-segment elevation in patients presenting with COVID-19: case series. *Eur Heart J Case Rep* 2021; **5**: ytaa553 [PMID: 33644657 DOI: 10.1093/ehjcr/ytaa553]

7 **Castagna F**, Cerrud-Rodriguez R, Villela MA, Bortnick AE. SARS-COV-2 infection presenting as ST-elevationmyocardial infarction. *Catheter Cardiovasc Interv* 2021; **97**: E339-E342 [PMID: 32473085 DOI: 10.1002/ccd.28974]

8 **Bujak K**, Kazik A, Wróbel M, Piegza J, Lekston A, Gąsior M. COVID-19 mimicking ST-elevation myocardial infarction. *Postepy Kardiol Interwencyjnej* 2020; **16**: 213-215 [PMID: 32636910 DOI: 10.5114/aic.2020.95632]

9 **Stefanini GG**, Montorfano M, Trabattoni D, Andreini D, Ferrante G, Ancona M, Metra M, Curello S, Maffeo D, Pero G, Cacucci M, Assanelli E, Bellini B, Russo F, Ielasi A, Tespili M, Danzi GB, Vandoni P, Bollati M, Barbieri L, Oreglia J, Lettieri C, Cremonesi A, Carugo S, Reimers B, Condorelli G, Chieffo A. ST-Elevation Myocardial Infarction in Patients With COVID-19: Clinical and Angiographic Outcomes. *Circulation* 2020; **141**: 2113-2116 [PMID: 32352306 DOI: 10.1161/CIRCULATIONAHA.120.047525]

10 **Popovic B**, Varlot J, Metzdorf PA, Jeulin H, Goehringer F, Camenzind E. Changes in characteristics and management among patients with ST-elevation myocardial infarction due to COVID-19 infection. *Catheter Cardiovasc Interv* 2021; **97**: E319-E326 [PMID: 32667726 DOI: 10.1002/ccd.29114]

11 **Bangalore S**, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, Ibrahim H, Friedman GH, Thompson C, Alviar CL, Chadow HL, Fishman GI, Reynolds HR, Keller N, Hochman JS. ST-Segment Elevation in Patients with Covid-19 - A Case Series. *N Engl J Med* 2020; **382**: 2478-2480 [PMID: 32302081 DOI: 10.1056/NEJMc2009020]

12 **Hamadeh A**, Aldujeli A, Briedis K, Tecson KM, Sanz-Sánchez J, Al Dujeili M, Al-Obeidi A, Diez JL, Žaliūnas R, Stoler RC, McCullough PA. Characteristics and Outcomes in Patients Presenting With COVID-19 and ST-Segment Elevation Myocardial Infarction. *Am J Cardiol* 2020; **131**: 1-6 [PMID: 32732010 DOI: 10.1016/j.amjcard.2020.06.063]

13 **Secco GG**, Tarantini G, Mazzarotto P, Garbo R, Parisi R, Maggio S, Vercellino M, Pistis G, Audo A, Kozel D, Centini G, Di Mario C. Invasive strategy for COVID patients presenting with acute coronary syndrome: The first multicenter Italian experience. *Catheter Cardiovasc Interv* 2021; **97**: 195-198 [PMID: 32400049 DOI: 10.1002/ccd.28959]

14 **Gross H**, Sternberg WH. Myocardial Infarction Without Significant Lesions of Coronary Arteries. *Arch Intern Med* 1939; **64**: 249-267. [DOI: 10.1001/archinte.1939.00190020035003]

15 **Lippi G**, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis. *Prog Cardiovasc Dis* 2020; **63**: 390-391 [PMID: 32169400 DOI: 10.1016/j.pcad.2020.03.001]

16 **Lala A**, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, Zhao S, Somani S, Van Vleck T, Vaid A, Chaudhry F, De Freitas JK, Fayad ZA, Pinney SP, Levin M, Charney A, Bagiella E, Narula J, Glicksberg BS, Nadkarni G, Mancini DM, Fuster V; Mount Sinai COVID Informatics Center. Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection. *J Am Coll Cardiol* 2020; **76**: 533-546 [PMID: 32517963 DOI: 10.1016/j.jacc.2020.06.007]

17 **Diaz-Arocutipa C**, Torres-Valencia J, Saucedo-Chinchay J, Cuevas C. ST-segment elevation in patients with COVID-19: a systematic review. *J Thromb Thrombolysis* 2021; **52**: 738-745 [PMID: 33646500 DOI: 10.1007/s11239-021-02411-9]

18 **El-Assaad I**, Hood-Pishchany MI, Kheir J, Mistry K, Dixit A, Halyabar O, Mah DY, Meyer-Macaulay C, Cheng H. Complete Heart Block, Severe Ventricular Dysfunction, and Myocardial Inflammation in a Child With COVID-19 Infection. *JACC Case Rep* 2020; **2**: 1351-1355 [PMID: 32835278 DOI: 10.1016/j.jaccas.2020.05.023]

19 **Khalid Y**, Dasu N, Dasu K. A case of novel coronavirus (COVID-19)-induced viral myocarditis mimicking a Takotsubo cardiomyopathy. *HeartRhythm Case Rep* 2020; **6**: 473-476 [PMID: 32817822 DOI: 10.1016/j.hrcr.2020.05.020]

20 **Hussain H**, Fadel A, Alwaeli H, Guardiola V. Coronavirus (COVID-19) Fulminant Myopericarditis and Acute Respiratory Distress Syndrome (ARDS) in a Middle-Aged Male Patient. *Cureus* 2020; **12**: e8808 [PMID: 32607304 DOI: 10.7759/cureus.8808]

21 **Rehman M**, Gondal A, Rehman NU. Atypical Manifestation of COVID-19-Induced Myocarditis. *Cureus* 2020; **12**: e8685

[PMID: 32577331 DOI: 10.7759/cureus.8685]

22 **Caforio AL**, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Heliö T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013; **34**: 2636-2648, 2648a [PMID: 23824828 DOI: 10.1093/eurheartj/eht210]

23 **Sala S**, Peretto G, Gramegna M, Palmisano A, Villatore A, Vignale D, De Cobelli F, Tresoldi M, Cappelletti AM, Basso C, Godino C, Esposito A. Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. *Eur Heart J* 2020; **41**: 1861-1862 [PMID: 32267502 DOI: 10.1093/eurheartj/ehaa286]

24 **Tavazzi G**, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, Sepe PA, Resasco T, Camporotondo R, Bruno R, Baldanti F, Paolucci S, Pelenghi S, Iotti GA, Mojoli F, Arbustini E. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. *Eur J Heart Fail* 2020; **22**: 911-915 [PMID: 32275347 DOI: 10.1002/ejhf.1828]

25 **John K**, Lal A, Mishra A. A review of the presentation and outcome of takotsubo cardiomyopathy in COVID-19. *Monaldi Arch Chest Dis* 2021; **91** [PMID: 33759445 DOI: 10.4081/monaldi.2021.1710]

26 **Thygesen K**, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation* 2018; **138**: e618-e651 [PMID: 30571511 DOI: 10.1161/CIR.0000000000000617]

27 **Feuchtner GM**, Barbieri F, Luger A, Skalla E, Kountchev J, Widmann G, Plank F. Myocardial injury in COVID-19: The role of coronary computed tomography angiography (CTA). *J Cardiovasc Comput Tomogr* 2021; **15**: e3-e6 [PMID: 32747170 DOI: 10.1016/j.jcct.2020.07.002]

28 **Varga Z**, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417-1418 [PMID: 32325026 DOI: 10.1016/S0140-6736(20)30937-5]

29 **Papanikolaou J**, Alharthy A, Platogiannis N, Balhamar A, Alqahtani SA, Memish ZA, Karakitsos D. Spontaneous coronary artery dissection in a patient with COVID-19. *Coron Artery Dis* 2021; **32**: 354-355 [PMID: 33394695 DOI: 10.1097/MCA.0000000000000991]

30 **Aparisi A**, Ybarra-Falcón C, García-Granja PE, Uribarri A, Gutiérrez H, Amat-Santos IJ. COVID-19 and spontaneous coronary artery dissection: causality? *REC Interv Cardiol* 2021; **3**: 134-143 [DOI: 10.24875/RECICE.M20000185]

31 **Shojaei F**, Habibi Z, Goudarzi S, Firouzabadi FD, Montazerin SM, Najafi H, Kahe F, Momenzadeh K, Mir M, Khan F, Jamil U, Jamil A, Lee JJ, Chi G. COVID-19: A double threat to takotsubo cardiomyopathy and spontaneous coronary artery dissection? *Med Hypotheses* 2021; **146**: 110410 [PMID: 33267999 DOI: 10.1016/j.mehy.2020.110410]

32 **Yapan Emren Z**, Emren V, Özdemir E, Karagöz U, Nazlı C. Spontaneous right coronary artery dissection in a patient with COVID-19 infection: A case report and review of the literature. *Turk Kardiyol Dern Ars* 2021; **49**: 334-338 [PMID: 34106068 DOI: 10.5543/tkda.2021.34846]

33 **Saw J**, Aymong E, Sedlak T, Buller CE, Starovoytov A, Ricci D, Robinson S, Vuurmans T, Gao M, Humphries K, Mancini GB. Spontaneous coronary artery dissection: association with predisposing arteriopathies and precipitating stressors and cardiovascular outcomes. *Circ Cardiovasc Interv* 2014; **7**: 645-655 [PMID: 25294399 DOI: 10.1161/CIRCINTERVENTIONS.114.001760]

34 **Rivero F**, Antuña P, Cuesta J, Alfonso F. Severe coronary spasm in a COVID-19 patient. *Catheter Cardiovasc Interv* 2021; **97**: E670-E672 [PMID: 32738164 DOI: 10.1002/ccd.29056]

35 **Collet JP**, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021; **42**: 1289-1367 [PMID: 32860058 DOI: 10.1093/eurheartj/ehaa575]

36 **Collste O**, Sörensson P, Frick M, Agewall S, Daniel M, Henareh L, Ekenbäck C, Eurenius L, Guiron C, Jernberg T, Hofman-Bang C, Malmqvist K, Nagy E, Arheden H, Tornvall P. Myocardial infarction with normal coronary arteries is common and associated with normal findings on cardiovascular magnetic resonance imaging: results from the Stockholm Myocardial Infarction with Normal Coronaries study. *J Intern Med* 2013; **273**: 189-196 [PMID: 22742529 DOI: 10.1111/j.1365-2796.2012.02567.x]

37 **Ojha V**, Verma M, Pandey NN, Mani A, Malhi AS, Kumar S, Jagia P, Roy A, Sharma S. Cardiac Magnetic Resonance Imaging in Coronavirus Disease 2019 (COVID-19): A Systematic Review of Cardiac Magnetic Resonance Imaging Findings in 199 Patients. *J Thorac Imaging* 2021; **36**: 73-83 [PMID: 33306666 DOI: 10.1097/RTI.0000000000000574]

38 **Reynolds HR**, Srichai MB, Iqbal SN, Slater JN, Mancini GB, Feit F, Pena-Sing I, Axel L, Attubato MJ, Yatskar L, Kalhorn RT, Wood DA, Lobach IV, Hochman JS. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. *Circulation* 2011; **124**: 1414-1425 [PMID: 21900087 DOI: 10.1161/CIRCULATIONAHA.111.026542]

39 **Philip AM**, George LJ, John KJ, George AA, Nayar J, Sahu KK, Selvaraj V, Lal A, Mishra AK. A review of the presentation and outcome of left ventricular thrombus in coronavirus disease 2019 infection. *J Clin Transl Res* 2021; **7**: 797-808 [PMID: 34988332]

40 **John KJ**, Nayar J, Mishra AK, Selvaraj V, Khan MS, Lal A. In-hospital clinical complications of COVID-19: a brief overview. *Future Virol* 2021 [PMID: 34777553 DOI: 10.2217/fvl-2021-0200]

41 **Ramasamy C**, Mishra AK, John KJ, Lal A. Clinical considerations for critically ill COVID-19 cancer patients: A systematic review. *World J Clin Cases* 2021; **9**: 8441-8452 [PMID: 34754852 DOI: 10.12998/wjcc.v9.i28.8441]

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ORIGINAL ARTICLE

Case Control Study

Plasma D-dimer level in early and late-onset neonatal sepsis

Mohammed Al-Biltagi, Ehab M Hantash, Mohammed Ramadan El-Shanshory, Enayat Aly Badr, Mohamed Zahra, Manar Hany Anwar

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Mohammed Al-Biltagi, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31511, Algharbia, Egypt

Mohammed Al-Biltagi, Department of Pediatrics, University Medical Center, Arabian Gulf University, Manama 26671, Manama, Bahrain

Mohammed Al-Biltagi, Department of Pediatrics, University Medical Center, Bahrain, Dr. Sulaiman Al Habib Medical Group, KSA, Manama 26671, Manama, Bahrain

Ehab M Hantash, Department of Anatomy, Faculty of Medicine, Tanta University, Tanta 31511, Alghrabia, Egypt

Ehab M Hantash, Neonatology Unit, Department of Pediatrics, Dr. Sulaiman Al Habib Medical Group, Riyadh 11636, Riyadh, Saudi Arabia

Mohammed Ramadan El-Shanshory, Department of Pediatrics, Hematol Unit, Tanta University, Faculty of Medicine, Tanta 31511, Algharbia, Egypt

Enayat Aly Badr, Mohamed Zahra, Department of Clinical Pathology, Faculty of Medicine, Tanta University, Tanta 31511, Alghrabia, Egypt

Manar Hany Anwar, Department of Clinical Pathology, Ministry of Health, Egypt, Tanta 31511, Alghrabia, Egypt

Corresponding author: Mohammed Al-Biltagi, MBChB, MD, MSc, PhD, Chairman, Professor, Department of Pediatrics, Faculty of Medicine, Tanta University, Medical Complex, AlBahr Street, Tanta 31511, Algharbia, Egypt. mbelrem@hotmail.com

Abstract

BACKGROUND

Neonatal sepsis is a life-threatening disease. Early diagnosis is essential, but no single marker of infection has been identified. Sepsis activates a coagulation cascade with simultaneous production of the D-dimers due to lysis of fibrin. D-dimer test reflects the activation of the coagulation system.

AIM

To assess the D-dimer plasma level, elaborating its clinicopathological value in neonates with early-onset and late-onset neonatal sepsis.

METHODS

The study was a prospective cross-sectional study that included ninety neonates; divided into three groups: Group I: Early-onset sepsis (EOS); Group II: Late-onset sepsis (LOS); and Group III: Control group. We diagnosed neonatal sepsis according to our protocol. C-reactive protein (CRP) and D-dimer assays were compared between EOS and LOS and correlated to the causative microbiological agents.

RESULTS

D-dimer was significantly higher in septic groups with a considerably higher number of cases with positive D-dimer. Neonates with LOS had substantially higher levels of D-dimer than EOS, with no significant differences in CRP. Neonates with LOS had a significantly longer hospitalization duration and higher gram-negative bacteriemia and mortality rates than EOS ($P < 0.01$). Gram-negative bacteria have the highest D-dimer levels (Acinetobacter, Klebsiella, and Pseudomonas) and CRP (Serratia, Klebsiella, and Pseudomonas); while gram-positive sepsis was associated with relatively lower levels. D-dimer had a significant negative correlation with hemoglobin level and platelet count; and a significant positive correlation with CRP, hospitalization duration, and mortality rates. The best-suggested cut-off point for D-dimer in neonatal sepsis was 0.75 mg/L, giving a sensitivity of 72.7% and specificity of 86.7%. The D-dimer assay has specificity and sensitivity comparable to CRP in the current study.

CONCLUSION

The current study revealed a significant diagnostic value for D-dimer in neonatal sepsis. D-dimer can be used as an adjunct to other sepsis markers to increase the sensitivity and specificity of diagnosing neonatal sepsis.

Key Words: Early-onset neonatal sepsis; Late-onset neonatal sepsis; C-reactive protein; D-dimer

Core Tip: The study aimed to define the diagnostic and prognostic value of the D-dimer assay in early and late-onset sepsis. We prospectively studied C-reactive protein and D-dimer levels in 90 neonates divided into control, Early-onset sepsis, and late-onset sepsis. D-dimer was significantly higher in the septic groups, more in late-onset than early-onset sepsis, and with gram-negative sepsis than gram-positive sepsis. The best-suggested cut-off point for D-dimer in neonatal sepsis was 0.75 mg/L, giving a sensitivity of 72.7% and specificity of 86.7%.

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INTRODUCTION

Neonatal sepsis is a severe systemic inflammatory response to blood-stream infection with high morbidity and mortality during the neonatal period. Early and proper diagnosis of neonatal sepsis is critical for timely-administered antibiotics, decreases the length of the hospital stay, and improves the prognosis, especially the neurodevelopmental outcome[1]. To diagnose neonatal sepsis, the physicians usually depend on the blood culture, the gold standard, and some screening tools such as acute phase reactants and cytokines, for instance, the white blood cell count, C-reactive protein (CRP), procalcitonin, interleukin-6, interleukin-8, CD11b, and CD64. However, the blood culture yield is not always accurate, with the possibility of false-negative and positive results. Acute phase reactants and cytokines may have high sensitivity to diagnose bacterial sepsis, but they may lack high specificity and good predictive value[2,3].

As sepsis is a clinical condition resulting from the interaction between the microbial agent and the host immune, inflammatory, and coagulation responses, some studies showed changes in the circulating coagulation proteins coupled with impaired fibrinolytic activity in patients with confirmed sepsis[4]. Activation of the coagulation cascade resulting from the released sepsis-induced; inflammatory cytokines enhance the degradation of cross-linked fibrin polymers with increased production of D-dimer[5]. Consequently, D-dimer is considered a specific marker for increased procoagulatory activity and fibrinolysis. Elevation of D-dimer and fibrinogen degradation products rapidly occurs after dissem-

inated intravascular coagulation (DIC) initiation, which may arise as a complication of sepsis[6]. Activation of the coagulation reflected by the increase in D-dimer levels contributes significantly to the sepsis outcome. Different ways to assess D-dimer levels are available, including enzyme-linked immunofluorescence immunoassay, microplate enzyme-linked immunosorbent assay, latex quantitative, latex semiquantitative, latex qualitative, and whole-blood assays[7]. In this study, we aimed to assess the plasma level of D-dimer in infants with neonatal sepsis to throw more light on its clinicopathological value in patients having neonatal sepsis.

MATERIALS AND METHODS

The present research was a prospective cross-sectional study conducted on ninety-four full-term neonates recruited serially from the Neonatal Intensive Care Unit (NICU), Pediatric department; the tertiary care hospital of Tanta University between January 2019 to January 2021. The recruited neonates were divided into three comparable groups: Group I included neonates with early sepsis (who developed sepsis within the first week after childbirth), Group II included neonates with late neonatal sepsis (who developed sepsis within the first week after birth), and Group III included healthy neonates with no clinical manifestation of sepsis and negative CRP and Gerdes sepsis screen less than two, recruited from the postnatal ward of the Obstetric Department and the outpatient clinic. All parents, guardians, or next of kin signed informed consent for the minors to participate in this study. The Institutional Ethical and Research Review Board of the Faculty of Medicine, Tanta University, approved the study.

We diagnosed neonatal sepsis based on the presence of suspected clinical signs of sepsis, positive CRP (≥ 10 mg/L), positive Gerdes' sepsis screen (≥ 2), and positive blood culture. Sepsis was suspected in the presence of fever or temperature instability, irritability, lethargy, feeding difficulty, apnea or respiratory distress, hepatomegaly, abdominal distention, convulsion, hypotonia, hemodynamic instability, or bleeding diathesis. As the diagnosis of neonatal sepsis is hampered by the frequent presence of non-infectious conditions that may mimic sepsis, we only included those with proven sepsis and positive blood culture in the study. According to Neonatal Intensive Care Unit protocol, all children with suspected sepsis receive the appropriate management.

We excluded premature neonates and neonates with congenital heart diseases, hypoxic-ischemic encephalopathy, liver diseases, renal diseases, hereditary coagulopathy, or other non-sepsis-related systemic disorders that could affect the level of CRP or D-dimer levels. All included neonates had thorough prenatal, natal, and postnatal history, thorough clinical examination, complete blood cell count (CBC) with differential, CRP levels, urine analysis and culture, blood culture, cerebrospinal fluid (CSF) analysis, and culture, and other infection markers as indicated. Chest X-ray, echocardiography, or abdominal X-ray were tailored according to the clinical indications. The D-dimer assay was performed using the D-dimer test device (NycoCard D-dimer, Axis-Shield, Oslo, Norway) and the Nycocard READER II (NycoCard READER II, Axis-Shield, Oslo, Norway). It is a single rapid test for detection of D-dimer in plasma and is based upon an immunometric flow-through, sandwich-format, immunofiltration principle. CRP levels were measured using high-sensitive Tinaquant CRP (Latex) immunoturbidimetric assay using Roche Modular P analyzer (CRP latex HS, Roche kit; Roche Diagnostics, GmbH, D-68298 Mannheim, Germany), following the manufacturer's instructions.

Statistical analysis

We used the Power and Precision V3 program to estimate the power level of the primary endpoint (serum level of D-dimer with a mean level of 1.0 ± 0.3 mg/L) (http://www.Power-Analysis.com, Englewood, New Jersey). The power level was 90% when using 30 patients for each group. The collected data were organized, tabulated, and statistically analyzed using SPSS version 19 (Statistical Package for Social Studies, IBM, Chicago, IL, United States). For numerical values, the range means and standard deviations were calculated. The differences between the two mean values were used using the student's *t*-test. Differences in mean values between more than two groups were tested by analysis of variance (F). We used the Scheffe test to compare every two groups when we found significance. The number and percentage were calculated for categorical variables, and differences between subcategories were tested by chi-square. Fisher and Monte Carlo exact tests were used when chi-square was not appropriate. We used the receiver operating characteristic (ROC) test to evaluate the diagnostic power of the different diagnostic techniques. We used Pearson's correlation coefficient to test the relations between two variables. Sensitivity, specificity, and predictive values were calculated to differentiate the ability to diagnose sepsis by CRP, Gerdes, and I/T ratio. We adopted the level of significance at $P < 0.05$.

RESULTS

Figure 1 shows the flow chart of the study, which included three groups: the control group (30 healthy

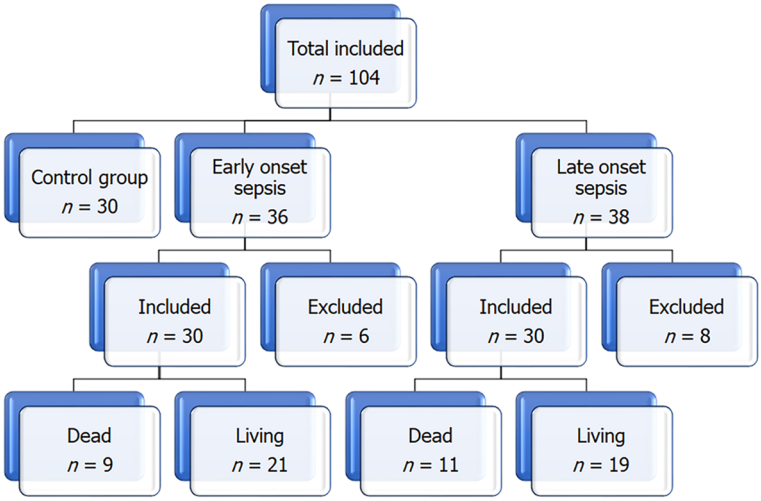

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Figure 1 The flow chart of the study.

neonates), Neonates with EOS (30 neonates after exclusion of 36 neonates), and neonates with LOS (30 neonates after exclusion of 8 neonates). The neonates were recruited sequentially. Table 1 and Figure 2 show the groups' demographics, clinical presentation, and laboratory testing. There were no significant differences between the groups in the male-to-female ratio, presentation weight, and cesarean section rate. However, LOS was more common in males than females. We found no significant differences in the clinical presentation between EOS and LOS, although respiratory distress was more common in the EOS while cyanosis was more common in LOS. However, the number of neonates with a positive Gerdes score (≥ 2) was significantly higher in the EOS than in LOS. Premature rupture of membranes was present in 20% of cases with EOS. While umbilical vein catheterization or endotracheal intubation was more common in EOS, combined umbilical vein catheterization and endotracheal intubation were significantly more common in LOS. Neonates with EOS had a substantially higher rate of thrombocytopenia than LOS. However, Neonates with LOS had considerably higher levels of D-dimer than EOS. Meanwhile, we found no significant differences in CRP levels in neonates with EOS or LOS. However, neonates with LOS had a significantly longer duration of hospitalization and higher mortality rates than neonates with EOS.

Table 2 shows the microbial profile of neonates with EOS and LOS. The gram-negative bacteremia rate was significantly higher in LOS than in EOS, while gram-positive bacteremia was markedly higher in EOS than in LOS ($P < 0.01$). *Klebsiella* was the most common isolated gram-negative organism, while *Group B Streptococcus* was the most common isolated gram-positive organism. Table 3 shows the blood levels of D-dimer and CRP according to the isolated organism, with gram-negative bacteria having the highest levels of D-dimer (*Acinetobacter, Klebsiella, and Pseudomonas*) and CRP (*Serratia, Klebsiella, and Pseudomonas*). On the other hand, gram-positive sepsis was associated with relatively lower levels of D-dimer and CRP. Table 4 showed that D-dimer had a significant negative correlation with hemoglobin level and platelet count while having a significant positive correlation with CRP, duration of the hospital stays, and mortality. The D-dimer levels were non-significantly higher in the neonates who died (1.91 ± 1.72) than those who survived (1.81 ± 1.68). We used the ROC curves to evaluate D-dimer's diagnostic power (discriminative ability) to diagnose neonatal sepsis. It revealed a significant diagnostic value for D-dimer for neonatal sepsis. The best-suggested cut-off point for D-dimer in neonatal sepsis is 0.75 mg/L, giving a sensitivity of 72.7% and specificity of 86.7% (Table 5).

DISCUSSION

The current study examined D-dimer yield in diagnosing neonatal sepsis in 90 neonates, divided into three groups, early-onset, last onset sepsis, and a control group. Despite there being no significant differences in gender among the studied group, we observed an increased rate of LOS in males than in females, which could be related to a diminished cell-mediated immune response in males as it is an X-chromosome-linked trait with the expression of some sex-specific pro-and anti-inflammatory cytokines [8].

D-dimers are the D fragments of fibrinogen resulting from fibrinolysis during the plasmin mediated lysis of fibrin and are more specific than fibrin/fibrinogen degradation products and can serve as an indicator of microcirculatory failure[9]. In the current study, we found a significant increase in serum level of D-dimer in both patient groups with sepsis compared to the control, being significantly higher

Table 1 The control and patients' demographic and clinical and laboratory data

		Control group (*n* = 30)	EOS group (*n* = 30)	LOS group (*n* = 30)	*t*/*Z*	*P* value
Age (mean ± SD, d)		2.10 ± 0.8	2.47 ± 0.57	12.47 ± 4.03	147.024	0.001
Weight (mean ± SD, g)		2.98 ± 0.4	2.85 ± 0.41	2.95 ± 0.3	0.895	NS
Male: Female		0.9:1	0.87: 1	1.5:1	0.356	NS
% of cesarean section		23 (76.7%)	22 (73.3%)	21 (70%)	0.381	NS
PROM		0	6 (20%)	0		
Risk factors (invasive procedure)	UVC	0	4 (13.3%)	0		0.001
	ETT	0	5 (16.7%)	4 (13.3%)		0.001
	UVC + ETT	0	7 (23.3%)	13 (43.3%)		0.001
	None	100%	14 (46.7%)	13 (43.3%)		0.001
Respiratory distress		0	27 (90%)	23 (77%)	1.920	NS
Apnea		0	3 (10%)	3 (10%)	FE	NS
Cyanosis		0	10 (33.3%)	14 (46.7%)	1.111	NS
Positive Gerdes score (≥ 2)		0	22 (73.3%)	19 (63.3 %)	38.258	0.001
Thrombocytopenia		2 (6.7%)	22 (73%)	12 (40%)	6.787	0.009
CRP (mg/dL)		4 ± 2	57.53 ± 38.82	65.47 ± 39.62	0.783	NS
D-dimer (mg/L)		0.60 ± 0.70	1.48 ± 1.44	2.27 ± 1.86	10.512	0.001
Hospital duration		0	21.6 ± 10	22 ± 9	0.051	NS
Mortality		0	9 (30%)	11 (36.7%)	0.300	NS

ETT: Endotracheal intubation; PROM: Premature rupture of membranes; UVC: Umbilical vein catheterization; NS: Not significant.

Table 2 Microbial profile in the patients' groups

		EOS group (*n* = 30)	LOS group (*n* = 30)	Total (*n* =60)	*t*	*P* value
Gram-negative bacteria	Total	21 (70.0%)	28 (93.3%)	49 (81.67%)	2.3	< 0.01
	Klebsiella	15 (50%)	20 (67%)	35 (58%)	1.3	NS
	E. coli	4 (13.30%)	1 (3.3%)	5 (8.33%)	-1.4	NS
	Acinetobacter	2 (6.66%)	4 (13.30%)	6 (10%)	0.85	NS
	Serratia	0%	1 (3.3%)	1 (1.66%)		
	Pseudomonas	0%	2 (6.66%)	2 (3.33%)		
Gram-positive bacteria	Total	8 (26.7%)	2 (6.7%)	10 (16.7%)	-2.07	< 0.01
	Group B Streptococcus	5 (16.60%)	0%	5 (8.33%)		
	CoNS	2 (6.66%)	1 (3.3%)	3 (5%)	-0.6	NS
	Enterococcus	1 (3.3%)	0%	1 (1.66%)		
	MRSA	0%	1 (3.3%)	1 (1.66%)		
Candida		1 (3.3%)	0%	1 (1.66%)		

EOS: Early-onset sepsis; LOS: Late-onset sepsis; *E. coli*: *Escherichia coli*; *CoNS*: *Coagulase-negative staphylococci*; *MRSA*: *Methicillin-resistant Staphylococcus aureus*; NS: Not significant.

in the LOS than the EOS. These findings agree with Peker *et al*[10] and Mautone *et al*[11], who found high D-dimer levels in neonates with sepsis. These results contrast with Brahmana *et al*[12], who found low D-dimer in neonates with sepsis. This difference could be related to the gestational age of the neonates recruited, as they included preterm babies in their study.

Table 3 Comparing D-dimer and C-reactive protein levels according to the isolated organisms

Organism		D-dimer (mean ± SD)	CRP (mean ± SD)
Gram-negative bacteria	*E. coli*	1.3 ± 0.81	44.2 ± 4.3
	Klebsiella	2.0971 ± 1.98916	71.1 ± 3.9
	Acinetobacter	2.1333 ± 1.63	37.7 ± 3.4
	Pseudomonas	1.95 ± 0.92	64.0 ± 5.65
	Serratia	1.8 ± 0.4	99.0 ± 0.79
Gram-positive bacteria	*Group B Streptococcus*	1.6 ± 10.6	39.7 ± 2.5
	CoNS	1.3 ± 0.51	53.7 ± 2.7
	MRSA	1.2 ± 0.60	58.0 ± 8.2

CRP: C-reactive protein; *E. coli*: *Escherichia coli*; *CoNS*: *Coagulase-negative staphylococci*; *MRSA*: *Methicillin-resistant Staphylococcus aureus*.

Table 4 Correlation between D-Dimer and other variables

Variables	D-dimer	
	R	*P* value
Hemoglobin	-0.246	0.020[1]
Platelets	-0.228	0.031[1]
CRP	0.249	0.018[1]
Duration of the hospital stays	0.4	0.001[1]
Mortality	0.43	0.001[1]

[1]Significant.
CRP: C-reactive protein.

Table 5 Recipient observer characteristics curve results for D-dimer to diagnose neonatal sepsis

ROC curve results	The area under the curve	*P* value	Cut off point	Sensitivity	Specificity
D-dimer (mg/L)	0.822	0.001	0.75	72.7%	86.7%

ROC: Receiver operating characteristic.

Our study found that D-dimer has a high sensitivity (72.7%) and specificity (86.7%) to diagnose neonatal sepsis with a cut-off point of 0.822 mg/L. This finding agrees with the work of Pancham *et al* [13], who found that D-dimer had a sensitivity (90.0%) and negative predictive value (84.4%) in predicting sepsis. Considering the relatively high sensitivity of D-dimer, it can be beneficial as an additional diagnostic tool for neonatal sepsis. However, we should consider the relatively low specificity of the D-dimer. The current study observed that D-dimer was higher in the LOS than in neonates with EOS. The increase of D-dimer in LOS than EOS may be related to increased frequency of gram-negative bacterial sepsis and rate of invasive procedures such as umbilical vein catheterization and endotracheal intubation compared to EOS, as we observed a significant increase of D-dimer plasma levels in gram-negative sepsis when compared to EOS. Previous studies showed that the inflammatory cytokines, reflecting the severity of infection, increased from 1.5-5 folds in gram-negative sepsis compared to gram-positive sepsis[14]. Unfortunately, we did not find previous studies comparing D-dimer levels between gram-negative and gram-positive sepsis. Meini *et al*[15] found that the D-dimer level can predict the severity and the course of severe invasive infections caused by the gram-negative bacteria *Neisseria meningitides* while failing to expect the course of the disease in invasive infections caused by *Streptococcus pneumoniae*. The increased rate of invasive procedures in LOS compared to EOS in our study could be an effect rather than a cause due to the increased rate of gram-negative sepsis with increasing severity. Meanwhile, there were higher rates of maternal risk factors such as premature rupture of membranes in the neonates with EOS than with LOS in our study. This finding could explain

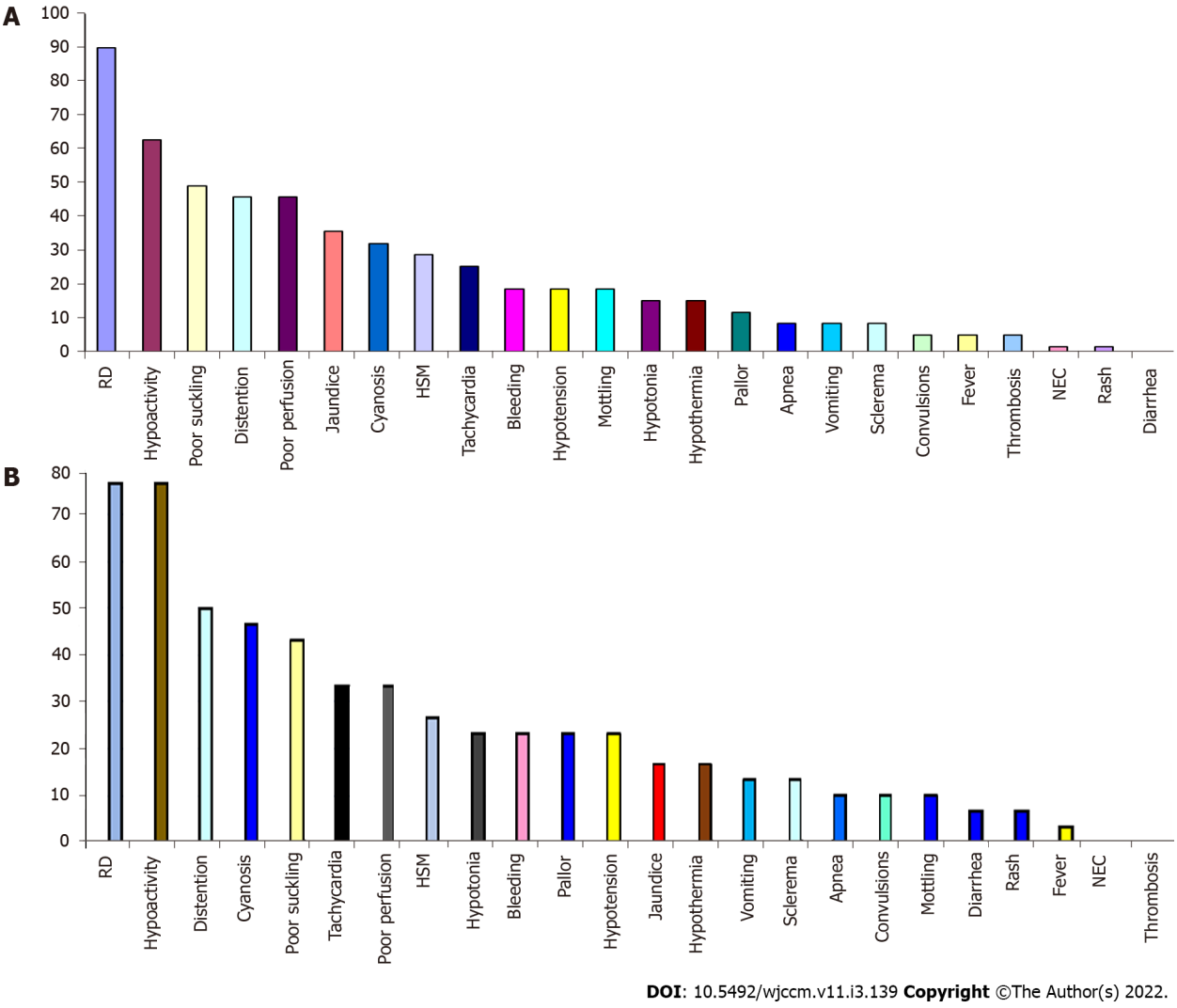

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Figure 2 The groups' demographics, clinical presentation, and laboratory testing. A: Frequency (%) of manifestations of sepsis in patients with early-onset sepsis; B: Frequency (%) of manifestations of sepsis in patients with late-onset sepsis.

why gram-positive sepsis was relatively more common in EOS than in LOS.

In the current study, we observed a significant positive correlation of D-dimer with CRP level, duration of hospitalization, and mortality rate. CRP is a marker of inflammation and plays a role in the inflammatory process itself, activating the complement pathway, phagocytosis, apoptosis, and the production and release of cytokines[16]. CRP evaluation has a role in neonatal sepsis diagnosis even though many studies showed low or at least variable validity in screening neonatal sepsis and being a non-specific test[17,18]. However, it is a good indicator of the success of the antibiotic treatment[19]. The addition of D-dimer to CRP can increase the sensitivity and specificity of both tests in the diagnosis of neonatal sepsis. We also observed a significant positive correlation of the level of D-dimer with the duration of hospitalization, which agrees with the results of previous studies[20,21]. The positive correlation of D-dimer level with the mortality rate observed in the current research is related to many factors, as high D-dimer is observed in gram-negative sepsis, which carries high mortality risk and is associated with elevated CRP, indicating the severity of inflammation.

The high mortality observed in the current study is related to the high percentage of gram-negative sepsis included in the study. Our NICU is the leading tertiary NICU in the region, receiving critically sick and septic neonates from peripheral units. Most of the isolated gram-negative organisms were Acinetobacter and Klebsiella; most were MDR. Meanwhile, many neonates had severe thrombocytopenia and markedly elevated CRP, which predict a worse prognosis. Our results agree with the meta-analysis done by Shah *et al*[22]. They found that patients with COVID-19 infection and elevated D-dimer levels had a higher risk of severe morbidity and mortality. Our results also agree with Ay *et al*[23], who found that a high D-dimer level was associated with a poor survival rate and high mortality rate in patients with cancer.

In the current study, we found a significant negative correlation of D-dimer with both hemoglobin (%) and the platelet count. Platelets have an active role in the host defense mechanisms as they can

perform phagocytosis. Their activation helps generate cytotoxic free radicals and oxidative molecules that destroy the invading organisms[24]. The current study found thrombocytopenia in 73% and 40% of EOS and LOS, respectively. Thrombocytopenia could be one of the presenting signs of neonatal sepsis but lack sensitivity and specificity and may appear late in the disease, which questions its usefulness as an initial marker of neonatal sepsis. However, we found a significant negative correlation between platelet count and plasma D-dimer levels. This correlation could reflect early or developing DIC, linked to increased fibrin degradation products (FDP) and D-dimer levels and increased platelet consumption [25]. Other possible causes of neonatal sepsis-associated thrombocytopenia could be increased platelet activation, diffuse endothelial cell injury, and bacterial/fungal toxins-associated platelet destruction [26]. Our results agree with Ree *et al*[27]. They reported that thrombocytopenia is independently associated with intravascular thrombosis and gram-negative sepsis, increasing the mortality risk nearly four to six-fold, especially in gram-negative sepsis.

Limitations

We have some limitations in the current study. We had a relatively small sample size. At the same time, the study was conducted in a single institution, so the results could not be generalized.

CONCLUSION

Neonatal sepsis is a life-threatening disease with high mortality and morbidity. The D-dimer is an exciting and promising biomarker for neonatal sepsis, able to predict morbidity and mortality. The current study revealed a significant diagnostic value for the D-dimer in neonatal sepsis. D-dimer can be used as an adjunct to other sepsis markers to increase the sensitivity and specificity of diagnosing neonatal sepsis.

ARTICLE HIGHLIGHTS

Research background

Neonatal sepsis is one of the critical conditions that put the life of neonates in danger. It is a severe systemic inflammatory response to blood-stream infections with significant neonatal morbidity and mortality. Early and proper diagnosis of neonatal sepsis is critical for timely-administered antibiotics, decreases the length of the hospital stay, and improves the prognosis, especially the neurodevelopmental outcome.

Research motivation

Early and proper diagnosis of neonatal sepsis is critical for appropriate and effective management with timely-administered antibiotics to decrease the hospitalization length and improve the prognosis, especially for the neurodevelopmental prospects.

Research objectives

We aimed to evaluate the significance of plasma D-dimer level in the early diagnosis of neonatal sepsis and elaborate on its clinicopathological value in neonates with early-onset and late-onset neonatal sepsis.

Research methods

The study was a prospective cross-sectional study that included ninety neonates; divided into early-onset sepsis (EOS) group (Group I), late-onset sepsis (LOS) group (Group II), and control group (Group III). We diagnosed neonatal sepsis according to our protocol. C-reactive protein (CRP) and D-dimer assay were compared and related to the causative microbiological agents.

Research results

D-dimer was significantly higher in septic groups. Septic groups showed a significantly higher number of cases with positive D-dimer. Neonates with LOS had considerably higher levels of D-dimer than EOS. At the same time, there were no significant differences in CRP levels in neonates with EOS or LOS. However, neonates with LOS had a significantly longer duration of hospitalization and higher mortality rates than neonates with EOS. The rate of gram-negative bacteremia was substantially higher in LOS than in EOS, while the rate of gram-positive bacteremia was significantly higher in EOS than in LOS ($P < 0.01$). Gram-negative bacteria have the highest D-dimer levels (Acinetobacter, Klebsiella, and Pseudomonas) and CRP (Serratia, Klebsiella, and Pseudomonas). On the other hand, gram-positive sepsis was associated with relatively lower levels of D-dimer and CRP. D-dimer had a significant negative correlation with hemoglobin level and platelet count while having a significant positive

correlation with CRP, duration of the hospital stays, and mortality. The best-suggested cut-off point for D-dimer in neonatal sepsis was 0.75 mg/L, giving a sensitivity of 72.7% and specificity of 86.7%. The D-dimer assay showed lower specificity and comparable sensitivity relative to CRP in the current study.

Research conclusions

The study revealed a significant diagnostic value for D-dimer in neonatal sepsis. D-dimer can be used as an adjunct to other sepsis markers to increase the sensitivity and specificity of diagnosing neonatal sepsis.

Research perspectives

To generalize our results, the authors need to include larger sample size and perform a multicenter study.

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FOOTNOTES

Author contributions: Anwar MH and El-Shanshory MR performed the clinical work and collected the data; Badr EA and Zahara MK performed the laboratory part; Hantash EM did the statistical analysis; Al-Biltagi M analyzed the data and wrote the manuscript; and All the authors revised and agreed to the final version of the manuscript.

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ORCID number: Mohammed Al-Biltagi 0000-0002-7761-9536; Ehab M Hantash 0000-0002-4164-6014; Mohammed Ramadan El-Shanshory 0000-0002-7995-8662; Enayat Aly Badr 0000-0002-9438-7255; Mohamed Zahra 0000-0002-1923-2659; Manar Hany Anwar 0000-0001-8927-2990.

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REFERENCES

1 **Simonsen KA**, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. *Clin Microbiol Rev* 2014; **27**: 21-47 [PMID: 24396135 DOI: 10.1128/CMR.00031-13]

2 **Marks L**, de Waal K, Ferguson JK. Time to positive blood culture in early-onset neonatal sepsis: A retrospective clinical study and review of the literature. *J Paediatr Child Health* 2020; **56**: 1371-1375 [PMID: 32621356 DOI: 10.1111/jpc.14934]

3 **Morad EA**, Rabie RA, Almalky MA, Gebriel MG. Evaluation of Procalcitonin, C-Reactive Protein, and Interleukin-6 as Early Markers for Diagnosis of Neonatal Sepsis. *Int J Microbiol* 2020; **2020**: 8889086 [PMID: 33061986 DOI:

10.1155/2020/8889086]
4 **Semeraro N**, Ammollo CT, Semeraro F, Colucci M. Sepsis-associated disseminated intravascular coagulation and thromboembolic disease. *Mediterr J Hematol Infect Dis* 2010; **2**: e2010024 [PMID: 21415977 DOI: 10.4084/MJHID.2010.024]
5 **Fiusa MM**, Carvalho-Filho MA, Annichino-Bizzacchi JM, De Paula EV. Causes and consequences of coagulation activation in sepsis: an evolutionary medicine perspective. *BMC Med* 2015; **13**: 105 [PMID: 25943883 DOI: 10.1186/s12916-015-0327-2]
6 **Trimaille A**, Thachil J, Marchandot B, Curtiaud A, Leonard-Lorant I, Carmona A, Matsushita K, Sato C, Sattler L, Grunebaum L, Hansmann Y, Fafi-Kremer S, Jesel L, Ohana M, Morel O. D-Dimers Level as a Possible Marker of Extravascular Fibrinolysis in COVID-19 Patients. *J Clin Med* 2020; **10** [PMID: 33374487 DOI: 10.3390/jcm10010039]
7 **Coskun F**, Yilmaz D, Ursavas A, Uzaslan E, Ege E. Relationship between disease severity and D-dimer levels measured with two different methods in pulmonary embolism patients. *Multidiscip Respir Med* 2010; **5**: 168-172 [PMID: 22958319 DOI: 10.1186/2049-6958-5-3-168]
8 **Angele MK**, Pratschke S, Hubbard WJ, Chaudry IH. Gender differences in sepsis: cardiovascular and immunological aspects. *Virulence* 2014; **5**: 12-19 [PMID: 24193307 DOI: 10.4161/viru.26982]
9 **Chapin JC**, Hajjar KA. Fibrinolysis and the control of blood coagulation. *Blood Rev* 2015; **29**: 17-24 [PMID: 25294122 DOI: 10.1016/j.blre.2014.09.003]
10 **Peker E**, Akbayram S, Geylani H, Dogan M, Kirimi E. Global fibrinolytic capacity in neonatal sepsis. *Clin Appl Thromb Hemost* 2011; **17**: E64-E69 [PMID: 21078608 DOI: 10.1177/1076029610384113]
11 **Mautone A**, Giordano P, Montagna O, Quercia M, Altomare M, De Mattia D. Coagulation and fibrinolytic systems in the ill preterm newborn. *Acta Paediatr* 1997; **86**: 1100-1104 [PMID: 9350893 DOI: 10.1111/j.1651-2227.1997.tb14816.x]
12 **Brahmana AR**, Lubis BM, Ali M. The role of d-dimer levels as a marker of neonatal sepsis. *Glob J Res Anal* 2019; **8**: 47-49 [DOI: 10.1136/archdischild-2019-epa.783]
13 **Pancham K**, Anjula C, Parveen B, Lokesh C, Mohit K. D-dimer: A useful marker in neonatal sepsis. *J Clin Neonatol* 2015; **4**: 101-103 [DOI: 10.4103/2249-4847.154552]
14 **Surbatovic M**, Popovic N, Vojvodic D, Milosevic I, Acimovic G, Stojicic M, Veljovic M, Jevdjic J, Djordjevic D, Radakovic S. Cytokine profile in severe Gram-positive and Gram-negative abdominal sepsis. *Sci Rep* 2015; **5**: 11355 [PMID: 26079127 DOI: 10.1038/srep11355]
15 **Meini S**, Sozio E, Bertolino G, Sbrana F, Ripoli A, Pallotto C, Viaggi B, Andreini R, Attanasio V, Rescigno C, Atripaldi L, Leonardi S, Bernardo M, Tascini C. D-Dimer as Biomarker for Early Prediction of Clinical Outcomes in Patients With Severe Invasive Infections Due to *Streptococcus Pneumoniae* and *Neisseria Meningitidis*. *Front Med (Lausanne)* 2021; **8**: 627830 [PMID: 33937280 DOI: 10.3389/fmed.2021.627830]
16 **Sproston NR**, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. *Front Immunol* 2018; **9**: 754 [PMID: 29706967 DOI: 10.3389/fimmu.2018.00754]
17 **Khan F**. C-reactive Protein as a Screening Biomarker in Neonatal Sepsis. *J Coll Physicians Surg Pak* 2019; **29**: 951-953 [PMID: 31564268 DOI: 10.29271/jcpsp.2019.10.951]
18 **Hisamuddin E**, Hisam A, Wahid S, Raza G. Validity of C-reactive protein (CRP) for diagnosis of neonatal sepsis. *Pak J Med Sci* 2015; **31**: 527-531 [PMID: 26150837 DOI: 10.12669/pjms.313.6668]
19 **Ahmed E**, Rehman A, Ali MA. Validation of serum C-reactive protein for the diagnosis and monitoring of antibiotic therapy in neonatal sepsis. *Pak J Med Sci* 2017; **33**: 1434-1437 [PMID: 29492073 DOI: 10.12669/pjms.336.13927]
20 **Dhainaut JF**, Shorr AF, Macias WL, Kollef MJ, Levi M, Reinhart K, Nelson DR. Dynamic evolution of coagulopathy in the first day of severe sepsis: relationship with mortality and organ failure. *Crit Care Med* 2005; **33**: 341-348 [PMID: 15699837 DOI: 10.1097/01.ccm.0000153520.31562.48]
21 **Rodelo JR**, De la Rosa G, Valencia ML, Ospina S, Arango CM, Gómez CI, García A, Nuñez E, Jaimes FA. D-dimer is a significant prognostic factor in patients with suspected infection and sepsis. *Am J Emerg Med* 2012; **30**: 1991-1999 [PMID: 22795996 DOI: 10.1016/j.ajem.2012.04.033]
22 **Shah S**, Shah K, Patel SB, Patel FS, Osman M, Velagapudi P, Turagam MK, Lakkireddy D, Garg J. Elevated D-Dimer Levels Are Associated With Increased Risk of Mortality in Coronavirus Disease 2019: A Systematic Review and Meta-Analysis. *Cardiol Rev* 2020; **28**: 295-302 [PMID: 33017364 DOI: 10.1097/CRD.0000000000000330]
23 **Ay C**, Dunkler D, Pirker R, Thaler J, Quehenberger P, Wagner O, Zielinski C, Pabinger I. High D-dimer levels are associated with poor prognosis in cancer patients. *Haematologica* 2012; **97**: 1158-1164 [PMID: 22371182 DOI: 10.3324/haematol.2011.054718]
24 **Ali RA**, Wuescher LM, Worth RG. Platelets: essential components of the immune system. *Curr Trends Immunol* 2015; **16**: 65-78 [PMID: 27818580]
25 **Sridhar A**, Sunil Kumar BM, Rau A, Rau ATK. A Correlation of the Platelet Count with D-Dimer Levels as an Indicator for Component Therapy in Children with Dengue Hemorrhagic Fever. *Indian J Hematol Blood Transfus* 2017; **33**: 222-227 [PMID: 28596655 DOI: 10.1007/s12288-016-0686-7]
26 **Sheu JR**, Hung WC, Wu CH, Ma MC, Kan YC, Lin CH, Lin MS, Luk HN, Yen MH. Reduction in lipopolysaccharide-induced thrombocytopenia by triflavin in a rat model of septicemia. *Circulation* 1999; **99**: 3056-3062 [PMID: 10368125 DOI: 10.1161/01.cir.99.23.3056]
27 **Ree IMC**, Fustolo-Gunnink SF, Bekker V, Fijnvandraat KJ, Steggerda SJ, Lopriore E. Thrombocytopenia in neonatal sepsis: Incidence, severity and risk factors. *PLoS One* 2017; **12**: e0185581 [PMID: 28977011 DOI: 10.1371/journal.pone.0185581]

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ORIGINAL ARTICLE

Retrospective Study

Stress cardiomyopathy in critical care: A case series of 109 patients

Parth Pancholi, Nader Emami, Melissa J Fazzari, Sumit Kapoor

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Parth Pancholi, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY 10467, United States

Nader Emami, Division of Critical Care Medicine, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY 10467, United States

Melissa J Fazzari, Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY 10461, United States

Sumit Kapoor, Division of Critical Care Medicine, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY 10467, United States

Corresponding author: Sumit Kapoor, MD, Division of Critical Care Medicine, Department of Medicine, Montefiore Medical Center, Bronx, NY 10467, United States.
drkapoorsumit@gmail.com

Abstract

BACKGROUND

Critically ill patients are at risk of developing stress cardiomyopathy (SC) but can be under-recognized.

AIM

To describe a case series of patients with SC admitted to critical care units.

METHODS

We conducted a retrospective observational study at a tertiary care teaching hospital. All adult (≥ 18 years old) patients admitted to the critical care units with stress cardiomyopathy over 5 years were included.

RESULTS

Of 24279 admissions to the critical care units [19139 to medical-surgical intensive care units (MSICUs) and 5140 in coronary care units (CCUs)], 109 patients with SC were identified. Sixty (55%) were admitted to the coronary care units (CCUs) and forty-nine (45%) to the medical-surgical units (MSICUs). The overall incidence of SC was 0.44%, incidence in CCU and MSICU was 1.16% and 0.25% respectively. Sixty-two (57%) had confirmed SC and underwent cardiac catheterization whereas 47 (43%) had clinical SC, and did not undergo cardiac catheterization. Forty-three (72%) patients in the CCUs were diagnosed with primary SC, whereas all (100%) patients in MSICUs developed secondary SC. Acute respiratory failure that required invasive mechanical ventilation and shock developed in twenty-nine (59%) MSICU patients. There were no statistically significant differences in

intensive care unit (ICU) mortality, in-hospital mortality, use of inotropic or mechanical circulatory support based on type of unit or anatomical variant.

CONCLUSION

Stress cardiomyopathy can be under-recognized in the critical care setting. Intensivists should have a high index of suspicion for SC in patients who develop sudden or worsening unexplained hemodynamic instability, arrhythmias or respiratory failure in ICU.

Key Words: Stress cardiomyopathy; Critical care; Shock; Respiratory failure

Core Tip: In our retrospective study, we found that stress cardiomyopathy (SC) is often under-recognized in the critical care setting. Primary SC is commonly seen in the coronary care units and the secondary form predominates in the medical-surgical intensive care unit setting. Presentation of secondary SC is often atypical and the majority of patients have simultaneous acute respiratory failure and sepsis. High index of clinical suspicion for SC is needed in patients who develop sudden or worsening unexplained hemodynamic instability, arrhythmias or respiratory failure. Cardiac catheterization may not be always feasible to confirm the diagnosis. Routine utilization of point of care ultrasound on all intensive care unit patients will help identify more cases. The outcomes of these patients are excellent as majority of them show reversibility of cardiac function on follow up imaging.

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INTRODUCTION

Stress cardiomyopathy (SC) or Takotsubo cardiomyopathy or broken heart syndrome, was first described three decades ago in Japan[1]. It is characterized by acute and transient (< 21 d) left ventricular systolic and diastolic dysfunction, often precipitated by emotional or physical stress[1-6]. The diagnosis is usually made by modified Mayo Clinic criteria comprising of echocardiographic pattern of left ventricular apical hypokinesia, akinesia, or dyskinesia (apical ballooning) and basal hyperkinesis, electrocardiogram (EKG) changes (ST segment elevation and/or T wave inversion), troponin elevation and clean coronaries during cardiac catheterization[7].

Primary or classic SC has a reported incidence of around 1%-2% in patients with a suspicion of acute coronary syndrome (ACS) and is usually precipitated by physical or psychological stress[1]. Secondary SC, on the other hand, usually develops in hospitalized medical, surgical and neurological patients who may be under the major stress of critical illness in the medical-surgical intensive care unit (MSICU) setting[2,3,6,8-24].

The diagnosis of secondary stress cardiomyopathy in critically ill intensive care unit (ICU) patients can be challenging, requires a high degree of clinical suspicion, and is often under-recognized and under-reported for a myriad of reasons[8]. First, ICU patients do not always present with or report typical cardiac symptoms such as chest pain, shortness of breath, and syncope as patients presenting from the community do[8]. Second, there are no established diagnostic criteria for secondary stress cardiomyopathy in ICU patients and extrapolation of 2008 modified Mayo criteria may not be ideal[8]. Third, cardiac catheterization cannot be routinely performed in critically ill patients to confirm the diagnosis[8]. Fourth, patients can present with atypical morphologic variants of stress cardiomyopathy and there can be overlap with other diagnoses like sepsis induced cardiomyopathy[25]. Lastly, various multicenter international registries' data did not include critically ill patients, thereby limiting understanding of the clinical presentation and outcomes of this disease in the ICU population[8].

Very few studies have reported the incidence, clinical features and outcomes of stress cardiomyopathy in the intensive care setting[3,9,10,12-19,25-27]. None of them compared characteristics and outcomes based on critical care unit [MSICU *vs* coronary care unit (CCU)]. The reported incidence of secondary stress cardiomyopathy in the ICU varies from 0.37% to as high as 28%[3,13,14,16,18,19]. Jo *et al*[15] described underlying malignancy, male sex, old age and high APACHE2 score as the predictors of in-hospital mortality in patients with stress cardiomyopathy.

The aim of our research was to describe the case series of patients with stress cardiomyopathy admitted to the critical care units (CCUs and MSICUs) and study their clinical presentation, complications, and outcomes.

MATERIALS AND METHODS

Study design

We performed a retrospective case series study where all adult (≥ 18 years old) patients with the diagnosis of Stress cardiomyopathy or Takotsubo cardiomyopathy admitted to the critical care units of three hospitals in the Montefiore Healthcare System were included. Electronic health records for the 5-year period from January 1, 2015, to December 31, 2019, were retrospectively analyzed incorporating Looking Glass Clinical Analytics (Streamline Health, Atlanta, GA) to identify the target population. Critical care units included two coronary care units (CCUs) and five medical surgical units (medical, surgical or neurosurgical ICUs). The study was approved by the Institutional Review Board of the Albert Einstein College of Medicine (IRB# 2019-10754) and waiver of informed consent was granted due to minimal risk. Data about patient demographics, baseline characteristics, laboratory values, hospital course, complications and outcomes were collected for patients admitted to the critical care units.

Study definitions

The diagnosis of stress cardiomyopathy was made by the ICU teams collectively using a combination of 2-dimensional echocardiography, cardiac enzymes, EKG changes, and in some cases, coronary angiography.

Confirmed SC: Patients with SC who underwent cardiac catheterization to prove the absence of underlying coronary artery disease.

Clinical SC: Patients with SC who did not undergo cardiac catheterization and diagnosis was made clinically using 2D-echocardiography, cardiac enzymes and EKG changes only.

Primary SC: Patients with SC presenting from the community with cardiac symptoms like angina, dyspnea or palpitations. Clinical presentation mimics ACS, often precipitated by physical or mental stress.

Secondary SC: Patients developing SC during the course of hospitalization with critical medical, surgical or neurosurgical illness.

Typical variant of SC: Echocardiography regional wall motion abnormality pattern showing apical akinesis with basal hyperkinesis (apical ballooning).

Atypical variant of SC: Echocardiography regional wall motion abnormality pattern showing midventricular, basal, focal, or global hypokinesia.

Statistical analysis

Continuous variables were reported as median and interquartile range (IQR), whereas categorical variables were reported as counts and percentages. Associations between categorical variables and unit were tested *via* chi-square or Fisher's exact test, as appropriate. Distributional differences between critical care units (CCU *vs* MS/ICU) with respect to continuous variables were assessed *via* Wilcoxon Mann-Whitney tests. Cumulative incidence functions for hospital discharge from the time of SC diagnosis stratified by critical care unit to allow for the competing risk of in-hospital death were estimated and differences tested using Grey's test[28]. Cumulative incidence functions for in-hospital death from the time of SC diagnosis with a competing risk of hospital discharge alive were computed similarly. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, United States) by the biomedical statistician. A two-sided P value of 0.05 or less was considered statistically significant.

RESULTS

Incidence and baseline characteristics

Of 24279 admissions to the critical care units (19139 MSICU and 5140 in CCU) over the five-year study period, 109 patients with SC were identified. Sixty (55%) of them were admitted to the coronary care units and forty-nine (45%) to the medical-surgical units. The overall incidence of SC was 0.44%, incidence in CCU and MSICU was 1.16% and 0.25% respectively. Sixty-two (57%) had confirmed SC and underwent cardiac catheterization whereas 47 (43.1%) had clinical SC and did not undergo cardiac

catheterization. Forty-three (72%) patients in the CCUs were diagnosed with primary SC, whereas all (100%) patients in MSICUs developed secondary SC.

Overall, the mean (SD) age was 67.2 (14.2) years and 72% were females. Hypertension and Diabetes Mellitus were the most common comorbidities seen in 65 (60%) and 40 (37%) patients respectively. Patients in the CCUs had more hypertension compared to those in MSICUs (70% *vs* 47%, $P = 0.01$). Table 1 lists the baseline characteristics of the study patients, both overall and stratified by critical care unit (CCU *vs* MSICU).

Unit course, complications and outcomes

Shortness of breath was the most common presenting symptom seen in 55 (50%) of the patients overall. Twenty-seven (45%) patients in the CCU complained of chest pain compared to only eight (16%) in MSICUs. Acute respiratory failure that required invasive mechanical ventilation was seen in twenty-nine (59%) MSICU patients, as opposed to only fifteen (25%) in CCU. Twenty-nine (59%) of patients in medical-surgical units also developed shock compared to twelve (20%) of the cardiac patients. Septic shock was the most common type of shock in MSICUs *vs* cardiogenic shock in CCUs (47% *vs* 8%, $P < 0.001$).

All SC patients had transthoracic echocardiography performed, with only 12 (24.5%) in MSICU getting cardiac catheterization, compared to 50 (83.3%) CCU patients. The majority ($n = 87$, 80%) of the cases were of typical anatomical type with apical akinesia/hypokinesia and basal hyperkinesia (apical ballooning). Inotropic support was required in ten patients and mechanical circulatory support in three patients. Follow up echocardiogram was performed in sixty-nine (63.3%) patients, all of them had complete reversibility of cardiac function. Of 47 patients with clinical SC, 27 had follow up echocardiography; all of them showed return to baseline cardiac function. Table 2 presents the complications and outcomes of SC by type of unit (MSICU *vs* CCU).

There was a statistically significant difference in the cumulative incidence function of hospital discharge stratified by critical care unit (0.56 *vs* 0.24 at 7 d, $P = 0.01$) but non-significant for in-hospital deaths stratified by critical care unit ($P = 0.33$) (Figure 1). Median length of stay from time of SC diagnosis to unit discharge was 1 d (range, 0-14) in CCU *vs* 5 d (range, 1-24) in MSICU.

A total of fifteen patients died out of which eight deaths were in the critical care units. There were no statistically significant differences in the peak laboratory values of creatine phosphokinase (CPK), troponin and pro-BNP (pro-B-type natriuretic peptide) or outcomes like ICU mortality, in-hospital mortality, use of inotropic or mechanical circulatory support based on type of unit (MSICU *vs* CCU) or anatomical variant (typical *vs* atypical) (Tables 3 and 4).

DISCUSSION

To our knowledge, this is the largest case series describing the clinical presentation, complications and outcomes of patients with stress cardiomyopathy admitted to the critical care units (MSICUs and CCUs). The overall incidence of SC in our patients was 0.44%, incidence in medical-surgical ICU was 0.25%, all of them having developed secondary SC. The incidence of SC in medical-surgical units varies per previous published reports. One of the earlier studies done by Park *et al*[13] in 2005 screened 92 consecutive critically ill patients admitted to medical ICU by serial echocardiography on day 1, 3, and 7. They observed a high incidence (28%) of left ventricular apical ballooning (LVAB) in medical ICU patients with no cardiac diseases. Patients with LVAB had higher prevalence of sepsis, hypotension upon ICU admission, use of inotropes, pulmonary edema, cardiomegaly and lower mean 2-month survival compared to patients without LVAB. The higher incidence of SC reported in the Park *et al*[13] study is likely because the diagnosis was solely made based on echocardiographic findings without integrating EKG, cardiac enzymes and coronary angiogram findings. An Australian study showed a much lower incidence of silent LVAB of around 3.5% in their medical ICU without any association of negative outcomes with silent LVAB[27]. Another prospective single center study by Doyen *et al*[14] in medical ICU patients found a high incidence of secondary SC of 4.6%. Our reported incidence of 0.25% in MSICUs is lower than the prior studies, because of the prospective nature of those studies, where all patients got echocardiographic screening for SC upon ICU admission. Muratsu *et al*[18] conducted a retrospective study on 5084 patients in Japan over a 5-year period and found a low incidence of clinical Takotsubo cardiomyopathy of 0.37%; a majority of their SC patients had the diagnosis of sepsis and subarachnoid hemorrhage. This demonstrates that there are likely many cases of SC which go under-recognized since formal echocardiography is not performed on every patient in the ICU. However, use of routine point of care ultrasound (POCUS) on critically ill ICU patients will likely identify many more cases of SC.

Sepsis and acute respiratory failure were the most common ICU diagnoses of patients developing secondary SC in these studies, which is similar to our patients in the MSICUs[13,14,18]. Kleber *et al*[29] reported a 15% prevalence of stress cardiomyopathy in the setting of acute respiratory failure requiring mechanical ventilation.

Table 1 Patient baseline characteristics and presentation by unit

	Overall, *n* = 109	MSICU, (*n* = 49)	CCU, (*n* = 60)	*P* value[1]
Age (yr), mean (SD)	67.2 (14.2)	64.9 (14.4)	69 (13.7)	0.13
Female gender – *n* (%)	78 (71.6)	30 (61.2)	48 (80.0)	**0.04**
Race/Ethnicity – *n* (%)				0.37
White	30 (27.5)	17 (34.7)	13 (21.7)	
Black	20 (18.4)	9 (18.4)	11 (18.3)	
Hispanic	42 (38.5)	15 (30.6)	27 (45.0)	
Other	17 (15.6)	8 (16.3)	9 (15.0)	
Comorbidities – *n* (%)				
Diabetes mellitus	40 (36.7)	19 (38.8)	21 (35)	0.68
Hypertension	65 (59.6)	23 (46.9)	42 (70)	**0.01**
Coronary disease	13 (11.9)	5 (10.2)	8 (13.3)	0.77
Heart failure	7 (6.4)	4 (8.2)	3 (5)	0.70
Arrhythmia	14 (12.8)	4 (8.2)	10 (16.7)	0.25
Asthma	16 (14.7)	6 (12.2)	10 (16.7)	0.52
COPD	13 (11.9)	6 (12.2)	7 (11.7)	0.93
Obesity	10 (9.2)	3 (6.1)	7 (11.7)	0.51
CKD	14 (12.8)	8 (16.3)	6 (10)	0.33
ESRD	3 (2.8)	1 (2)	2 (3.3)	1.00
Cancer	23 (21.1)	10 (20.4)	13 (21.7)	1.00
Cirrhosis	6 (5.5)	5 (10.2)	1 (1.7)	0.09
HIV	2 (1.8)	1 (2)	1 (1.7)	1.00
Social risk factors – *n* (%)				
Alcohol use	25 (22.9)	13 (26.5)	12 (20)	0.42
Current smoker	15 (13.8)	4 (8.2)	11 (18.3)	0.17
Former smoker	36 (33)	21 (42.9)	15 (25)	0.05
Presenting symptoms- *n* (%)				
Chest pain	35 (32.1)	8 (16.3)	27 (45)	**0.001**
SOB	55 (50.5)	23 (46.9)	32 (53.3)	0.51
Shock	41 (37.6)	29 (59.2)	12 (20)	**< 0.001**
Reason for unit admission- *n* (%)				
Cardiac	44 (40.3)	0 (0.0)	44 (73.3)	**< 0.001**
Respiratory	14 (12.8)	9 (18.4)	5 (8.3)	0.54
Sepsis	24 (22.0)	19 (38.8)	5 (8.3)	**< 0.001**
GI	11 (10.0)	9 (18.4)	2 (3.3)	0.14
Neurological	7 (6.4)	6 (12.2)	1 (1.7)	0.04
Metabolic	4 (3.7)	3 (6.1)	1 (1.7)	0.32
Other	5 (4.6)	3 (6.1)	2 (3.3)	0.66

[1]Corresponds to chi-square or Fisher's exact test for association for categorical variables, Wilcoxon Mann-Whitney test for continuous variables. Data are summarized as mean (SD) or *n* (%), where *n* = available sample size. MSICU: Medical surgical intensive care unit; CCU: Coronary care unit; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; ESRD: End stage renal disease; HIV: Human immunodeficiency virus; SOB: Shortness of breath; GI: Gastrointestinal.

Table 2 Stress cardiomyopathy diagnosis, complications and outcomes by unit

	Overall, *n* = 109	MSICU, (*n* = 49)	CCU, (*n* = 60)	*P* value[1]
Confirmed SC	62 (56.9)	12 (24.5)	50 (83.3)	**< 0.0001**
Clinical SC	47 (43.1)	37 (75.5)	10 (16.7)	
Hospital day of diagnosis1; median [IQR]	2 [1-3]	3 [2-4]	1 [1-2]	**0.0002**
Diagnostic Studies – *n* (%)				
Cardiac catherization	62 (56.9)	12 (24.5)	50 (83.3)	**< 0.001**
Transthoracic echo	109 (100)	49 (100)	60 (100)	
Lowest ejection fraction – (%); median [IQR]	35 [28-40]	30 [30-40]	35 [30-45]	0.38
TTE anatomical variant- *n* (%)				
Atypical	22 (20.2)	12 (24.5)	10 (16.7)	0.31
Typical	87 (79.8)	37 (75.5)	50 (83.3)	
Type of SC- *n* (%)				**< 0.001**
Primary	43 (39.4)	0 (0.0)	43 (71.6)	
Secondary	66 (60.5)	49 (100.0)	17 (28.3)	
EKG Findings- *n* (%)				
Normal EKG	21 (19.2)	14 (28.6)	7 (11.7)	**0.03**
ST-Segment elevation	54 (49.5)	15 (30.6)	39 (65.0)	**< 0.001**
ST-Segment depression	4 (3.7)	2 (4.08)	2 (3.3)	1.00
T-Wave inversion	23 (21.1)	13 (26.5)	10 (16.7)	0.24
Other	25 (22.9)	14 (28.6)	11 (18.3)	0.25
Complications – *n* (%)				
ECMO/IABP use	3 (2.8)	1 (2.0)	2 (3.3)	1.00
Inotrope use	10 (9.2)	7 (14.3)	3 (5)	0.11
New arrythmia	14 (12.8)	5 (10.2)	9 (15.0)	0.57
AKI	37 (33.9)	21 (42.9)	16 (26.7)	0.08
RRT	14 (12.8)	4 (8.2)	2 (3.3)	0.41
Acute respiratory failure – *n* (%)				
Mechanical ventilation	44 (40.4)	29 (59.2)	15 (25.0)	**< 0.001**
NIPPV only	15 (13.8)	8 (16.3)	7 (11.7)	0.48
Shock – *n* (%)	41 (37.6)	29 (59.2)	12 (20.0)	**< 0.001**
Cardiogenic shock	14 (12.8)	5 (10.2)	9 (15.0)	0.46
Septic shock	28 (25.7)	23 (46.9)	5 (8.3)	**< 0.001**
Other shock	2 (1.8)	2 (4.1)	0 (0.0)	0.11
Follow-up echocardiogram- *n* (%)				
Repeat echo (% Total)	69 (63.3)	30 (61.2)	39 (65.0)	0.69
Reversibility (% Echo)	69 (100.0)	30/30 (100.0)	39/39 (100.0)	1.00
Clinical SC patients				
Repeat Echo (% Total)	27/47 (57.4)	21/47 (44.7)	6/47 (12.8)	0.01
Reversibility (% Echo)	27/27 (100.0)	21/21 (100.0)	6/6 (100.0)	1.00
Hospital outcomes – *n* (%)				
In-hospital mortality	15 (13.8)	9 (18.4)	6 (10)	0.27

ICU mortality	8 (7.3)	3 (6.1)	5 (8.3)	0.73

[1]*n* = 3 patients diagnosed prior to intensive care unit admission, corresponds to chi-square or Fisher's exact test for association for categorical variables, Wilcoxon Mann-Whitney test for continuous variables.
27 patients with clinical SC got follow up echocardiogram, reversibility seen in all of them. Data are summarized as median (IQR) or *n* (%), where *n* = available sample size. SC: Stress cardiomyopathy; MSICU: Medical surgical intensive care unit; CCU: Coronary care unit; EKG: Electrocardiogram; ECMO: Extracorporeal membrane oxygenation; IABP: Intraaortic balloon pump; AKI: Acute kidney injury; RRT: Renal replacement therapy; NIPPV: Non invasive positive pressure ventilation.

Table 3 Peak laboratory values by unit

	MSICU (*n* = 49)	CCU (*n* = 60)	*P* value[1]
Troponin-T (ng/mL)	0.42 [0.23-1.2]	0.87 [0.29-1.54]	0.11
CPK (U/L)	427 [148.5-1348.5]	276.5 [161-695]	0.48
Pro-BNP (pg/mL)	5395 [1458-15000]	3363.5 [944.5-15369]	0.72

[1]Corresponds to a Wilcoxon Mann-Whitney test. Data are summarized as median (IQR).
MSICU: Medical surgical intensive care unit; CCU: Coronary care unit; CPK: Creatine phosphokinase; Pro-BNP: N-terminal pro- brain natriuretic peptide.

Table 4 Peak laboratory values and outcomes of stress cardiomyopathy by anatomical variant

	Typical (*n* = 87)	Atypical (*n* = 22)	*P* value[1]
Lab findings- median (IQR)			
Troponin-T (ng/mL)	0.65 [0.23–1.57]	0.58 [0.25-0.94]	0.61
CPK (U/L)	297.5 [151-919]	278 [168-631]	0.94
Pro-BNP (pg/mL)	3722 [874-11932]	5599 [1608.5-17373.0]	0.29
Hospital complications- *n* (%)			
Inotrope use	8 (9.2)	2 (9.1)	1
ECMO/IABP use	2 (2.3)	1 (4.5)	0.5
RRT	3 (3.4)	3 (13.6)	0.1
Hospital outcomes- *n* (%)			
In-hospital mortality	12 (13.8)	3 (13.6)	1
ICU mortality	7 (8)	1 (4.5)	1

[1]Corresponds to a Wilcoxon Mann-Whitney test.
Data are summarized as median (IQR) or *n* (%), where *n* = available sample size. CPK: Creatine phosphokinase, Pro-BNP: N-terminal pro- brain natriuretic peptide; ECMO: Extracorporeal membrane oxygenation; IABP: Intraaortic balloon pump; RRT: Renal replacement therapy; NIPPV: Non invasive positive pressure ventilation.

We found that CCU patients mostly presented with primary SC from the community, many of them developing typical chest pain, shortness of breath and classic ST segment elevation on electrocardiogram.

It is reported that patients with secondary SC usually have an atypical presentation in the ICU, with the majority of them developing sudden or worsening unexplained shock/hemodynamic instability and shortness of breath[9,13,14,18,19]. Fifty-nine (59%) percent of our MSICU patients developed shock compared to 20% of CCU patients. In the prospective study by Doyen *et al*[14], 53.8% medical ICU patients developed cardiogenic shock. This is different from our findings as the most common type of shock in our study was septic shock. The likely explanation for this discrepancy is that 47% of our population in medical surgical ICUs had the diagnosis of severe sepsis and septic shock compared to 38% in the Doyen study.

The 2008 modified Mayo Clinic criteria and European Society of Cardiology (ESC) Heart Failure Association diagnostic criteria for stress cardiomyopathy require that patients have the absence of obstructive culprit coronary artery disease[30,31].

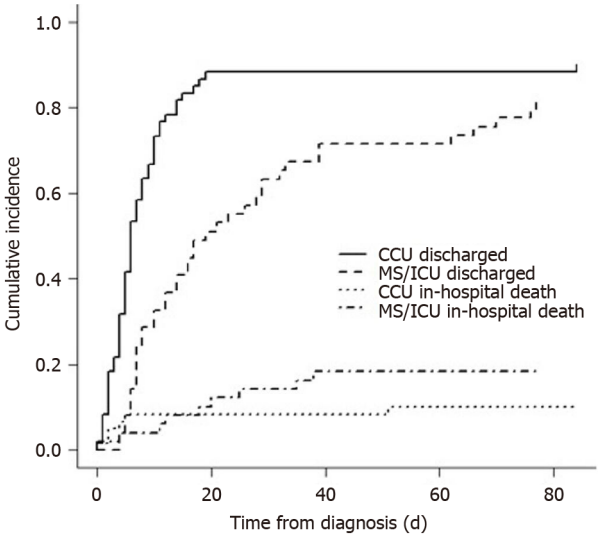

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Figure 1 Cumulative incidence function curve for hospital discharge *vs* death. *P* = 0.01 for hospital discharge stratified by type of unit, *P* = 0.33 for in hospital death stratified by type of unit.

However, there are many reasons for forgoing cardiac catheterization in the critically ill ICU patients, such as hemodynamic instability, multi-organ failure, risk of acute kidney injury (AKI) due to contrast induced nephropathy or established AKI amongst others.

Only 25% of our patients in medical-surgical units underwent cardiac catheterization, compared to 83% in the cardiac units. The mainstay of diagnosis of clinical SC in these critically ill patients was the combination of transthoracic echocardiography, cardiac enzymes and electrocardiogram findings.

Previous reports of SC in medical-surgical ICUs also relied mainly on transthoracic echocardiography along with cardiac enzymes and EKG changes for diagnostic purposes for similar reasons[13,14,18]. With the integration of POCUS as a routine diagnostic tool in the management of ICU patients, there will be an earlier recognition and an increase in the number of patients diagnosed with Stress cardiomyopathy at bedside by Intensivists, thereby improving care of these patients[32].

Patients with secondary SC in MSICUs also had longer ICU and hospital lengths of stay compared to CCU patients, primarily because MSICU patients were sicker with stressors such as acute respiratory failure, septic shock, neurologic disorders and multi system organ failure. Interestingly, we found that 11% (n = 12) of our cases developed SC in the perioperative setting. Agarwal *et al*[33] performed a systematic review of perioperative SC and found 102 cases in 93 articles. Management of our perioperative SC cases was similar to non-perioperative cases.

We report a low overall mortality for patients with SC. This is similar to prior studies that also report favorable outcomes of this patient population[3,9,10,13,14,18,19]. A relatively fast and complete recovery of cardiac function may explain this finding. Fifty-seven percent of our clinical SC patients had follow up echocardiogram, all showing reversibility of cardiac function, further supporting the diagnosis of SC. We also did not find any differences in mortality based on unit type (MSICU *vs* CCU) or anatomical type (typical *vs* atypical).

The major strength of our study is that we describe a large case series of patients with stress cardiomyopathy over the five-year period. We report and compare for the first time, characteristics, complications and outcomes of stress cardiomyopathy stratified by the type of unit and anatomical type. Our study has few limitations that need to be acknowledged. First, it is a single center study. Second, it is retrospective in nature and hence some data elements may not be captured accurately. Third, we believe that our incidence is likely underestimated, as many cases of SC may have gone unrecognized. Fourth, our definition of clinical SC could include cases of myocardial ischemia, showing improvement with development of collateral circulation. Fifth, follow up echocardiograms were only available in only 69 (63.3%) patients.

CONCLUSION

Stress cardiomyopathy can be under-recognized in the critical care setting. Primary stress cardiomyopathy is commonly seen in the CCUs and the secondary form predominates in the MSICU setting. Presentation of secondary SC is often atypical and the majority of patients have simultaneous acute respiratory failure and sepsis. Intensivists should have a high index of clinical suspicion for SC in patients who develop sudden or worsening unexplained hemodynamic instability, arrhythmias, or

respiratory failure. Many of the SC cases in MSICU may be diagnosed clinically as cardiac catheterization is not always feasible. Routine utilization of POCUS on all ICU patients will help identify more cases. The outcomes of these patients are excellent as majority of them show reversibility of cardiac function on follow up imaging.

ARTICLE HIGHLIGHTS

Research background

Critically ill patients are at risk of developing stress cardiomyopathy (SC) but can be under-recognized.

Research motivation

Our goal was to learn more about patients with SC in the intensive care unit (ICU) setting.

Research objectives

To study the patient characteristics, clinical course, and outcomes of critically ill patients with SC.

Research methods

We conducted a retrospective observational study at a tertiary care teaching hospital. All adult patients admitted to the critical care units with Stress cardiomyopathy over 5 years were included.

Research results

One hundred and nine patients were identified with SC, with 55% of them in the coronary care units (CCU) and 45% in the medical-surgical intensive care units (MSICUs). 57% of patients had SC confirmed by cardiac catherization while 43% were diagnosed clinically with echocardiography. 72% of CCU patients had primary SC whereas all MSICU patients had secondary SC. 59% of MSICU patients developed shock and acute respiratory failure that required mechanical ventilation. There were no statistically significant differences in ICU mortality, in-hospital mortality, use of inotropic or mechanical circulatory support based on type of unit or anatomical variant.

Research conclusions

Primary SC was commonly seen in the CCUs while secondary SC was seen more commonly in the MSICUs. Secondary SC often presents atypically and many patients have acute respiratory failure and sepsis. Many of the SC cases in the MSICU may be diagnosed clinically as cardiac catherization is not always feasible. Patients with SC in the ICUs have excellent outcomes with the majority of them showing reversibility of cardiac function.

Research perspectives

Stress Cardiomyopathy is often under-recognized in the critical care setting. In the MSICUs, secondary SC is the main form of SC encountered, where is it is often diagnosed clinically. Routine use of Point-of-care ultrasound may help with early identification of these cases.

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FOOTNOTES

Author contributions: Pancholi P contributed with data acquisition, data analysis, and manuscript writing; Emami N contributed with data acquisition, analysis and manuscript editing; Fazzari MJ performed the data analysis; Kapoor S designed the study, contributed to manuscript writing, and provided overall supervision; all authors have read and approve the final manuscript.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author. Participant consent was not obtained but the presented data are anonymized and risk of identification is low.

Country/Territory of origin: United States

ORCID number: Parth Pancholi 0000-0002-1319-4882; Nader Emami 0000-0002-9001-9287; Melissa J Fazzari 0000-0002-5674-3589; Sumit Kapoor 0000-0002-5683-3445.

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REFERENCES

1 **Medina de Chazal H**, Del Buono MG, Keyser-Marcus L, Ma L, Moeller FG, Berrocal D, Abbate A. Stress Cardiomyopathy Diagnosis and Treatment: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2018; **72**: 1955-1971 [PMID: 30309474 DOI: 10.1016/j.jacc.2018.07.072]
2 **Boland TA**, Lee VH, Bleck TP. Stress-induced cardiomyopathy. *Crit Care Med* 2015; **43**: 686-693 [PMID: 25565459 DOI: 10.1097/CCM.0000000000000851]
3 **Champion S**, Belcour D, Vandroux D, Drouet D, Gaüzère BA, Bouchet B, Bossard G, Djouhri S, Jabot J, Champion M, Lefort Y. Stress (Tako-tsubo) cardiomyopathy in critically-ill patients. *Eur Heart J Acute Cardiovasc Care* 2015; **4**: 189-196 [PMID: 25202025 DOI: 10.1177/2048872614547686]
4 **Antonopoulos A**, Kyriacou C. Apical ballooning syndrome or Takotsubo cardiomyopathy: a new challenge in acute cardiac care. *Cardiol J* 2008; **15**: 572-577 [PMID: 19039766]
5 **Pullara A**, Chinaglia A, Giammaria M, Bequaraj F, Orlando F, Coda L, Lucciola MT, Forno D, Ravera L, Cecchi E, Gaita F, Belli R. Takotsubo cardiomyopathy: real life management in the intensive coronary care unit. *Minerva Med* 2013; **104**: 537-544 [PMID: 24101111]
6 **Chockalingam A**, Mehra A, Dorairajan S, Dellsperger KC. Acute left ventricular dysfunction in the critically ill. *Chest* 2010; **138**: 198-207 [PMID: 20605820 DOI: 10.1378/chest.09-1996]
7 **Ghadri JR**, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF, Templin C. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. *Eur Heart J* 2018; **39**: 2032-2046 [PMID: 29850871 DOI: 10.1093/eurheartj/ehy076]
8 **Chockalingam A**. Stress cardiomyopathy of the critically ill: Spectrum of secondary, global, probable and subclinical forms. *Indian Heart J* 2018; **70**: 177-184 [PMID: 29455775 DOI: 10.1016/j.ihj.2017.04.005]
9 **Haghi D**, Fluechter S, Suselbeck T, Saur J, Bheleel O, Borggrefe M, Papavassiliu T. Takotsubo cardiomyopathy (acute left ventricular apical ballooning syndrome) occurring in the intensive care unit. *Intensive Care Med* 2006; **32**: 1069-1074 [PMID: 16550374 DOI: 10.1007/s00134-006-0111-z]
10 **Ruiz Bailén M**, Aguayo de Hoyos E, López Martnez A, Daz Castellanos MA, Ruiz Navarro S, Fierro Rosón LJ, Gómez Jiménez FJ, Issa-Masad Khozouz Z. Reversible myocardial dysfunction, a possible complication in critically ill patients without heart disease. *J Crit Care* 2003; **18**: 245-252 [PMID: 14691898 DOI: 10.1016/j.jcrc.2003.10.008]
11 **Ruiz Bailén M**. Reversible myocardial dysfunction in critically ill, noncardiac patients: a review. *Crit Care Med* 2002; **30**: 1280-1290 [PMID: 12072682 DOI: 10.1097/00003246-200206000-00020]
12 **Marcelino PA**, Marum SM, Fernandes AP, Germano N, Lopes MG. Routine transthoracic echocardiography in a general Intensive Care Unit: an 18 mo survey in 704 patients. *Eur J Intern Med* 2009; **20**: e37-e42 [PMID: 19393476 DOI: 10.1016/j.ejim.2008.09.015]
13 **Park JH**, Kang SJ, Song JK, Kim HK, Lim CM, Kang DH, Koh Y. Left ventricular apical ballooning due to severe physical stress in patients admitted to the medical ICU. *Chest* 2005; **128**: 296-302 [PMID: 16002949 DOI: 10.1378/chest.128.1.296]
14 **Doyen D**, Moschietto S, Squara F, Moceri P, Hyvernat H, Ferrari E, Dellamonica J, Bernardin G. Incidence, clinical features and outcome of Takotsubo syndrome in the intensive care unit. *Arch Cardiovasc Dis* 2020; **113**: 176-188 [PMID: 31983655 DOI: 10.1016/j.acvd.2019.11.005]
15 **Jo YY**, Chang HJ, Na S, Sim J, Choi YS. Predictors of mortality in patients with stress-induced cardiomyopathy developed during critical care. *J Crit Care* 2013; **28**: 618-624 [PMID: 23683567 DOI: 10.1016/j.jcrc.2013.03.014]
16 **Belcour D**, Jabot J, Grard B, Roussiaux A, Ferdynus C, Vandroux D, Vignon P. Prevalence and Risk Factors of Stress Cardiomyopathy After Convulsive Status Epilepticus in ICU Patients. *Crit Care Med* 2015; **43**: 2164-2170 [PMID: 26237133 DOI: 10.1097/CCM.0000000000001191]
17 **Nasr DM**, Tomasini S, Prasad A, Rabinstein AA. Acute Brain Diseases as Triggers for Stress Cardiomyopathy: Clinical Characteristics and Outcomes. *Neurocrit Care* 2017; **27**: 356-361 [PMID: 28612130 DOI: 10.1007/s12028-017-0412-9]
18 **Muratsu A**, Muroya T, Kuwagata Y. Takotsubo cardiomyopathy in the intensive care unit. *Acute Med Surg* 2019; **6**: 152-

157 [PMID: 30976441 DOI: 10.1002/ams2.396]
19 **Oras J**, Lundgren J, Redfors B, Brandin D, Omerovic E, Seeman-Lodding H, Ricksten SE. Takotsubo syndrome in hemodynamically unstable patients admitted to the intensive care unit - a retrospective study. *Acta Anaesthesiol Scand* 2017; **61**: 914-924 [PMID: 28718877 DOI: 10.1111/aas.12940]
20 **Shah R**, Shelton MR, Ramanathan KB. Lesson of the month 1: broken heart in the intensive care unit. *Clin Med (Lond)* 2014; **14**: 447-448 [PMID: 25099853 DOI: 10.7861/clinmedicine.14-4-447]
21 **Bourenne J**, Jeremy B, Fresco R, Raphaëlle F, Kerbaul F, François K, Michelet P, Pierre M, Gainnier M, Marc G. Stress Cardiomyopathy Managed with Extracorporeal Support after Self-Injection of Epinephrine. *Case Rep Crit Care* 2017; **2017**: 3731069 [PMID: 28928991 DOI: 10.1155/2017/3731069]
22 **Choi JH**, Oh ID, Shin E, Lee S, Jeon JM, Kim HT, Youn HC. Extracorporeal membrane oxygenation for takotsubo cardiomyopathy that developed after mitral valve replacement. *Acute Crit Care* 2020; **35**: 51-55 [PMID: 31743637 DOI: 10.4266/acc.2018.00304]
23 **Rennyson SL**, Parker JM, Symanski JD, Littmann L. Recurrent, severe, and rapidly reversible apical ballooning syndrome in status asthmaticus. *Heart Lung* 2010; **39**: 537-539 [PMID: 20561882 DOI: 10.1016/j.hrtlng.2009.11.004]
24 **Taniguchi K**, Takashima S, Iida R, Ota K, Nitta M, Sakane K, Fujisaka T, Ishizaka N, Umegaki O, Uchiyama K, Takasu A. Takotsubo cardiomyopathy caused by acute respiratory stress from extubation: A case report. *Medicine (Baltimore)* 2017; **96**: e8946 [PMID: 29310390 DOI: 10.1097/MD.0000000000008946]
25 **Y-Hassan S**, Settergren M, Henareh L. Sepsis-induced myocardial depression and takotsubo syndrome. *Acute Card Care* 2014; **16**: 102-109 [PMID: 24955937 DOI: 10.3109/17482941.2014.920089]
26 **Madias JE**. What is the real incidence of Takotsubo syndrome in intensive care units? *Acta Anaesthesiol Scand* 2017; **61**: 1371 [PMID: 28990180 DOI: 10.1111/aas.13004]
27 **Rowell AC**, Stedman WG, Janin PF, Diel N, Ward MR, Kay SM, Delaney A, Figtree GA. Silent left ventricular apical ballooning and Takotsubo cardiomyopathy in an Australian intensive care unit. *ESC Heart Fail* 2019; **6**: 1262-1265 [PMID: 31556249 DOI: 10.1002/ehf2.12517]
28 **Gray RJ**. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. The Annals of Statistics 16, No. 3. 1988; 1141-154
29 **Kleber HD**. Drug abuse liability testing: human subject issues. *NIDA Res Monogr* 1989; **92**: 341-356 [PMID: 2512500 DOI: 10.1016/j.ijcard.2014.07.188]
30 **Prasad A**, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J* 2008; **155**: 408-417 [PMID: 18294473 DOI: 10.1016/j.ahj.2007.11.008]
31 **Lyon AR**, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, Sheppard MN, Figtree GA, Parodi G, Akashi YJ, Ruschitzka F, Filippatos G, Mebazaa A, Omerovic E. Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2016; **18**: 8-27 [PMID: 26548803 DOI: 10.1002/ejhf.424]
32 **Lee JW**, Kim JY. Stress-induced cardiomyopathy: the role of echocardiography. *J Cardiovasc Ultrasound* 2011; **19**: 7-12 [PMID: 21519485 DOI: 10.4250/jcu.2011.19.1.7]
33 **Agarwal S**, Bean MG, Hata JS, Castresana MR. Perioperative Takotsubo Cardiomyopathy: A Systematic Review of Published Cases. *Semin Cardiothorac Vasc Anesth* 2017; **21**: 277-290 [PMID: 29098955 DOI: 10.1177/1089253217700511]

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Observational Study

Need for oxygen therapy and ventilatory support in premature infants in a hospital in Southern Brazil

Amanda Meier, Kelser de Souza Kock

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Amanda Meier, Kelser de Souza Kock, Department of Physiotherapy, University of South of Santa Catarina, Tubarão 88704-001, SC, Brazil

Corresponding author: Kelser de Souza Kock, PhD, Physiotherapist, Professor, Department of Physiotherapy, University of South of Santa Catarina, José Acácio Moreira Street-787, Tubarão 88704-001, SC, Brazil. kelserkock@yahoo.com.br

Abstract

BACKGROUND

Prematurity in newborns is a condition that is associated with worse hospital outcomes when compared to birth to term. A preterm infant (PI) is classified when gestational age (GA) < 37 wk.

AIM

To analyze prognostic indicators related to the use of oxygen therapy, non-invasive ventilation (continuous positive airway pressure) and mechanical ventilation (MV) in PI.

METHODS

This is a retrospective cohort. The sample was composed of PIs from a private hospital in southern Brazil. We included neonates with GA < 37 wk of gestation in the period of January 1, 2018 to December 31, 2018. For data collection, electronic records were used in the Tasy Philips™ system, identifying the variables: maternal age, type of birth, prenatal information, GA, Apgar score, birth weight, neonatal morbidities, vital signs in the 1st hour at birth, need for oxygen therapy, continuous positive airway pressure and MV, hospitalization in the neonatal intensive care unit, length of stay and discharge or death.

RESULTS

In total, 90 PI records were analyzed. The median (p25-p75) of GA was 34.0 (31.9-35.4) wk, and there were 45 (50%) males. The most common morbidity among PIs was the acute respiratory discomfort syndrome, requiring hospitalization in the neonatal intensive care unit in 76 (84.4%) cases. The utilization rate of oxygen therapy, continuous positive airway pressure and MV was 12 (13.3%), 37 (41.1%) and 13 (14.4%), respectively. The median (p25-p75) length of stay was 12.0 (5.0-22.2) d, with 10 (11.1%) deaths. A statistical association was observed with the use of MV and GA < 28 wk, lower maternal age, low birth weight, Apgar < 8 and neonatal deaths.

CONCLUSION
The identification of factors related to the need for MV in prematurity may help in the indication of a qualified team and technologies to promptly meet the unforeseen events that may occur after birth.

Key Words: Premature; Continuous positive airway pressure; Artificial respiration; Non-invasive ventilation

Core Tip: This is an observational study evaluating the need for oxygen therapy and ventilatory support in preterm infants. In our analysis, we present the odds ratio of the use of mechanical ventilation when compared to maternal and preterm epidemiological parameters.

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INTRODUCTION

Prematurity in newborns is a condition that is associated with worse hospital outcomes when compared to birth to term. However, in recent years there has been an increase in survival rates due to the improvement in neonatal intensive care, supported by technological evolution and the qualification of professionals in the field[1]. Even with all these progressions, prematurity rates at the present time remain high, reaching 10.94% of live births in 2018 in Brazil[2].

The determining gestational age of a preterm birth (PTB) is less than 37 wk, related to some resultants that generate the anticipation of childbirth[3]. Obstetric complications can interfere with the natural process of pregnancy, causing premature delivery, some of which are infections, hypertensive diseases, diabetes and hemorrhages that are more common[4]. According to DATASUS in Brazil in 2018 (its last census), the duration of pregnancy between 22 wk and 36 wk was 322234 live births, among them single, double, and triple births; in the South region there were 43313 live births[2].

Among the factors related to the clinical evolution of the PTB are gestational age (GA), Apgar score, weight at birth, congenital malformations/morbidities and vital signs. The Apgar scale is a tool for systematic assessment of the newborn, created by Virginia Apgar in 1953, for this reason the name Apgar. It uses a numerical score from 0 to 10, which has five variables, heart rate, respiratory effort, color, muscle tone and reflex irritability. It is used as an indicator of fetal distress if less than 5 on the scale is determined. Oxygen therapy (O2) is offered to reduce respiratory difficulty and collaborate in hemodynamic stabilization[5]. Newborns under 2500 kg have an increased risk of death in the 1st year of life and of developing infectious diseases, respiratory diseases, growth retardation and development[6]. Constant monitoring and early initiation of appropriate therapy prevent possible complications of disease and prematurity[7].

In Brazil, 24061 live births and 268 neonatal deaths were named, with a neonatal mortality rate of 11.1 deaths per thousand live births. Causes of neonatal death prevailed in the prematurity group, accounting for about one-third of the cases, followed by congenital malformation (22.8%), infections (18.5%), maternal factors (10.4%) and asphyxia/hypoxia (7%)[8].

At-risk birth, as in PTB, a physiological and/or hemodynamic imbalance occurs, where the extrauterine environment generates numerous adaptations involving morphophysiological and biochemical maturation of the lung parenchyma[9]. The inability to achieve effective breathing, lack of a powerful respiratory drive, reduced muscle strength, lack of surfactant and high compliance of the chest wall are contributing factors to respiratory failure[10]. As a result of these factors, premature babies need respiratory assistance to perform and/or adapt gas exchange and establish consistent functional residual capacity[10].

Several methods are used to provide respiratory support to premature infants, including intubation, prophylactic surfactant, oxygen therapy and non-invasive ventilation. Intubation requires all airway control, reducing support according to tolerance, with as little intubation time as possible, avoiding related morbidities. Surfactant administration is prophylactic, preventing lung damage and respiratory implications[11].

Due to the importance in early recognition of PTBs that will need ventilatory support, this work sought to analyze prognostic indicators related to the need for invasive mechanical ventilation in PTB[8, 12]. The use of maternal and newborn epidemiological parameters as well as physiological signs of the

premature infant in the first 24 h can be used as indicators for respiratory failure. In this sense, the general objective of this study was to analyze factors related to the need for ventilatory support in PTB in 2018 in a hospital in southern Brazil.

MATERIALS AND METHODS

This is a retrospective cohort type study. The sample was composed of premature infants in a private hospital in the city of Tubarão, Santa Catarina, Brazil. It has 8 beds in the neonatal intensive care unit, 10 adult beds in the intensive care unit, 50 adult inpatient beds and 21 adult and pediatric beds as required.

The following criteria were adopted for inclusion: newborns of both sexes and preterm born with less than 37 wk of gestation in the period from January 1, 2018 to December 31, 2018. The exclusion criteria were incomplete medical records and newborns transferred to another hospital. Electronic records were used in the Tasy Philips™ system for data collection.

This research project was approved by the Ethics Committee in Human Beings of UNISUL under the number of the opinion 3.529.438, CAAE: 17573519.2.0000.5369.

The following variables were extracted from the electronic records: gestational age, Apgar score, birth weight, congenital malformations/morbidities, vital signs at the first hour of birth, maternal age, type of delivery, previous adequate prenatal, mother's morbidity, number of gestations, use of O2, non-invasive ventilation [continuous positive airway pressure (CPAP)] and mechanical ventilation (MV), need for admission to the neonatal intensive care unit, length of stay and discharge or death.

The data were stored in a database created with the Excel® software and later exported to the SPSS 20.0® software. They were presented through absolute numbers and percentages, measures of central tendency and dispersion. A logistic regression analysis was performed to obtain the odds ratio in comparison to the use of mechanical ventilation. Considering the 95% confidence interval, a 5% statistical significance level was used.

RESULTS

We analyzed 90 PTB records and their maternal antecedents. Of these, 81 were cesarean deliveries and 45 (50%) were boys. The median (p25-p75) age of the mother was 31.0 (28.0-35.0) years, the most common comorbidity was premature rupture of membranes, and other comorbidities included fetal malformations and inadequate fluid in the amniotic sac. The highest frequency of prenatal visits was 4 to 7, which 64 women performed.

The median gestational age was 34.0 (31.9-35.4) wk, where the most common morbidity among the PTB was respiratory distress syndrome. The Apgar in the first and fifth minute were higher than 8 in the majority, where 37 needed CPAP and 13 needed orotracheal intubation. The need of admission to the neonatal intensive care unit occurred for 76 patients, where the median length of hospital stay was 12.0 (5.0-22.2) d, of which 10 deaths occurred, totaling 11.1% of the PTB. Tables 1 and 2 summarize the information from maternal data and PTB.

In the present study, lower maternal age, lower gestational age, lower birth weight, Apgar < 8 and death were statistically significant and were associated with patients who required MV compared to those who did not require oxygen support (Table 3).

DISCUSSION

Prematurity all over the world is an evident problem in perinatal health, and in Brazil it is one of the major causes of infant mortality. Preterm infants (PIs) are at an increased risk of adapting to life in the extrauterine environment, mainly due to the immaturity of the physiological and anatomical system[9, 13].

The main findings of the study showed that the need for MV is associated with extreme prematurity with gestational age < 32 wk, a lower maternal age, low birth weight, Apgar < 8 in the first and fifth minutes of life and neonatal deaths compared to PIs who did not use oxygen therapy. More than half of the studied PIs required some form of oxygen support, whether helmet or incubator O2, CPAP or MV.

Premature rupture of membranes is determined by the loss of amniotic fluid before birth. According to the Hackenhaar *et al*[14] study, that rupture may be associated with a pregnant woman's age above 29 years. The study explained that it may be related to endogenous changes in the fetus and its annexes. In the present study we noticed that one-third of the pregnant women had premature rupture of membranes as a comorbidity and that a little more than half of the women were older than 30 years.

Prenatal care should be initiated in the first trimester of pregnancy; a total of at least six consultations should be performed. During the consultations, physical examinations should be performed, and if necessary, specific tests should be performed. The early initiation of prenatal care provides access to

Table 1 Maternal data

	n (%)
Mother's age	
≤ 25 yr	9 (10.0)
> 25 and ≤ 30 yr	27 (30.0)
> 35 and ≤ 40 yr	20 (22.2)
> 40 yr	1 (1.1)
Maternal/gestational comorbidities	
PROM	30 (32)
Preeclampsia	11 (12.1)
UTI	8 (8.8)
HDP	6 (6.6)
HELLP Syndrome	2 (2.2)
DM	1 (1.1)
Others	32 (32.8)
Number of pregnancies	
1	50 (55.6)
2	31 (34.4)
3	6 (6.7)
4	3 (3.3)
Prenatal consultations	
< 4	2 (2.2)
4-7	64 (71)
≥ 8	24 (26.7)

PROM: Premature rupture of membranes; UTI: Urinary tract infection; HDP: Hypertensive disease of pregnancy DM: Diabetes mellitus; HELLP Syndrome: Hemolysis, elevated liver enzymes, low platelet count.

diagnostic and therapeutic methods to prevent possible pregnancy complications[14]. More than half of the pregnant women had 4 to 7 consultations, showing that consultations do not prevent prematurity but that a more thorough follow-up can prevent maternal and child complications.

Cesarean delivery was predominant in more than 85% of PIs, and most pregnancies were uniparous, according to the Miranda-Flores study[15]. Cesarean section is indicated in pregnancies from 26 wk to 31 wk + 6 d, and vaginal delivery in pregnancies under 26 and over 31, depending on maternal and fetal conditions, in which the cesarean section represents a higher percentage[15].

The median gestational age found was similar to the study by Galleta *et al*[16]. It is during this period that the formation of surfactant takes place by the type II pneumocytes, which are responsible for preventing the alveoli from collapsing when in contact with air. Newborn respiratory distress syndrome (NRDS) remains one of the most frequent complications in infants weighing 1500g or less.

The data in relation to neonatal death in this study are similar to the works of Lansky *et al*[8] and Andegiorgish *et al*[17]. In the study by Myrhaug *et al*[18], in infants born alive, the survival rate increased from 74.0% for infants born at 25 wk GA to 90.1% for those born at 27 wk GA. The study by Glass *et al*[19] reported the morbidity and mortality of 1765 PIs (birth weight 500-1500 g) in the period after implementation of neonatal intensive care units and mechanical respiratory support. In a meta-analysis evaluating the outcome in PIs, survival improved significantly with each week of GA and for each 100-g increase in birth weight. Specifically, survival in the 500-600 g group was only 20% compared to 56% in the 700-800 g birth weight group. It can be observed that in the studies there was a higher survival rate in infants with lower GA who had support in the neonatal intensive care unit where more and more medical and technological advances are showing a better prognosis regarding the prediction of ventilatory support[18]. In this study, it was observed that lower GA and low birth weight were associated with the use of MV, and this in turn was related to death.

Table 2 Preterm infant data

	Median (p25-p75)
Gestational Age (wk)	34 (31.9-35.4)
< 28, *n* (%)	7 (7.8)
≥ 28 and < 30, *n* (%)	5 (5.6)
≥ 30 and < 34, *n* (%)	27 (30.0)
≥ 34 and < 37, *n* (%)	51 (56.7)
Birth weight (grams)	2240.0 (1588.7-2520.0)
PI Morbidities, *n* (%)	
NRDS	55 (60.9%)
Low birth weight	5 (5.5%)
Tachypnea	4 (4.4%)
Apnea	1 (1.1%)
Others	25 (28.1%)
HR (bpm), 1st h after birth	145.0 (134.7-153.2)
RR (cpm), 1st h after birth	52.0 (41.7-64.0)
SpO2 (%)-1st h after birth	96.0 (93.0- 97.0)
Apgar (1st min)	8.0 (6.0-8.0)
< 8, *n* (%)	39 (43.2%)
≥ 8, *n* (%)	51 (56.7%)
Apgar (5th min)	9.0 (8.0-9.0)
< 8, *n* (%)	6 (6.6)
≥ 8, *n* (%)	84 (93.3%)
Need for oxygen therapy or ventilatory support	
Oxygen therapy	12 (13.3%)
CPAP	37 (41.1%)
MV	13 (14.4%)
ICU admission	76 (84.4%)
Length of stay (d)	12.0 (5.0-22.2)
Death	10 (11.1%)
Death by gestational age	
< 28 wk, *n* (%)	6 (6.7)
≥ 28 and < 30 wk, *n* (%)	0 (0.0)
≥ 30 and < 34 wk, *n* (%)	2 (2.2)
≥ 34 and < 37 wk, *n* (%)	2 (2.2)

PI: Preterm infant; ICU: Intensive care unit; NRDS: Newborn respiratory distress syndrome; HR: Heart rate; RR: Respiratory rate; SpO2: Peripheral oxygen saturation; CPAP: Constant positive airway pressure; MV: Mechanical ventilation.

The main morbidity found in PIs was NRDS. According to Sweet *et al*[20], NRDS is a significant problem for premature infants, and they sought to maximize survival with the creation of guidelines for better management of these patients. CPAP should be initiated from birth in all infants at risk of respiratory distress, such as those at < 30 wk GA who do not require intubation for stabilization. After stabilization, MV should be used in infants with respiratory distress when other methods of respiratory support fail. The duration of MV should be minimized whenever possible. To achieve the best outcomes for PIs with respiratory distress, optimal supportive care with monitoring of physiological variables is important. In the neonatal intensive care unit, there should be access to continuous pulse oximetry,

Table 3 Comparison of data according to the need for mechanical ventilation

	Ambient air-O2-CPAP Median (p25-p75) *n* (%) = 77 (85.6)	MV Median (p25-p75) *n* (%) = 13 (14.4)	OR (95%CI)	*P* value
Maternal age	32.0 (28.5 - 36.0)	28.0 (25.0 - 31.5)	0.823 (0.710-0.954)	0.010[a]
GA in wk	34.1 (33.1-35.4)	29.4 (25.4-32.0)	0.632 (0.504-0.790)	< 0.001[b]
< 28[1]	1 (14.3)	6 (85.7)	147.000 (11.527-1874.655)	< 0.001[b]
≥ 28 and < 30[1]	4 (80.0)	1 (20.0)	6.125 (0.451-83.116)	0.173
≥ 30 and < 34[1]	23 (85.2)	4 (14.8)	4.261 (0.727-24.970)	0.108
≥ 34 and < 37[1]	49 (96.1)	2 (3.9)	1.000	
Birth weight (g)	2260.0 (1707.5-2621.5)	1035.0 (605.0-1819.0)	0.997 (0.996-0.999)	< 0.001[b]
HR (bpm)	145.0 (135.0-153.5)	139.0 (129.5-155.0)	1.001 (0.970-1.032)	0.969
RR (com)	52.0 (41.0-64.0)	53.0 (46.5-64.5)	1.014 (0.971-1.059)	0.525
SpO2 (%)	93.0 (93.0-97.0)	96.0 (84.0-97.5)	0.975 (0.939-1.012)	0.178
Length of stay (d)	12.0 (5.0-21.0)	15.0 (1.5-39.0)	1.028 (0.990-1.067)	0.154
Apgar 1 min[1]				
< 8	28 (71.81)	11 (28.2)	9.625 (1.989-46.569)	0.003[a]
≥ 8	49 (96.1)	2 (3.9)	1.000	
Apgar 5 min[1]				
< 8	2 (33.3)	4 (66.7)	16.667 (2.666-104.189)	0.003[a]
≥ 8	75 (89.3)	9 (10.7)	1.000	
Outcome[1]				
Discharge	76 (95.0)	4 (5.0)	1.000	< 0.001[b]
Death	1 (10.0)	9 (90.0)	171.000 (17.185-1701.583)	

[1]*n* (%).

[a]*P* < 0.05.

[b]*P* < 0.001. GA: Gestational age; HR: Heart rate; RR: Respiratory rate; SpO2: Peripheral oxygen saturation; O2: Oxygen therapy; CPAP: Constant positive airway pressure; MV: Mechanical ventilation; OR: Odds ratio; CI: Confidence interval.

electrocardiogram monitoring and monitoring of PaCO2 levels.

Regarding vital signs in the first hour, no association was observed with the need for ventilatory support. According to the study by Kumar *et al*[21], where clinical assessment and nursing observation are very important, some vital sign data are not used and the update in the medical records can still be improved. Vital sign monitoring is constantly monitored on monitors at the incubator bedside. Short and long-term monitoring can predict sepsis risks and neurological and respiratory problems, as slowing heart rate may be indicative of some pathologies. Lower peripheral oxygen saturation (85%-89%) has a higher incidence of intermittent hypoxemia compared to higher peripheral oxygen saturation (91%-95%) during the first 3 d of life. Respiratory rate monitoring is important for detection of apnea associated with decreased heart rate and peripheral oxygen saturation. Perhaps, dynamic monitoring of vital signs could provide more prognostic information than those assessed only at the first hour.

The comparison of data from PIs with low Apgar scores at the fifth minute and birth weight less than 1500g are closely linked to the need for MV and neonatal mortality, corroborating the study by Dalili *et al*[22]. The study by Oliveira *et al*[23] states that mortality increased for those with Apgar scores 4-7 in relation to PIs weighing between 1500 g and 2999 g, which shows that the lower the birth weight, the higher the mortality. The Apgar score was the best known and oldest form of measurement of neonatal asphyxia. New knowledge, such as the determination of fetal blood pH, among others, has changed this concept, and the score of 6 or less at the fifth minute has become the most important reference in the diagnosis and prognosis of asphyxia, along with the proposal not to wait for the first minute score to start resuscitation maneuvers. Despite this, the first minute score still seems to have importance in the

prognosis of mortality[21,22].

Limitations found in this study were the small sample size, research conducted in a hospital that provides health care only to health insurance companies/private entities, and not being able to generalize the findings to other hospitals.

CONCLUSION

We conclude that the need for mechanical ventilation is associated with extreme prematurity with GA < 28 wk, lower maternal age, low birth weight, Apgar < 8 at the first and fifth minutes of life and neonatal deaths. NRDS is the most frequent morbidity in premature infants, where more than half of those studied required some form of oxygen support, whether O2, CPAP or MV. The identification of factors related to the need for MV in prematurity may help in the indication of a qualified team and technologies to promptly meet the unforeseen events that may occur after birth.

ARTICLE HIGHLIGHTS

Research background

Prematurity may be associated with some degree of respiratory failure.

Research motivation

Clinical recognition of premature infants at risk is important for appropriate management of ventilatory support.

Research objectives

To assess maternal and newborn factors related to the need for ventilatory support.

Research methods

A retrospective cohort conducted in a private hospital in southern Brazil consisted of preterm infants with gestational age < 37 wk.

Research results

We evaluated 90 premature infants with median (p25-p75) gestational age of 34.0 (31.9-35.4) wk. The utilization rate of oxygen therapy, continuous positive airway pressure and mechanical ventilation was 12 (13.3%), 37 (41.1%) and 13 (14.4%), respectively. The median (p25-p75) length of stay was 12.0 (5.0-22.2) d, with 10 (11.1%) deaths. A statistical association was observed with the use of mechanical ventilation and gestational age < 28 wk, lower maternal age, low birth weight, Apgar < 8 and neonatal deaths.

Research conclusions

The need for mechanical ventilation in premature infants was related to low birth weight, extreme prematurity and low Apgar.

Research perspectives

Other clinical indicators for predicting ventilatory support in premature infants can be used, such as monitoring vital signs and their variability measures.

FOOTNOTES

Author contributions: Meier A performed the data collection and wrote the manuscript; Kock KS performed the statistical analysis and revision and editing of the manuscript.

Institutional review board statement: This research project was approved by the Ethics Committee in Human Beings of (University of Southern Santa Catarina, Brazil) UNISUL under the number of the opinion 3.529.438, CAAE: 17573519.2.0000.5369.

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Country/Territory of origin: Brazil

ORCID number: Amanda Meier 0000-0002-9856-5215; Kelser de Souza Kock 0000-0002-0117-6142.

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REFERENCES

1 **Roussenq KR**, Scalco JC, Rosa GJ, Honório GJS, Schivinski CIS. Reequilíbrio tóraco-abdominal em recém-nascidos prematuros: efeitos em parâmetros cardiorrespiratórios, no comportamento, na dor e no desconforto respiratório. *Acta Fisiatr* 2015; **20**: 118-123 [DOI: 10.5935/0104-7795.20130019]
2 **Brasil**, Ministério da Saúde. Banco de dados do Sistema Único de Saúde-DATASUS. [cited 8 march 2018]. Available from: http://www.datasus.gov.br
3 **Almeida TSO**, Lins RP, Camelo AL, Mello DCCL. Investigação sobre os Fatores de Risco da Prematuridade: uma Revisão Sistemática. *R bras ci Saúde* 2013; **17**: 301-308 [DOI: 10.4034/RBCS.2013.17.03.14]
4 **Moura BLA**, Alencar GP, Silva ZPD, Almeida MF. [Hospitalizations due to complications of pregnancy and maternal and perinatal outcomes in a cohort of pregnant women in the Brazilian Unified National Health System in São Paulo, Brazil]. *Cad Saude Publica* 2018; **34**: e00188016 [PMID: 29412326 DOI: 10.1590/0102-311X00188016]
5 **Chauhan S**, Singh PK, Gahalaut P, Prasad PL. Correlation of pulse oximetry and apgar scoring in the normal newborns. *J Clin Neonatol* 2013; **2**: 20-24 [PMID: 24027740 DOI: 10.4103/2249-4847.109241]
6 **Carniel EF**, Zanolli ML, Antônio MARGM, Morcilio AM. Determinantes do baixo peso ao nascer a partir das Declarações de Nascidos Vivos. *Rev Bras Epidemiol* 2008; **11**: 169-179 [DOI: 10.1590/S1415-790X2008000100016]
7 **Barbosa AL**, Cardoso MV. Alterações nos parâmetros fisiológicos dos recém-nascidos sob oxigenoterapia na coleta de gasometria. *Acta Paul Enferm* 2014; **27**: 367-372 [DOI: 10.1590/1982-01942014000061]
8 **Lansky S**, Lima Friche AA, Silva AA, Campos D, Azevedo Bittencourt SD, Carvalho ML, Frias PG, Cavalcante RS, Cunha AJ. Birth in Brazil survey: neonatal mortality, pregnancy and childbirth quality of care. *Cad Saude Publica* 2014; **30** Suppl 1: S1-15 [PMID: 25167179 DOI: 10.1590/0102-311X00133213]
9 **Oliveira CS**, Casagrande GA, Grecco LC, Golin MO. Perfil de recém-nascidos pré-termo internados na unidade de terapia intensiva de hospital de alta complexidade. *ABCS Health Sci* 2015; **40**: 28-32 [DOI: 10.7322/abcshs.v40i1.700]
10 **Vento M**, Nuñez A, Cubells E. Updating the management of preterm infants in the 1st min after birth. *J Clin Neonatol* 2014; **3**: 133-138 [DOI: 10.4103/2249-4847.140384]
11 **Dunn MS**, Reilly MC. Approaches to the initial respiratory management of preterm neonates. *Paediatr Respir Rev* 2003; **4**: 2-8 [PMID: 12615026 DOI: 10.1016/S1526-0542]
12 **Viana CC**, Nicolau CM, Juliani RCTP, Carvalho WB, Krebs VLJ. Effects of manual hyperinflation in preterm newborns under mechanical ventilation. *Rev Bras Ter Intensiva* 2016; **28**: 341-347 [DOI: 10.5935/0103-507X.20160058]
13 **Leal MD**, Esteves-Pereira AP, Nakamura-Pereira M, Torres JA, Theme-Filha M, Domingues RM, Dias MA, Moreira ME, Gama SG. Prevalence and risk factors related to preterm birth in Brazil. *Reprod Health* 2016; **13**: 127 [PMID: 27766978 DOI: 10.1186/s12978-016-0230-0]
14 **Hackenhaar AA**, Albernaz EP, da Fonseca TM. Preterm premature rupture of the fetal membranes: association with sociodemographic factors and maternal genitourinary infections. *J Pediatr (Rio J)* 2014; **90**: 197-202 [PMID: 24184300 DOI: 10.1016/j.jped.2013.08.003]
15 **Miranda-Flores AF**. Resultados maternos y perinatales del manejo conservador de la rotura prematura de membranas en gestantes de 24 a 33 semanas. Acta Med Per 2014; 31: 84-89 [cited 8 march 2018]. Available from: http://www.scielo.org.pe/scielo.php?script=sci_arttext&pid=S1728-59172014000200004&lng=es
16 **Galletta MAK**, Bittar RE, Agra I, Guerra ECL, Francisco RPV, Zugaib M. Epidemiological profile of patients with preterm premature rupture of membranes at a tertiary hospital in São Paulo, Brazil. *Clinics* 2019; **74**: e1231 [DOI: 10.6061/clinics/2019/e1231]
17 **Andegiorgish AK**, Andemariam M, Temesghen S, Ogbai L, Ogbe Z, Zeng L. Neonatal mortality and associated factors in the specialized neonatal care unit Asmara, Eritrea. *BMC Public Health* 2020; **20**: 10 [PMID: 31907008 DOI: 10.1186/s12889-019-8118-x]
18 **Myrhaug HT**, Brurberg KG, Hov L, Markestad T. Survival and Impairment of Extremely Premature Infants: A Meta-analysis. *Pediatrics* 2019; **143** [PMID: 30705140 DOI: 10.1542/peds.2018-0933]

19 **Glass HC**, Costarino AT, Stayer SA, Brett CM, Cladis F, Davis PJ. Outcomes for extremely premature infants. *Anesth Analg* 2015; **120**: 1337-1351 [PMID: 25988638 DOI: 10.1213/ANE.0000000000000705]

20 **Sweet DG**, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, Saugstad OD, Simeoni U, Speer CP, Vento M, Visser GH, Halliday HL. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2016 Update. *Neonatology* 2017; **111**: 107-125 [PMID: 27649091 DOI: 10.1159/000448985]

21 **Kumar N**, Akangire G, Sullivan B, Fairchild K, Sampath V. Continuous vital sign analysis for predicting and preventing neonatal diseases in the twenty-first century: big data to the forefront. *Pediatr Res* 2020; **87**: 210-220 [PMID: 31377752 DOI: 10.1038/s41390-019-0527-0]

22 **Dalili H**, Sheikh M, Hardani AK, Nili F, Shariat M, Nayeri F. Comparison of the Combined versus Conventional Apgar Scores in Predicting Adverse Neonatal Outcomes. *PLoS One* 2016; **11**: e0149464 [PMID: 26871908 DOI: 10.1371/journal.pone.0149464]

23 **Oliveira TG**, Freire PV, Moreira FT, Moraes JSB, Arrelaro RC, Rossi S, Ricardi VS, Juliano Y, Novo NF, Bertagnon JRD. Escore de Apgar e mortalidade neonatal em um hospital localizado na zona sul do município de São Paulo. *Einstein* 2012; **10**: 22-28 [DOI: 10.1590/S1679-45082012000100006]

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ORIGINAL ARTICLE

Observational Study

Critical care practices in the world: Results of the global intensive care unit need assessment survey 2020

Faisal A Nawaz, Neha Deo, Salim Surani, William Maynard, Martin L Gibbs, Rahul Kashyap

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Faisal A Nawaz, College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai 505055, United Arab Emirates

Neha Deo, Department of Medicine, Mayo Clinic Alix School of Medicine, Rochester, MN 55905, United States

Salim Surani, Rahul Kashyap, Critical Care Medicine, Mayo Clinic, Rochester, MN 55905, United States

Salim Surani, Texas A&M University, College Station, TX 77843, United States

William Maynard, Rahul Kashyap, Internal Medicine, TriStar Centennial Medical Center, HCA Healthcare, Nashville, TN 37203, United States

Martin L Gibbs, Pulmonary and Critical Care, Tulane University School of Medicine, New Orleans, LA 70112, United States

Corresponding author: Salim Surani, FACP, FCCP, MD, MSc, Doctor, Professor, Critical Care Medicine, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, United States.
srsurani@hotmail.com

Abstract

BACKGROUND

There is variability in intensive care unit (ICU) resources and staffing worldwide. This may reflect variation in practice and outcomes across all health systems.

AIM

To improve research and quality improvement measures administrative leaders can create long-term strategies by understanding the nature of ICU practices on a global scale.

METHODS

The Global ICU Needs Assessment Research Group was formed on the basis of diversified skill sets. We aimed to survey sites regarding ICU type, availability of staffing, and adherence to critical care protocols. An international survey 'Global ICU Needs Assessment' was created using Google Forms, and this was distributed from February 17th, 2020 till September 23rd, 2020. The survey was shared with ICU providers in 34 countries. Various approaches to motivating healthcare providers were implemented in securing submissions, including use of

emails, phone calls, social media applications, and WhatsApp™. By completing this survey, providers gave their consent for research purposes. This study was deemed eligible for category-2 Institutional Review Board exempt status.

RESULTS

There were a total 121 adult/adult-pediatrics ICU responses from 34 countries in 76 cities. A majority of the ICUs were mixed medical-surgical [92 (76%)]. 108 (89%) were adult-only ICUs. Total 36 respondents (29.8%) were 31-40 years of age, with 79 (65%) male and 41 (35%) female participants. 89 were consultants (74%). A total of 71 (59%) respondents reported having a 24-h in-house intensivist. A total of 87 (72%) ICUs were reported to have either a 2:1 or ≥ 2:1 patient/nurse ratio. About 44% of the ICUs were open and 76% were mixed type (medical-surgical). Protocols followed regularly by the ICUs included sepsis care (82%), ventilator-associated pneumonia (79%); nutrition (76%), deep vein thrombosis prophylaxis (84%), stress ulcer prophylaxis (84%), and glycemic control (89%).

CONCLUSION

Based on the findings of this international, multi-dimensional, needs-assessment survey, there is a need for increased recruitment and staffing in critical care facilities, along with improved patient-to-nurse ratios. Future research is warranted in this field with focus on implementing appropriate health standards, protocols and resources for optimal efficiency in critical care worldwide.

Key Words: Intensive care unit; Critical care; Global; Survey; Intensive care unit survey; Intensive care unit needs

Core Tip: Intensive care unit (ICU) practices are variable across the world. Most common admitting diagnoses for ICUs worldwide are similar to Western reporting in literature. We aimed to survey sites regarding ICU type, availability of staffing, and adherence to critical care protocols. There is variable protocol penetration for processes of care in ICUs. Future research is warranted in this field with focus on implementing appropriate health standards, protocols and resources for optimal efficiency in critical care worldwide.

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INTRODUCTION

Critical care is defined by varying practices across countries worldwide. This is affected by multi-factorial trends in epidemiology, finance, and cultural and human resources that in turn influence patient outcomes[1].

Intensive care units (ICUs) are at the center of diverse practices in health systems around the world. Their needs are dictated by hierarchical arrangements, resource designation, patient demographics, and health practices, including the allied goals of health providers[2]. With a necessity for standardization deemed essential for efficiency and high-quality patient care, it is vital to understand the context of epidemiological variability, resource accessibility, and local health practices[3] in such sophisticated settings. Moreover, the current understanding and comparison of clinical practices, guidelines, equipment, and facilities available in different countries can help identify potential areas of quality improvement *via* protocol development and enhancement of unified care delivery. Current literature on this topic can be found in developed countries[4,5]; however, it is significantly limited in multinational settings[6-8] on a global level.

We aimed to delineate the critical care practices that are found worldwide and their characteristics, including staffing, ICU resources, and adherence to protocols. This study sets a novel benchmark in sharing insights on key areas of critical care by highlighting the state of ICUs across different countries and understanding the trends in contemporary health systems. By defining gaps in knowledge, resources, and protocols, this study can facilitate the development of best practice strategies and thereby

lay a strong foundation for critical care provision worldwide[9].

MATERIALS AND METHODS

Study design

This was a cross-sectional, multinational, survey-based study. We proposed the formation of a multidisciplinary, diverse team of skilled researchers who established the "Global ICU Needs Assessment Research Group".

A questionnaire was developed under the guidance of this research group with the goal of evaluating most common patient presentations, and resource needs in terms of ICU equipment and assisting technology.

Study variables

Furthermore, we asked about other variables, such as the availability of intensivists, residents, fellows, 12-h in-house intensivists, and patient/nurse ratio, along with other demographics of those surveyed, such as their level of qualification, duration of clinical experience, and overall expertise in this field. It was also deemed crucial to include outcome variables, such as mechanical ventilation (MV) duration, MV mortality, ICU length of stay, ICU mortality, and sepsis mortality as well. Using a pilot study approach, we implemented this strategy within a randomized group of ICU clinicians before proceeding with the main study phase. This was done for internal validation purposes in the form of a survey shown in the digital supplement.

Sample of convenience was done. Intensivists were contacted using social media platforms and personal networking and *via* critical care societies. The survey was designed using Google™ forms online and sent out from February 17th, 2020 to 23rd September, 2020, to critical care professionals in 34 countries worldwide (Figure 1). The need for regular follow-ups and motivation within critical care professionals was a vital factor to this study. This was achieved by leveraging various online platforms, such as e-mail and social media applications including WhatsApp™[20].

Using a diverse set of researchers, critical care physicians, and digital platforms, a sample of 122 ICUs was acquired through this questionnaire.

Statistical analyses

The responses were presented as stratified data in the form of mean, with standard deviation, or median with interquartile range. It was also deemed necessary to include relevant pictographic presentation of this data.

Descriptive statistical analysis was used after obtaining eligibility for category-2 Institutional Review Board exempt status.

ICU practices at a given healthcare facility, including details about the respondents and demographics of the facility. The survey asked about the state of the ICU being open or closed, type of patients receiving care, number of ICU beds, protocols implemented for efficient practice.

RESULTS

The respondents of this survey primarily reflected a young adult population, with the respondents of this survey primarily reflected a young adult population with the greatest proportion 31-40 years old and males representing the majority, n = 79 (65%) with an average ICU experience of 3 years. Moreover, consultants were the main constituents of the survey respondents at n = 89 (74%), followed by residents from post-graduate year 3 and above (18, 15%). The ICU settings were mostly designed as a mixed medical-surgical environment (92, 76%) in academic teaching hospitals (38, 32%) with an average of 16 (interquartile range 11-20) beds. Furthermore, the ICUs were commonly open type, (53, 44%) (Table 1).

The need for intensivists and nurses to lead critical care is noted worldwide[1]. The analysis showed a patient/nurse ratio of 2:1 being implemented in the majority (55%) of the ICU units, and only (10%) of responders were following a 1:1 nursing care approach. Moreover, 34% of ICUs, which typically functioned at 2:1 patient/nurse ratios, transferred to 1:1 for complicated cases. There was also a significant number of ICUs (20, 16.5%) working with more than a 2:1 patient/nurse ratio. It is also noteworthy that a vast majority of the ICUs (101, 84%) were led by certified intensivists with 24-h intensivists deployed in 71 (59%) of the ICUs for optimal patient care. Other notable providers were residents/fellows/medical students active in 101 (84%) ICU units (Table 2).

Critical care was driven by protocols that were followed within all ICU facilities. There was a strong predominance of protocols for Advanced Cardiac Life Support (93%), glucose control (89%), stress ulcer prophylaxis (84%), deep vein thrombosis (DVT) prophylaxis (84%) and sepsis care (82%). The protocols least reported included palliative care/end of life (44%), acute lung injury (55%), transfusion restriction (59%), hypothermia after cardiac arrest (61%), and delirium (67%) (Table 3).

Table 1 Demographic variables

Demographic variables	Responses in % (*n* = 121)
Age (yr)	
31-40	29.8
41-50	23.1
20-30	23.1
> 50	24.0
Gender	
Male	65.3
Female	34.7
Intensive care unit experience (yr)	
< 10	50.4
10-20	35.5
21-30	9.9
> 30	4.1
Designation	
Consultant staff	73.6
Resident-PGY-3 and above	14.9
Resident-PGY-1	5.0
Resident-PGY-2	6.6
Intensive care unit specialty wise distribution	
Mixed medical-surgical	76.0
Medical	7.4
Others	16.6
Institution type	
Private/non-academic	16.5
Government hospital (tertiary care)	19.8
Academic teaching hospital	31.5
Corporate teaching hospital	8.2
Other	0.9
Number of intensive care unit beds	
< 11	28.1
11-20	31.4
21-30	23.1
> 30	17.4
Intensive care unit type	
Open	43.8
Closed	56.2

PGY-3: Post-graduate year 3.

The sample population was analyzed across a total 121 adult/adult-pediatrics ICU responses from 34 countries in 76 cities. Distribution of the respondents was spread amongst North America (41.3%), Asia (30.5%), Europe (18.2%), Africa (5.8%), South Africa (2.6%) and Oceania (1.6%) (Figure 1).

Table 2 Clinical resource parameters

Clinical resource parameters	Responses in % (*n* = 121)
Patient/nurse ratio (*n*)	
Usually 2:1 (for complicated patients 1:1) (*n* = 41)	33.9
2:1 (*n* = 26)	21.5
> 2:1 (*n* = 20)	16.5
1:1 (*n* = 31)	25.6
No fixed patient/nurse (*n* = 3)	2.5
24 h in-house intensivist (*n* = 71)	58.7
Certified intensivist (*n* = 101)	83.5
Residents/fellows/medical students rotate through or cover intensive care units along with staff intensivists (*n* = 101)	83.5

Table 3 Critical care protocols self-reporting

High (%)		Medium (%)		Low (%)	
Glucose control	89.3	Daily interruption of sedation	69.4	Palliative care/end of Life	43.8
Advanced cardiac life support	93.4	Acute coronary syndrome	81.0	Delirium	66.9
Deep vein thrombosis prophylaxis	83.5	Acute lung injury	54.5	Early mobility	68.6
Stress ulcer prophylaxis	83.5	Transfusion restriction	58.7	Hypothermia after cardiac arrest	61.2
Severe sepsis	81.7				
Ventilator-associated pneumonia bundle	78.5				
Nutrition	76.0				

The most common diagnoses for patients admitted into the ICU settings in this study included sepsis (88%), respiratory failure (88%) and heart failure (55%), as shown in Table 4.

The average ICU mortality (*n* = 36) assessed in this survey was 14% (interquartile range 2-40); ICU length of stay (*n* = 41) was 5.2 d (interquartile range 2-21); mechanical ventilation (MV) duration (*n* = 34) was 4.3 d (1-15); MV patient mortality (*n* = 27) was 20% (1-64) and sepsis mortality (*n* = 27) was at 21% (5-70) across the survey respondents (Table 5).

DISCUSSION

In a multi-national study that evaluates the critical care practices of 121 ICUs in 34 countries, the majority of the centers were from mixed medical-surgical or medical practices, with consultants comprising the majority of respondents. The most common diagnoses included sepsis/septic shock and respiratory failure. The largest proportion of responders were young adult males who identified as intensivists, suggesting that this field is expanding to include more learners who are early in their training.

Considering that this was a multinational study, it is important to note that local practices and resources may vary between different regions. A lack of resources may limit the total number of beds available, or even result in a lower number of monthly admissions[10] in a given center relative to other regions. Because financial resources may influence how patients are triaged or how the healthcare organization is structured[11], it is important to keep this in mind when evaluating multi-center data from different countries.

The predominant diagnosis in the ICU was sepsis. Studies show that sepsis has a mortality rate varying from 13% to 39%[12]. The second most common diagnosis was respiratory failure, with studies indicating a mortality rate of 26.2%[13]. Both sepsis and respiratory failure followed the same trend that is observed in country-specific ICU studies[14]. Considering that the mortality rates of both diseases are so high, it is imperative that ICUs are equipped with the resources and training to achieve best practice guidelines[15].

Many of the reported surveys were from individuals in mixed medical-surgical ICUs that were closed in nature and had 24-h intensivists. Additionally, the greatest number of the respondents reported

Table 4 Common diagnoses

Common diagnoses	No	% of intensive care unit
Sepsis or septic shock	106	87.6
Respiratory failure	106	87.6
Heart failure	67	55.4
Post-operative observation	68	56.2
Poisoning	15	12.4
Head trauma	37	30.6
Renal failure	46	38.0
Alcohol withdrawal	13	10.7
Epilepsy or uncontrolled seizures	18	14.9
Chronic obstructive pulmonary disease exacerbation	37	30.6
Hypertension	15	12.4
Cardiogenic shock	37	30.6
Electrolyte imbalance	20	16.5
Hypotension or hypovolemic shock	44	36.4
Heat stroke	4	3.3

Table 5 Critical care outcomes

Variables	Outcome
Intensive care unit mortality (response n =36)	14%
Intensive care unit length of stay, in days (response n = 41)	5.2
Mechanical ventilation mortality (response n = 27)	19.5%
Mechanical ventilation duration, in days (response n = 34)	4.3
Sepsis mortality (response n = 27)	21.2%

having 11-20 beds in the ward. Most of these centers were within academic or privately-owned hospitals. Although it is believed that ICUs with more beds will achieve better optimal care, it is important to consider that more money shifted towards ICUs will limit funding to other departments [16]. This predominantly impacts areas of low-resource settings, which is why the median ICU beds in low-income countries is 8[7]. Closed ICUs are associated with better outcomes, such as shorter ICU stay and decreased ICU costs[17]. North America is reported to have the lowest amount of closed ICUs (63%), with Western Europe having the highest (89%) (17). Since closed ICUs require an intensivist working on site, more and more ICUs are now including a 24-h intensivist, which can lead to decreased risk of in-hospital death and rate of complications[1].

Respondents most often reported a patient/nurse ratio of 2:1, which flexed to 1:1 for complicated patients. In a study by Sakr *et al*[1] it was reported that a patient/nurse ratio of more than 1.5:1 was associated with a higher risk of in-hospital death. Adequate care in ICUs requires proper staffing of nurses. This can greatly impact patient outcomes, especially if there are limited nurses available to provide care[1]. A high patient/nurse ratio can result in more mistakes being made due to a stressful work environment and fatigue[18]. It is imperative that adequate staffing is provided to ICUs to best provide patient care in an optimized environment.

Kredo *et al*[19] noted that evidence-informed best practice guidelines are imperative to optimizing patient care. A multifaceted, team-based approach in the ICU is the best way of reinforcing these guidelines and developing strategies that can better manage the patient or prevent complications[15]. In our survey, we found that a majority of centers are able to follow best practice guidelines related to glucose control, advanced cardiac life support, DVT prophylaxis, and stress ulcer prophylaxis. However, challenges exist with protocols related to palliative care, acute lung injury, and transfusion restriction. It is important to address barriers to guideline adherence, which can differ from region to region. Some commonly reported barriers include lack of knowledge[20] or needing effective leadership to promote adoption of guidelines[21].

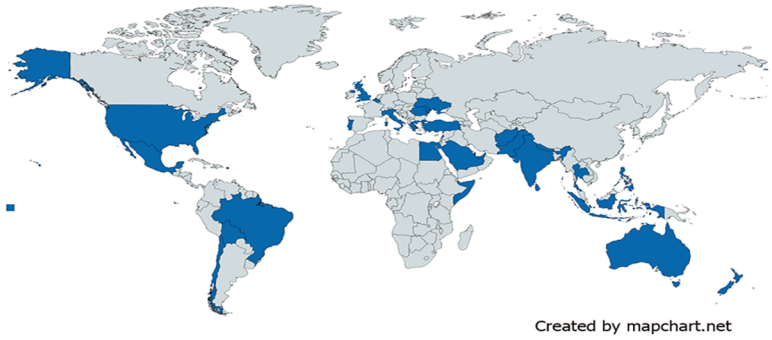

Figure 1 The survey was designed using Google™ forms online and sent out from February 17th, 2020 to 23rd September, 2020, to critical care professionals in 34 countries worldwide. Created by mapchart.net.

Strengths

The strengths of this study include being one of the first multinational surveys to collect data from 34 countries during the pandemic of the century[22]. Having more regions participate in a survey like this is beneficial because it provides a snapshot of the ICU statistics in that area. A multi-center design allows for a broader range of data representing the resources of each area *vs* a single center study. These data can be used to evaluate current ICU resources and limitations worldwide and can therefore help administration create designs to optimize care for patients who are in the critical care unit. Such multi-national collaborations would lead to robust data collection during pandemic and peace times[23-25].

Limitations

Our study has several limitations. First, since our primary recruitment method was through social media and networking at critical care societies, we may be missing out on data from remote areas or sites that did not see our recruitment invitation online. Second, as we had only 34 countries represented, a larger sample size from different geographical locations would allow us to understand the needs of the ICU in those regions better. Recall bias is also a factor in survey studies, as participants may not be able to fill in all the information as accurately as possible. Additionally, since this survey was filled out during the year of the coronavirus disease 2019 pandemic, ICUs may have been impacted or changed very drastically to meet the needs of their community. Therefore, the reported results may not accurately reflect ICU data prior to the pandemic. A final limitation to our study is that we did not stratify our data into geographical regions to evaluate differences from region to region. Further research could aim to delineate this data.

CONCLUSION

This international, multi-dimensional, needs-assessment survey reflects a need for increased recruitment and staffing in critical care facilities, along with improved patient-to-nurse ratios. Multi-center ICU data are imperative in designing future critical care delivery models that reflect the needs of the patient and address barriers to their care. Understanding current trends in health systems helps us develop quality improvement interventions that can lead to better outcomes in patients.

ARTICLE HIGHLIGHTS

Research background

There is variability in intensive care unit (ICU) resources and staffing worldwide. This may reflect variation in practice and outcomes across all health systems.

Research motivation

By understanding the nature of ICU practices on a global scale, administrative leaders can create long-term strategies for improved research and quality improvement measures.

Research objectives

We aimed to delineate the critical care practices that are found worldwide and their characteristics, including staffing, ICU resources, and adherence to protocols.

Research methods

An international survey 'Global ICU Needs Assessment 2020' was created using Google Forms, and this was distributed from February 17th, 2020 till September 23rd, 2020. The survey was shared with ICU providers in 34 countries.

Research results

There were a total 121 adult/adult-pediatrics ICU responses from 34 countries in 76 cities. A majority of the ICUs were mixed medical-surgical (92, 76%). 108 (89%) were adult-only ICUs. Total 36 respondents (29.8%) were 31-40 years of age, with 79 (65%) male and 41 (35%) female participants. 89 were consultants (74%). A total of 71 (59%) respondents reported having a 24-h in-house intensivist.

Research conclusions

Based on the findings of this international, multi-dimensional, needs-assessment survey, there is a need for increased recruitment and staffing in critical care facilities, along with improved patient-to-nurse ratios.

Research perspectives

Future research is warranted in this field with focus on implementing appropriate health standards, protocols and resources for optimal efficiency in critical care worldwide.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Faisal A Nawaz 0000-0002-0701-7628; Neha Deo 0000-0002-0583-8916; Salim Surani 0000-0001-7105-4266; William Maynard 0000-0002-0958-4183; Martin L Gibbs 0000-0003-1689-0012; Rahul Kashyap 0000-0002-4383-3411.

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REFERENCES

1 **Sakr Y**, Moreira CL, Rhodes A, Ferguson ND, Kleinpell R, Pickkers P, Kuiper MA, Lipman J, Vincent JL; Extended Prevalence of Infection in Intensive Care Study Investigators. The impact of hospital and ICU organizational factors on outcome in critically ill patients: results from the Extended Prevalence of Infection in Intensive Care study. *Crit Care Med* 2015; **43**: 519-526 [PMID: 25479111 DOI: 10.1097/CCM.0000000000000754]

2 **Kartik M**, Gopal PBN, Amte R. Quality Indicators Compliance Survey in Indian Intensive Care Units. *Indian J Crit Care Med* 2017; **21**: 187-191 [PMID: 28515601 DOI: 10.4103/ijccm.IJCCM_164_15]

3 **Smith GR Jr**, Ma M, Hansen LO, Christensen N, O'Leary KJ. Association of hospital admission service structure with early transfer to critical care, hospital readmission, and length of stay. *J Hosp Med* 2016; **11**: 669-674 [PMID: 27091410 DOI: 10.1002/jhm.2592]

4 **Fowler RA**, Abdelmalik P, Wood G, Foster D, Gibney N, Bandrauk N, Turgeon AF, Lamontagne F, Kumar A, Zarychanski R, Green R, Bagshaw SM, Stelfox HT, Foster R, Dodek P, Shaw S, Granton J, Lawless B, Hill A, Rose L, Adhikari NK, Scales DC, Cook DJ, Marshall JC, Martin C, Jouvet P; Canadian Critical Care Trials Group; Canadian ICU Capacity Group. Critical care capacity in Canada: results of a national cross-sectional study. *Crit Care* 2015; **19**: 133 [PMID: 25888116 DOI: 10.1186/s13054-015-0852-6]

5 **Juneja D**, Nasa P, Singh O. Physician staffing pattern in intensive care units: Have we cracked the code? *World J Crit Care Med* 2012; **1**: 10-14 [PMID: 24701396 DOI: 10.5492/wjccm.v1.i1.10]

6 **Chittawatanarat K**, Sataworn D, Thongchai C; Thai Society of Critical Care Medicine Study Group. Effects of ICU characters, human resources and workload to outcome indicators in Thai ICUs: the results of ICU-RESOURCE I study. *J Med Assoc Thai* 2014; **97** Suppl 1: S22-S30 [PMID: 24855839]

7 **Murthy S**, Leligdowicz A, Adhikari NK. Intensive care unit capacity in low-income countries: a systematic review. *PLoS One* 2015; **10**: e0116949 [PMID: 25617837 DOI: 10.1371/journal.pone.0116949]

8 **Vukoja M**, Riviello E, Gavrilovic S, Adhikari NK, Kashyap R, Bhagwanjee S, Gajic O, Kilickaya O; CERTAIN Investigators. A survey on critical care resources and practices in low- and middle-income countries. *Glob Heart* 2014; **9**: 337-42.e1 [PMID: 25667185 DOI: 10.1016/j.gheart.2014.08.002]

9 **Kashyap R**, Nawaz F, Deo N, Surani SR, Global ICU Need Assessment (GINA) study group. Critical Care Practice in the World: Results of the Global ICU Need Assessment Survey (GINA 2020). *Am J Respir Crit Care Med* 2021; **203**: A1699 [DOI: 10.1164/ajrccm-conference.2021.203.1_MeetingAbstracts.A1699]

10 **Singer DE**, Carr PL, Mulley AG, Thibault GE. Rationing intensive care--physician responses to a resource shortage. *N Engl J Med* 1983; **309**: 1155-1160 [PMID: 6413862 DOI: 10.1056/NEJM198311103091905]

11 **Vestergaard AH**, Christiansen CF, Nielsen H, Christensen S, Johnsen SP. Geographical variation in use of intensive care: a nationwide study. *Intensive Care Med* 2015; **41**: 1895-1902 [PMID: 26239728 DOI: 10.1007/s00134-015-3999-3]

12 **Sakr Y**, Jaschinski U, Wittebole X, Szakmany T, Lipman J, Ñamendys-Silva SA, Martin-Loeches I, Leone M, Lupu MN, Vincent JL; ICON Investigators. Sepsis in Intensive Care Unit Patients: Worldwide Data From the Intensive Care over Nations Audit. *Open Forum Infect Dis* 2018; **5**: ofy313 [PMID: 30555852 DOI: 10.1093/ofid/ofy313]

13 **Zahar JR**, Azoulay E, Klement E, De Lassence A, Lucet JC, Regnier B, Schlemmer B, Bedos JP. Delayed treatment contributes to mortality in ICU patients with severe active pulmonary tuberculosis and acute respiratory failure. *Intensive Care Med* 2001; **27**: 513-520 [PMID: 11355119 DOI: 10.1007/s001340000849]

14 **Kashyap R**, Vashistha K, Saini C, Dutt T, Raman D, Bansal V, Singh H, Bhandari G, Ramakrishnan N, Seth H, Sharma D, Seshadri P, Daga MK, Gurjar M, Javeri Y, Surani S, Varon J; ININ-2018 Investigators Team. Critical care practice in India: Results of the intensive care unit need assessment survey (ININ2018). *World J Crit Care Med* 2020; **9**: 31-42 [PMID: 32577414 DOI: 10.5492/wjccm.v9.i2.31]

15 **Aragon D**, Sole ML. Implementing best practice strategies to prevent infection in the ICU. *Crit Care Nurs Clin North Am* 2006; **18**: 441-452 [PMID: 17118299 DOI: 10.1016/j.ccell.2006.08.003]

16 **Valley TS**, Noritomi DT. ICU beds: less is more? *Intensive Care Med* 2020; **46**: 1594-1596 [PMID: 32335703 DOI: 10.1007/s00134-020-06042-1]

17 **Vincent JL**. Evidence supports the superiority of closed ICUs for patients and families: Yes. *Intensive Care Med* 2017; **43**: 122-123 [PMID: 27586991 DOI: 10.1007/s00134-016-4466-5]

18 **Sasichay-Akkadechanunt T**, Scalzi CC, Jawad AF. The relationship between nurse staffing and patient outcomes. *J Nurs Adm* 2003; **33**: 478-485 [PMID: 14501564 DOI: 10.1097/00005110-200309000-00008]

19 **Kredo T**, Bernhardsson S, Machingaidze S, Young T, Louw Q, Ochodo E, Grimmer K. Guide to clinical practice guidelines: the current state of play. *Int J Qual Health Care* 2016; **28**: 122-128 [PMID: 26796486 DOI: 10.1093/intqhc/mzv115]

20 **Jansson M**, Ala-Kokko T, Ylipalosaari P, Syrjälä H, Kyngäs H. Critical care nurses' knowledge of, adherence to and barriers towards evidence-based guidelines for the prevention of ventilator-associated pneumonia--a survey study. *Intensive Crit Care Nurs* 2013; **29**: 216-227 [PMID: 23566622 DOI: 10.1016/j.iccn.2013.02.006]

21 **Sinuff T**, Cook D, Giacomini M, Heyland D, Dodek P. Facilitating clinician adherence to guidelines in the intensive care unit: A multicenter, qualitative study. *Crit Care Med* 2007; **35**: 2083-2089 [PMID: 17855822 DOI: 10.1097/01.ccm.0000281446.15342.74]

22 **Shah A**, Kashyap R, Tosh P, Sampathkumar P, O'Horo JC. Guide to Understanding the 2019 Novel Coronavirus. *Mayo Clin Proc* 2020; **95**: 646-652 [PMID: 32122636 DOI: 10.1016/j.mayocp.2020.02.003]

23 **Walkey AJ**, Kumar VK, Harhay MO, Bolesta S, Bansal V, Gajic O, Kashyap R. The Viral Infection and Respiratory Illness Universal Study (VIRUS): An International Registry of Coronavirus 2019-Related Critical Illness. *Crit Care Explor* 2020; **2**: e0113 [PMID: 32426754 DOI: 10.1097/CCE.0000000000000113]

24 **Walkey AJ**, Sheldrick RC, Kashyap R, Kumar VK, Boman K, Bolesta S, Zampieri FG, Bansal V, Harhay MO, Gajic O. Guiding Principles for the Conduct of Observational Critical Care Research for Coronavirus Disease 2019 Pandemics and Beyond: The Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study Registry. *Crit Care Med* 2020; **48**: e1038-e1044 [PMID: 32932348 DOI: 10.1097/CCM.0000000000004572]

25 **Domecq JP**, Lal A, Sheldrick CR, Kumar VK, Boman K, Bolesta S, Bansal V, Harhay MO, Garcia MA, Kaufman M, Danesh V, Cheruku S, Banner-Goodspeed VM, Anderson HL 3rd, Milligan PS, Denson JL, St Hill CA, Dodd KW, Martin GS, Gajic O, Walkey AJ, Kashyap R; Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 Registry Investigator Group. Outcomes of Patients With Coronavirus Disease 2019 Receiving Organ Support Therapies: The International Viral Infection and Respiratory Illness Universal Study Registry. *Crit Care Med* 2021; **49**: 437-448 [PMID: 33555777 DOI: 10.1097/CCM.0000000000004879]

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META-ANALYSIS

Diuretic combinations in critically ill patients with respiratory failure: A systematic review and meta-analysis

Jean Maxime Côté, Nadir Goulamhoussen, Blaithin A McMahon, Patrick T Murray

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Jean Maxime Côté, Nadir Goulamhoussen, Division of Nephrology, Department of Medicine, Centre Hospitalier de l'Université de Montréal, Montréal H2X0C1, Québec, Canada

Blaithin A McMahon, Division of Nephrology, Department of Medicine, Medical University of South Carolina, Charleston, SC 29425, United States

Patrick T Murray, Department of Medicine, School of Medicine, University College Dublin, Dublin D078NN, Ireland

Corresponding author: Jean Maxime Côté, FRCP (C), MD, MSc, Consultant Physician, Division of Nephrology, Department of Medicine, Centre Hospitalier de l'Université de Montré al, CHUM 1000 St Denis, Montréal H2X0C1, Québec, Canada.
jean-maxime.cote@umontreal.ca

Abstract

BACKGROUND

In patients with respiratory failure, loop diuretics remain the cornerstone of the treatment to maintain fluid balance, but resistance is common.

AIM

To determine the efficacy and safety of common diuretic combinations in critically ill patients with respiratory failure.

METHODS

We searched MEDLINE, Embase, Cochrane Library and PROSPERO for studies reporting the effects of a combination of a loop diuretic with another class of diuretic. A meta-analysis using mean differences (MD) with 95% confidence interval (CI) was performed for the 24-h fluid balance (primary outcome) and the 24-h urine output, while descriptive statistics were used for safety events.

RESULTS

Nine studies totalling 440 patients from a total of 6510 citations were included. When compared to loop diuretics alone, the addition of a second diuretic is associated with an improved negative fluid balance at 24 h [MD: -1.06 L (95%CI: -1.46; -0.65)], driven by the combination of a thiazide plus furosemide [MD: -1.25 L (95%CI: -1.68; -0.82)], while no difference was observed with the combination of a loop-diuretic plus acetazolamide [MD: -0.40 L (95%CI: -0.96; 0.16)] or spironolactone [MD: -0.65 L (95%CI: -1.66; 0.36)]. Heterogeneity was high and the report of clinical and safety endpoints varied across studies.

CONCLUSION
Based on limited evidence, the addition of a second diuretic to a loop diuretic may promote diuresis and negative fluid balance in patients with respiratory failure, but only when using a thiazide. Further larger trials to evaluate the safety and efficacy of such interventions in patients with respiratory failure are required.

Key Words: Respiratory failure; Diuretics; Fluid management; Furosemide; Thiazide; Systematic review

Core Tip: Loop diuretics are a cornerstone treatment to maintain fluid balance in patients with respiratory failure, but resistance is common. In the caveat of a substantial heterogeneity, this meta-analysis shows a significant increase in urine output with negative fluid balance with the combination of loop diuretics plus thiazides compared to loop diuretics alone in patients with respiratory failure. Further trials are required to confirm the safety and efficacy of such interventions in patients with respiratory failure.

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INTRODUCTION

Progressive fluid accumulation is a commonly encountered scenario in critically ill patients and in patients with acute kidney injury (AKI), acute heart failure, and other edematous states. Fluid overload is associated with increased mortality[1,2] and numerous systemic complications such as poor wound healing, AKI and pulmonary edema with acute hypoxemic respiratory failure (AHRF)[3]. Interpretation of studies evaluating the relationship between fluid balance and mortality in AHRF is complex, especially in the context of other organ outcomes[4]. Early observational studies of fluid management in the specific context of patients with AHRF have shown that a negative fluid balance is associated with improved survival, particularly in the context of acute respiratory distress syndrome (ARDS)[5,6]. Though, the definitive trial evaluating fluid management during ARDS showed that a conservative fluid balance achieved with diuretics did not statistically affect mortality but did increase the number of ventilator-free days and intensive care unit (ICU)-free days survival[7].

In the ICU, loop diuretics remain the most widely used class of diuretics, and are used in up to 49% of all ICU admissions[8]. However, prolonged use of loop diuretics may be associated with therapeutic resistance, which is a frequent observation in the ICU and associated with increased risk of mortality[9]. Combining multiple diuretics with different mechanisms of action may achieve a sequential nephron blockade, further limiting the kidney's ability to reabsorb fluid and electrolytes. These actions may further increase urine output, but also potentially lead to complications such as electrolyte and acid-base disorders and worsening kidney function[10,11]. Diuretic combinations are routinely used in the management of heart failure, and there is a significant body of evidence supporting that practice[12,13]. Both American and European Heart Failure Guidelines recommend that when diuresis remains inadequate with loop diuretic therapy despite dose escalation, the addition of thiazide diuretics may be considered[14,15]. Recent data have also shown that the addition of a second diuretic can help to mitigate loop-diuretic resistance in a broad cohort of patients hospitalised in the ICU[16].

However, in patients with AHRF, only few data exist on the additional efficacy of various diuretic regimens to promote diuresis in resistant edematous states, despite the use of this approach in up to 6% of all ICU admissions[8]. Instead of progressively escalate the dose in patients resistant to loop diuretics, a proactive administration of a second diuretic may help to quickly increase the urine output, and therefore minimize respiratory complications. On the other hand, as opposed to patients with heart failure where the extravascular fluid retention usually represents multiple liters, patients with AHRF may have a relatively small fluid retention but enough to significantly affect the perturbed pulmonary physiology. In these patients, the risks of quickly increasing the diuresis, and therefore having a substantial negative fluid balance, may be higher regarding renal function, electrolyte homeostasis or hypotension. To date, no systematic review has evaluated different protocols of diuretic combinations in this population regarding their efficacy but also their safety.

Scope

The aim of this systematic review was to determine the efficacy of common diuretic combinations to promote negative fluid balance in patients hospitalised in the ICU with AHRF. The objective was to compare the use of loop diuretics in monotherapy to the use of a loop diuretic with an adjunctive non-loop diuretic agent paying particular attention to rates of AKI and electrolyte disturbance.

MATERIALS AND METHODS

This systematic review with meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines[17]. The protocol was registered on the PROSPERO international prospective register of systematic reviews (CRD42020218381).

Eligibility criteria

Inclusion criteria: Eligible studies compared diuretic combinations to loop diuretics alone in adult patients hospitalised in ICU with respiratory failure receiving diuretics for volume control. Respiratory failure was defined as receiving invasive or non-invasive positive ventilation for an acute hypoxemic or hypercapnic respiratory failure, or for severe pulmonary edema requiring oxygen therapy. Patients with non-primary pulmonary aetiology, such as acute decompensated heart failure, were included if signs of severe pulmonary edema requiring oxygen, with or without mechanical ventilation, were clearly reported. Studies evaluating a combination of diuretic agents without a comparison group were included in the systematic review if at least one efficacy clinical outcome of interest was reported, but were not included in the final meta-analysis. The following classes of non-loop diuretics in combination with a loop diuretic were included: Thiazide or thiazide-like agents, carbonic anhydrase inhibitors, Epithelial sodium channel (ENaC) inhibitors and mineralocorticoid antagonists. No study design, date or language limits were imposed on the literature search, although only studies in English, Spanish and French were included in the analysis.

Exclusion criteria: Studies reporting patients with peripheral edema only were excluded. Studies reporting patients with chronic kidney disease (CKD) treated with maintenance kidney replacement therapy (KRT) were also excluded. Studies of the use of loop diuretic agents in pediatric populations were excluded.

Literature search

According to the predetermined protocol, a systematic literature search of 4 databases (MEDLINE, Embase, Cochrane Library and PROSPERO) was performed from inception until May 5, 2021 in collaboration with a trained medical librarian (covering from 1946 to May 2021). The literature search strategy was developed using medical subject headings and text words related to all classes of diuretics included and their individual name, fluid balance, respiratory failure and hypoxemia, and critical care (Supplementary Table 1). We also scanned the reference lists of included studies and searched the grey literature for all abstracts listed into the annual meeting archives of the *American Society of Nephrology*, the *European Society of Intensive Care Medicine* and the *Society of Critical Care Medicine*. Finally, a bibliography of all potentially included articles was circulated to all authors, to prompt consideration of any other relevant publications.

Study selection

Eligible studies were clinical trials, observational cohort studies, case-control studies and cross-sectional studies. Cases series with more than five patients and abstracts not yet published were also included when at least one outcome of interest was described quantitatively. Literature search results were uploaded and screened using *Rayyan QCRI* application. Two reviewers (JMC and NG) independently screened the titles and abstracts of all identified articles. These reviewers then screened the full-text reports for all potential studies and decided whether these met the inclusion criteria, reporting the reason(s) for exclusions. When necessary, the authors (JMC and BMcM) contacted the corresponding author of potential studies to obtain additional information. Once the final list of included articles was determined, there was no disagreements between authors.

Data extraction

RevMan (Version 5.4, The Cochrane Collaboration, 2020) was used to extract data from each eligible study. Data extracted included eligibility criteria, demographics, methodology, diuretic name, class and dosage, risk of bias and results. The prespecified primary efficacy outcome of interest was the cumulative fluid balance, and secondary outcomes were the 24-h urine output (diuresis), ventilation-free survival, number of days on mechanical ventilation, need of therapeutic paracentesis, hospital and ICU length-of-stay, in-hospital and 90-d mortality. Due to lack of data regarding the cumulative ICU fluid balance for all included studies, the 24-h fluid balance was therefore reported as primary outcome. Safety endpoints included AKI incidence and progression to KRT, electrolyte and acid-base

abnormalities, creatinine and electrolyte changes from baseline (sodium, potassium, bicarbonate) and, finally, hypotensive events, arrythmias and ototoxicity occurrence. Reports of 24-h natriuresis, not planned in the original protocol, were also captured as this endpoint was considered clinically relevant.

The risk of bias was assessed using the Cochrane Collaboration tool for assessing the risk of bias for randomised controlled trials (RCTs) (RoB2)[18], and non-randomised trials (n-RCTs)(ROBINS-I)[19], and the Newcastle-Ottawa Scale for observational studies. These assessments were based on the reporting of fluid balance, the primary outcome of the current review. When insufficient details were reported, the risk of bias was judged as unclear.

Statistical analysis

A meta-analysis using mean differences (MD) with 95% confidence interval (CI) was performed for the primary outcome and for the 24-h urine output (secondary efficacy endpoint), while descriptive statistics were used for all other endpoints reported. The statistical heterogeneity for pooled results was reported using I^2. As the clinical heterogeneity of included studies was considered high, a random-effects model was used for both meta-analyses. In studies reporting the endpoint using median and IQR, the statistical method described by Wan *et al*[20] was used to convert the reported value to mean ± SD allowing meta-analysis. None of the preplanned sub-analyses (dosage of loop diuretics and the type of respiratory failure) were performed due to limited data. All statistical analyses were performed on *RevMan* (Version 5.4, The Cochrane Collaboration, 2020) and SPSS (Version 26, IBM, Armonk NY).

RESULTS

Study selection

Study selection is depicted in Figure 1. After removal of duplicates, there were 6510 studies. Of these, 6476 were excluded after screening titles and abstracts. A total of 34 studies were assessed for eligibility, from which 25 were excluded for not meeting inclusion criteria (Supplementary Table 2). Therefore, a total of 9 studies were included[21-29], from which 8 presented quantitative results for endpoints meta-analysis[21-23,25-29].

Study characteristics

A detailed summary of each of the study characteristics is presented in Table 1. The included studies investigated the combination of furosemide with either spironolactone[21], indapamide[22], chlorothiazide[23,27,29], metolazone[23,27,28], acetazolamide[24,25] or a combination of hydrochlorothiazide and amiloride[26] at various doses in patients with respiratory failure. These studies were published between 1997 and 2019, and included a total of 440 participants. Three studies were RCTs[21,22,25] and 5 were observational[23,24,27-29], and one was a prospective non-randomised interventional study[26].

For the study by Heming *et al*[24], only 29 from the 68 participants were receiving a loop diuretic in addition to acetazolamide. All results reported from this study were calculated using the subset of the entire cohort receiving that combination of diuretics based on the dataset shared by the authors. Similarly, only patients with confirmed ICU admission with respiratory failure from the Shulenberger *et al*[29] study (n = 78, from 177 in total) were included in this review, after access to the original dataset. Overall, in this review, females were the minority and the median age ranged from 57 to 77 years. Most patients were admitted following cardiac surgery or acute decompensated heart failure. The duration of the diuretic combination intervention varied from 24 to 96 h, while the median furosemide dose (equivalent to intravenous furosemide) ranged from approximately 80 to 351 mg *per* day. The doses of the second diuretic are reported in Table 1.

Risk of bias

The quality assessment and risks of bias are presented in the Supplementary Material (Supplementary Table 3). All 3 RCTs included[21,22,25], despite limited sample size, were good quality with an overall low risk of bias. The non-randomised interventional trial was classified with an overall unclear risk of bias, due to missing data[26] and potential uncontrolled confounders. The observational cohort studies included were of good quality, where the risk of bias was adequately minimized for most components of the Newcastle-Ottawa Assessment Scale. No unpublished data was included in this review. Heterogeneity was substantial across all included studies, regarding study design, intervention duration and timing of administration, dose of loop-diuretics administered, baseline kidney function and safety endpoints reported. Notably, the intervention duration, defined as the period of diuretics administration during which clinical endpoints were measured, ranged between 24 h to 96 h. In addition, regarding the second diuretic, some studies reported a fixed dose for all patients, while other reported a titratable dose. The comparison group receiving only a loop-diuretic was an independent and parallel-group for 4 studies[21,22,25,26], and a sequential paired group–where clinical endpoints were compared before and after the addition of a second diuretic within the same group–for 4 studies[23,27-

Table 1 Characteristics of included studies

Ref.	Country, design	Inter-vention duration	Major eligibility criteria	Study groups (sample size)	Median daily dose of diuretic (route)	Patients characteristics	
Apte *et al*[21], 2008	Australia; RCT	72 h	(1) Mechanically ventilated; and (2) On continuous IV furosemide	Furosemide + Spironolactone (*n* = 10)	97 mg (71-288) (IV); 300 mg (PO)	(1) Age: 68 (55-79); (2) Male sex: 7 (70%); (3) SCr, μmol/L: -; (4) Apache II Score: 21 (15-28); and (5) Positive ventilation: 10 (100%)	ICU admission for (1) Sepsis: 4 (40%); (2) Cardiovascular: 2 (20%); and (3) COPD/Resp. failure: 2 (20%). In-hospital mortality: -
				Furosemide + Placebo (*n* = 10)	168 mg (74-295) (IV)	(1) Age: 67 (52-76); (2) Male sex: 6 (60%); (3) SCr, umol/L: -; (4) Apache II Score: 24 (17-26); and (5) Positive ventilation: 10 (100%)	ICU admission for (1) Sepsis: 6 (60%); (2) Cardiovascular: 1 (10%); and (3) COPD/Resp. failure: 0 (0%). In-hospital mortality: -
Bihari *et al* [22], 2016	Australia; RCT	24 h	(1) Fluid overload (> 10% ICU admission weight); and (2) No prior diuretic last 48 h	Furosemide (*n* = 20)	1 mg/kg (IV); Median weight: 78 kg	(1) Age: 75 (62-86); (2) Male sex: 12 (60%); (3) SCr, μmol/L: 97 (69-133); (4) Apache III Score: 68 ± 21; and (5) Positive ventilation: 14 (70%)	ICU admission for (1) Sepsis: 3 (15%); (2) Cardiovascular: 3 (15%); and (3) COPD/Resp. failure: 12 (60%). In-hospital mortality: 5 (25)
				Furosemide + Indapamide (*n* = 20)	1 mg/kg (IV); 5 mg (PO)	(1) Age: 70 (53-75); (2) Male sex: 14 (70%); (3) SCr, μmol/L: 91 (63-141); (4) Apache III Score: 74 (29); and (5) Positive ventilation: 10 (50%)	ICU admission for (1) Sepsis: 3 (15%); (2) Cardiovascular: 4 (20%); and (3) COPD/Resp. failure: 10 (50%). In-hospital mortality: 5 (25)
Bohn *et al*[27], 2019[1]	United States; Observa-tional (paired groups)	24 h	(1) ADHF with reduced ejection fraction; and (2) Not responding to furosemide monotherapy	Furosemide + Chlorothiazide (*n* = 34, from 108)[1]	≥ 80 mg (IV); 500 to 1000 mg (IV)	(1) Age: 64 (54-69); (2) Male sex: 74 (69%); (3) SCr, umol/L: 132 (90-187); (4) Apache II Score: 12 (9-15); and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 108 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: 21 (19)
				Furosemide (*n* = 34, from 108)[1]	≥ 80 mg (IV)	-	-
				Furosemide + Metolazone (*n* = 16, from 60)[1]	≥ 80 mg (IV); 5 to 10 mg (PO)	(1) Age: 63 (54-74); (2) Male sex: 41 (68%); (3) SCr, umol/L: 142 (102-188); (4) Apache II Score: 10 (7-14); and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 60 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: 1 (2)
				Furosemide (*n* = 16, from 60)[1]	≥ 80 mg (IV)	-	-
Heming *et al* [24], 2011	France; Observa-tional	24 h	(1) Mechanically ventilated; and (2) Acute respiratory failure	Furosemide + Acetazolamide (*n* = 29, from 68)[2]	80 mg (40-80) (IV); 500 to 1000 mg (PO)	(1) Age: 77 (73-83); (2) Male sex: 9 (31%); (3) SCr, umol/L: 66 (57-89); (4) Apache II Score: 25 (20-30); and (5) Positive ventilation: 29 (100%)	ICU admission for (1) Sepsis: 6 (21%); (2) Cardiovascular: 5 (17%); and (3) COPD/Resp. failure: 16 (55%). In-hospital mortality: 10 (34)
Imiela and Budaj[25], 2017	Poland; RCT	96 h	(1) ADHF not responding to furosemide; and (2) Significant pulmonary overload	Furosemide[3] + Acetazolamide (*n* = 10)	110 mg (± 73) (IV); 250 to 500 mg (PO)	(1) Age: 73 (± 8.6); (2) Male sex: 8 (80%); (3) SCr, μmol/L: 137 (± 42); (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 10 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: -
				Furosemide[3] (*n* = 10)	152 mg (± 97) (IV)	(1) Age: 71 (± 14); (2) Male sex: 9 (90%); (3) SCr, umol/L: 141 (±	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 10 (100%);

						77); (4) Apache II Score: -; and (5) Positive ventilation: -	and (3) COPD/Resp. failure: -
Michaud and Mintus[23], 2017	United States; Observational (paired groups)	24 h	(1) Hospitalized at the ICU; and (2) Received IV furosemide + 2nd diuretics for severe fluid overload	Furosemide + Chlorothiazide (*n* = 58)	280 mg (40-720) (IV); 392 mg (± 225) (IV)	(1) Age: 61 (± 12); (2) Male sex: 35 (60%); (3) SCr, μmol/L: 124 (± 53); (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: 4 (6.8%); (2) Cardiovascular: 25 (43%); and (3) COPD/Resp. failure: 15 (26%). In-hospital mortality: 11 (19)
				Furosemide (*n* = 58)	193 mg (20-710) (IV)	-	-
				Furosemide + Metolazone (*n* = 64)	240 mg (20-960) (IV); 6.8 mg (± 3.3) (PO)	(1) Age: 65 (± 14); (2) Male sex: 31 (48%); (3) SCr, μmol/L: 115 (± 44); (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: 9 (14%); (2) Cardiovascular: 24 (38%); and (3) COPD/Resp. failure: 12 (19%). In-hospital mortality: 17 (27)
				Furosemide (*n* = 64)	130 mg (20-750) (IV)	-	-
Ng *et al*[28], 2013	United States; Observational (paired groups)	48 h	(1) Hospitalized at the ICCU; and (2) Failed to respond to intermittent furosemide	Furosemide + Metolazone (*n* = 42)	80 mg (80-160) (IV); 5 mg (2.5-10) (PO)	(1) Age: 57 (± 13); (2) Male sex: 22 (52%); (3) SCr, μmol/L: 148 (± 88); (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 42 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: 0 (0)
				Furosemide (*n* = 42)	80 mg (0-160) (IV)	-	-
Shulenberger *et al*[29], 2016	United States; Observational (paired groups)	24 h	(1) ADHF with loop-diuretic resistance defined as > 160 mg/d of furosemide; and (2) Admitted in the ICU	Furosemide + Chlorothiazide (*n* = 40, from 88)[4]	346 mg (± 144) (IV); 508 mg (± 273) (IV)	(1) Age: 59 (± 12); (2) Male sex: 26 (65%); (3) SCr, μmol/L: -; (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 40 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: 3 (8.5)
				Furosemide (*n* = 40)[4]	351 mg (± 143) (IV)		
				Furosemide + Metolazone (*n* = 38, from 89)[4]	261 mg (± 111) (IV); 5.7 mg (± 2.5)	(1) Age: 57 (± 13); (2) Male sex: 19 (50%); (3) SCr, umol/L: -; (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 38 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: 9 (24%)
				Furosemide (*n* = 38)[4]	263 mg (± 102) (IV)		
Vánky *et al* [26], 1997	Sweden; n-RCT (unpaired groups)	24 h	(1) Hospitalized at the ICU post-Cardiac surgery; and (2) Received IV furosemide for severe fluid overload	Furosemide + HCTZ + Amiloride (*n* = 20)	87 mg (± 4) (IV); 50 mg (PO); 5 mg (PO)	(1) Age: 70 (± 1.4); (2) Male sex: 15 (75%); (3) SCr, μmol/L: 98 (± 3); (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 20 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: -
				Furosemide (*n* = 57)	117 mg (± 18) (IV)	(1) Age: 67 (± 1.2); (2) Male sex: 40 (70%); (3) SCr, μmol/L: 105 (± 4); (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 57 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: -

[1]Bohn *et al*[27]: Baseline characteristics reported are from the whole cohort. However, only critically ill patients receiving vasopressors (Chlorothiazide: 34, Metolazone: 16) were included in aggregated data.

[2]Heming *et al*[24]: Only 29 participants from the whole cohort (*n* = 68) received a loop-diuretic in combination with acetazolamide. All aggregated data were re-analysed using the original dataset shared by the authors.

[3]Some patients received torsemide. The dose was converted to furosemide equivalent.

[4]Shulenberger *et al*[29]: Only intensive care unit patients (Chlorothiazide: 40, Metolazone: 38) were included in aggregated data, after re-analysis based on the original dataset shared by the authors.

RCT: Randomized Controlled Trial; ADHF: Acute decompensated heart failure; SCr: Baseline Serum creatinine; ICU: Intensive care unit; ICCU: Intensive cardiac care unit.

29].

Primary endpoint: Daily fluid balance

When combining all studies using various combinations of non-loop-diuretic plus loop-diuretic compared to loop-diuretics alone, a significant difference was observed in the primary outcome, with a MD in the 24-h fluid balance in favour of the combination group [overall MD: -1.06 L (95%CI: -1.46; -0.65), I^2 = 68%] (Figure 2A). However, when each combination diuretic class was analyzed separately, no significant difference was observed for the spironolactone-furosemide [MD: -0.65 L (95%CI: -1.66; 0.36), I^2 = NA] or the acetazolamide-furosemide combination [MD: -0.40 L (95%CI: -0.96; 0.16), I^2 = NA]. Thus, the observed effect on the daily fluid balance was mainly driven by the thiazide-furosemide combinations [MD: -1.25 L (95%CI: -1.68; -0.82), I^2 = 60%]. Inspection of the funnel plot (Supplementary Figure 1) showed no substantial publication bias toward specific studies.

Secondary efficacy endpoints

Similar findings were reported for the 24-h urine output, where the addition of a second diuretic was associated with an increase in the urine output by 1.08 L (95%CI: 0.65; 1.52, I^2 = 73%). Once again, that effect was mainly attributed to the thiazide-furosemide combination [MD: 1.30 L (95%CI: 0.81-1.79), I^2 = 76%] as no difference was observed for other combinations (Figure 2B). Overall, while the addition of spironolactone or acetazolamide to furosemide had a limited effect on fluid and sodium balance (Supplementary Table 4), the addition of a thiazide was associated with an increase in urine output by 14% for indapamide, 31% for hydrochlorothiazide plus amiloride, ranged from 52%-101% for metolazone and, finally, from 89%-114% for chlorothiazide, with corresponding effects on the negative fluid balance. In-hospital mortality, ICU length-of-stay, and hospital length-of-stay are depicted in Supplementary Table 5. Due to limited data, no pooled analysis was performed for these outcomes. No study reported the 28-d or 90-d mortality, need of therapeutic paracentesis and ventilation free-survival.

Safety endpoints

Available data on the physiological effects of these diuretic combinations on electrolytes and serum creatinine is shown in Table 2, but reporting was inconsistent. Due to significant heterogeneity across these studies, results for these endpoints were not pooled, but instead reported separately. No diuretic combination was associated with a substantial serum creatinine change at 24-h from baseline. According to the specific segment of the nephron targeted, varied impacts on electrolytes were observed for these three diuretic classes; for example, whereas a limited increase in serum potassium was observed with the spironolactone combination, a decrease in serum potassium was observed in all thiazide studies reporting this endpoint. Notably, as opposed to thiazide and loop-diuretic combinations, with which an increased in serum bicarbonate was observed, treatment with acetazolamide for 24-h reduced serum bicarbonate levels by 3.6 ± 5.1 mmol/L.

The risk of all other adverse (safety) events, where definitions and follow-up varied across included studies, are reported in Supplementary Table 6. Notably, hypokalemia was documented in 6 studies and ranged from 0% to 85%, while hyponatremia was documented in 4 studies and ranged from 0% to 43% when combining a thiazide with a loop-diuretic. No study reported arrythmia or ototoxicity events.

DISCUSSION

To our knowledge, this is the most comprehensive systematic review and meta-analysis to address the clinical efficacy and safety of various diuretic combinations in the context of patients hospitalised at the ICU with fluid overload and respiratory failure. A significant increase in the 24-h urine output leading to a negative fluid balance was observed in the pooled analyses, mainly attributed to the thiazide-furosemide combination. Reporting of other clinical endpoints including the efficacy, safety, and clinical outcomes of groups treated with each combination was inconsistent and generally incomplete.

Currently, strategies to manage fluid balance in critically ill patients with acute lung injury and other causes of respiratory failure include fluid restriction but this may be difficult given the requirement of fluid for carriers for vasopressors, antibiotics, and nutrition. A preferred option is augmenting urine output with diuretics. In addition, positive sodium balance specifically, rather than simple fluid balance, has recently been associated with respiratory dysfunction in mechanically ventilated patients[30,31], and with worsening prognosis in decompensated heart failure[32]. Ensuring adequate negative sodium balance along with increased urine output may be crucial to optimising extracellular fluid volume and outcomes. This approach is now endorsed by the European Society of Cardiology[33]. Also, as recently confirmed by the STARRT-AKI trial, delaying initiation of KRT based on a watchful waiting approach (in the absence of emergency indications for RRT initiation) can be beneficial by reducing RRT complications including prolonged KRT requirement[34]. Therefore, refining the ways to achieve a negative fluid balance with a diuretic combination strategy might potentially delay or avoid the need for RRT initiation (including ultrafiltration) to treat volume overload and control fluid balance in patients with loop-diuretic resistance.

Table 2 Safety events and change in serum creatinine and electrolytes at 24-h for all included studies

Ref.	Treatment group	24-h biochemical changes[1]				Safety events, *n* (%)	
		Creatinine, μmol/L	Sodium, mmol/L	Potassium, mmol/L	Bicarbonate, mmol/L	Hyponatremia	Hypokalemia
Mineralocortocoid-antagonist							
Apte *et al*[21], 2008	Spironolactone + Furosemide (*n* = 10)	+4.8 (4.1-6.9)	-1.0 (?)	+0.13 (?)	-	-	-
	Furosemide (*n* = 10)	+23 (-4.4-39)	+3.0 (?)	+0.13 (?)	-	-	-
Thiazides							
Bihari *et al*[22], 2016	Indapamide + Furosemide (*n* = 20)	-5.2 ± 38	0 ± 0	-0.4 ± 1.8	+1.4 ± 6.3	0 (0)	0 (0)
	Furosemide (*n* = 20)	-2.3 ± 14	+2.0 ± 4.0	-0.2 ± 0.6	+0.9 ± 2.5	0 (0)	0 (0)
Bohn *et al*[27], 2019	CTZ + Furosemide (*n* = 34)	-	-	-	-	-	8 (24)
	MTZ + Furosemide (*n* = 16)	-	-	-	-	-	3 (19)
Michaud and Mintus [23], 2017	CTZ + Furosemide (*n* = 58)	-18 ± 57	+0.5 ± 5.6	-0.4 ± 0.6	+3.3 ± 5.1	15 (26)	10 (17)
	MTZ + Furosemide (*n* = 64)	-18 ± 73	-1.2 ± 5.3	-0.3 ± 0.6	+2.6 ± 5.6	25 (39)	11 (17)
Ng *et al*[28], 2013	MTZ + Furosemide (*n* = 42)	+2.7 ± 28	-	-	-	18 (43)	15 (35)
Shulenberger *et al* [29], 2016	CTZ + Furosemide (*n* = 40)	+8.8 ± 27	+0.1 ± 2.3	-	-	2 (5)[2]	34 (85)[3]
	MTZ + Furosemide (*n* = 38)	+18 ± 35	-0.7 ± 3.1	-	-	2 (5)[2]	27 (71)[3]
Vánky *et al*[26], 1997	HCTZ + Amiloride + Furosemide (*n* = 20)	-2.0 ± 7.1	-	-	-	-	-
	Furosemide (*n* = 57)	-2.0 ± 7.6	-	-	-	-	-
Carbonic anhydrase inhibitor							
Heming *et al*[24], 2011	Acetazo + Furosemide (*n* = 29)	+4.3 ± 9.4	-	-0.3 ± 0.4	-3.6 ± 5.1	-	9 (31)
Imiela and Budaj [25], 2017	Acetazo + Furosemide (*n* = 10)	-	-	-	-	-	-
	Furosemide (*n* = 10)	-	-	-	-	-	-

[1]Results are presented in median (IQR), or mean ± SD change within 24-h, from baseline.
[2]Only severe hyponatremia event (Na^+ < 125 mmol/L) were reported.
[3]Hypokalemia was defined as K^+ < 4.0 mmol/L, instead of 3.5 mmol/L for all other studies.
CTZ: Chlorothiazide; MTZ: Metolazone; HCTZ: Hydrochlorothiazide; Acetazo: Acetazolamide.

The mechanisms of resistance to furosemide and other loop diuretics is multifactorial[35]. They include a decrease in sodium delivery to the site of action by systemic and renal hypoperfusion[36], as well as an increase in sodium and water retention due to neurohormonal, renin-angiotensin-aldosterone and antidiuretic hormone systems activation in critically ill patients. In addition, proximal tubular injury or loss in AKI or CKD results in diminished loop diuretic secretion into the tubular lumen and reduced effects more distally in the thick ascending limb of Henle's loop, while in chronic exposure to furosemide, adaptive changes in the nephron occur with hypertrophy of the distal tubule leading to an increase of its reabsorptive capacity[37]. For patients who do not respond to an increasing dose of furosemide, sequential nephron blockade of sodium reabsorption with other classes of diuretics can overcome these resistance mechanisms[16], which was confirmed in the current review focusing on patients with AHRF.

In order to promote liberation from mechanical ventilation in patients with metabolic alkalosis and associated hypoventilation, normalisation of the acid-base state while improving fluid balance with acetazolamide has also been investigated[38-40]. Also, the combination of an aldosterone receptor antagonist with furosemide is recommended as first line therapy in cirrhotic patients with ascites[41], due to the efficacy of that combination to promote natriuresis while minimising the risk of hypokalemia. This combination is also widely recommended in the management of patients with chronic heart failure and has been shown to reduce morbidity and mortality in patients with reduced ejection fraction[42].

In this review, various factors may explain the limited efficacy of these combinations to promote diuresis and a negative fluid balance in some included studies. First, the dose of furosemide was not

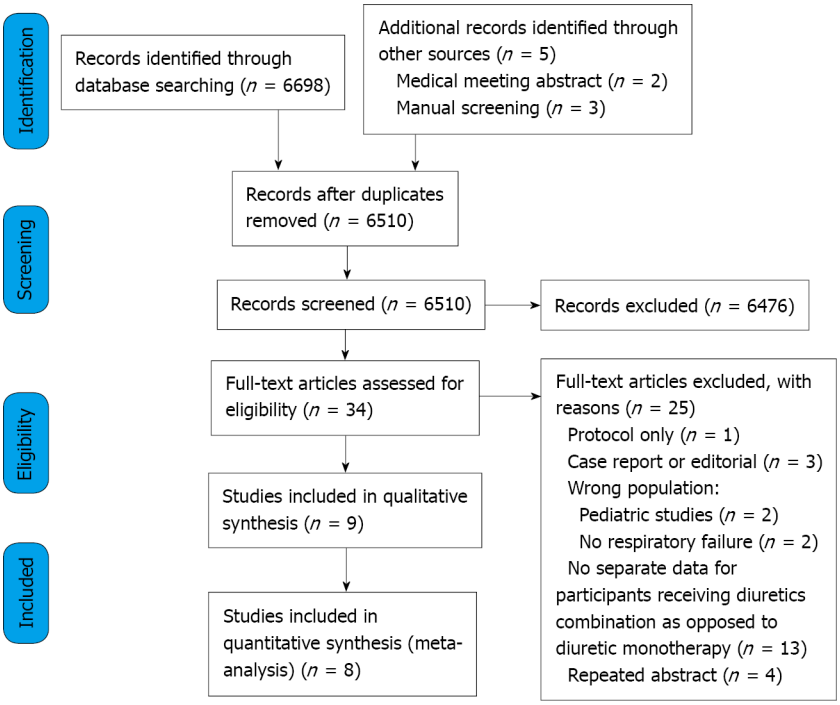

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Figure 1 Flow chart of included studies.

maximised for most studies, unlike recent RCTs on acute heart failure[12]. Indeed, the studies with higher median daily doses of furosemide were associated with higher and significant increases in urine output, even before addition of the second diuretic[23,29], which was also confirmed in previous cohorts[16]. On the other hand, the use of sub-maximal doses of multiple drugs in combination may additively or synergistically augment efficacy, while avoiding the adverse effects of higher doses of these drugs. Secondly, in the context of respiratory failure, the total negative fluid balance required to improve respiratory parameters may be less than the diuresis desired in patients with acute heart failure, in which the cumulative volume overload is usually greater[1]. As this review focused on the net fluid balance achieved instead of respiratory outcomes, it is still possible that the limited diuresis observed for these patients was judged as clinically sufficient to maintain an even fluid balance (rather than targeting negative fluid balance), as opposed to a fluid-liberal approach[7]. Also, none of these studies reported the use of an integrated tool, such as point-of-care ultrasound, bioimpedance, or other hemodynamic and volume measures[3], to evaluate the volume status of these patients, once again limiting the capacity to determine if the urine output achieved was adequate to optimise volume status.

All diuretic agents have a safety profile that varies according to their intrinsic mechanism of action. This review showed that combination of acetazolamide and furosemide may reduce serum bicarbonate and induce potassium loss, causing hypokalemia in up to 31% of patients[24] after only 24 h of treatment. In contrast, when furosemide is combined with thiazides, a trend toward an increase in bicarbonate and lower potassium levels was observed, reflecting the greater natriuretic and kaliuretic effects of reabsorption blockade in sequential nephron segments. The rate of hypokalemia was considerable, emphasizing the need to regularly monitor electrolyte levels, acid-base parameters, and kidney function (which is under-reported in this literature) when choosing such combinations. The role of potassium-sparing diuretics in the prevention of hypokalemia with aggressive diuretic regimens warrants further research.

In sum, this study brings new data on the use of diuretic combinations in the subgroup of ICU patients with AHRF, which has never been systematically reported before. The pooled analysis confirmed an increased efficacy regarding urine output and net fluid balance, which is interesting in a clinical setting, but also brings relevant data on the potential risk of substantial electrolyte disturbances in patients exposed to these combinations. Indeed, the study also confirms the need for additional lab monitoring when prescribing such combinations especially if no pre-emptive electrolytes administration is planned.

There are several limitations to the current systematic review. First, no study reported the pre-planned endpoint of cumulative fluid balance, which required us to deviate from the original protocol and to use the daily fluid balance as primary outcome. Also, no study reported the use of ENaC inhibitors alone (*e.g.* triamterene, amiloride) in conjunction with furosemide, which did not allow this review to evaluate that combination. This highlights the importance of future studies using ENaC inhibitors in combination with loop-diuretics in the management of respiratory failure. In addition, the

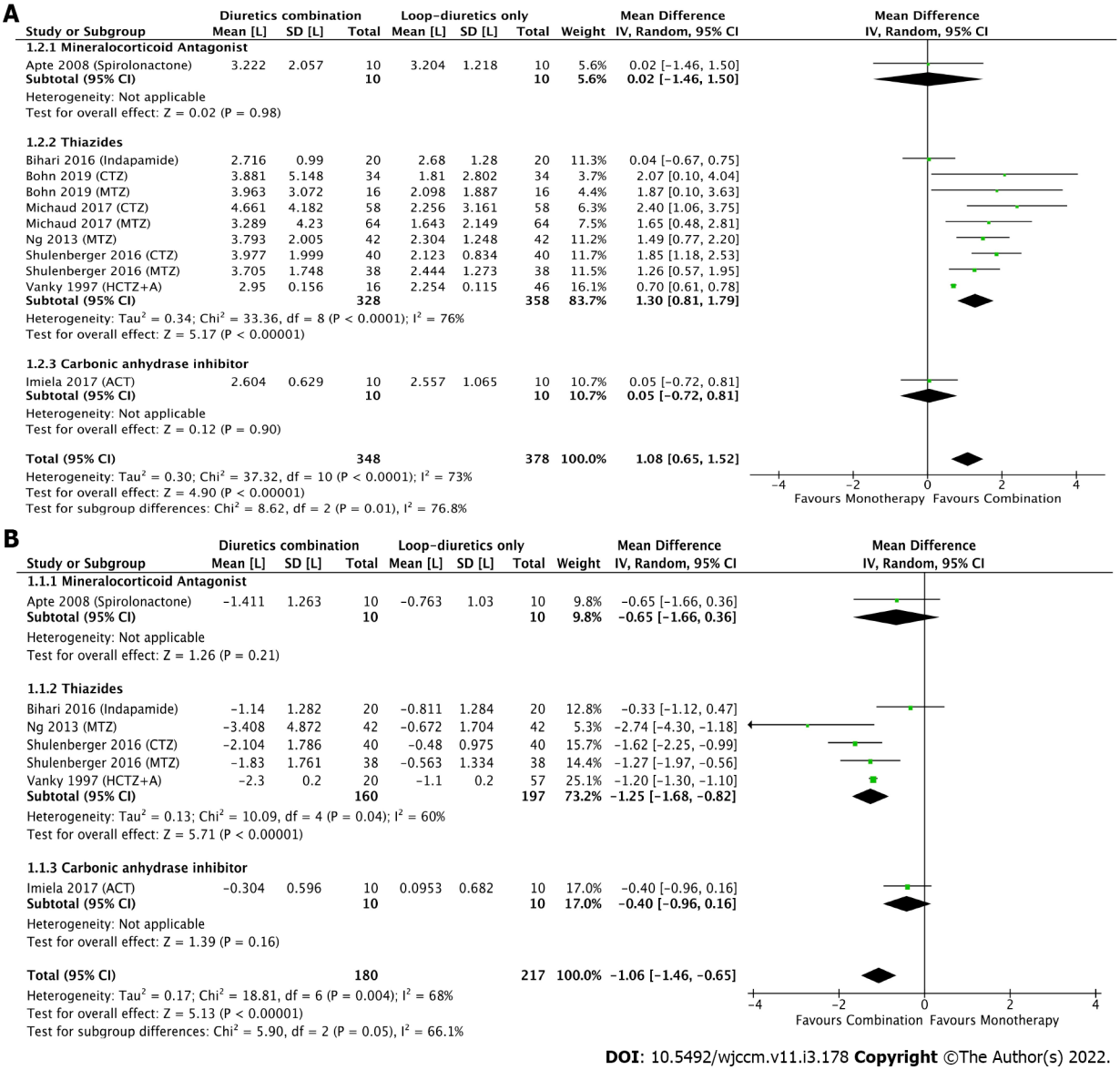

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Figure 2 Forest plot. A: Daily fluid balance; B: Urine output. Comparing loop diuretic in monotherapy to three combinations of diuretics (mineralocorticoid antagonist, thiazides and carbonic anhydrase inhibitor). Mean difference and 95% confidence intervals are shown for each study and the pooled analysis using a random effects model and the Mantel-Haenszel method. Mean difference > 0 means that urine output is higher in the group receiving the combination of diuretics.

literature strategy was limited to generic name. The limited duration of these interventional periods, from 24 to 96 h, may not have substantially affected clinical outcomes such as in-hospital mortality, ICU length-of-stay and ventilation-free survival, which were only partially reported in these studies. Most importantly, the heterogeneity across all included studies was high, including for diuretics doses, renal function, reasons of ICU admission with notable inconsistencies in clinical endpoints reporting. We contacted corresponding authors of all included references to confirm eligibility criteria, but we cannot independently confirm with certainty that all included patients were on mechanical ventilation or required high oxygen volume as some did not respond. Finally, the risk of publication bias is significant, since only limited data has been published in the context of critically ill patients receiving such diuretic strategies.

CONCLUSION

In critically ill patients with respiratory failure receiving a loop diuretic, we showed that addition of another class of diuretic is associated with an increased 24-h urine output leading to a negative fluid balance, where the thiazide and loop-diuretic combination had the higher efficacy. However, given the significant heterogeneity, the risk of publication bias and the lack of adequately powered RCTs, no definitive evidence can be drawn, especially for non-thiazide combinations. In addition, electrolytes

disturbance secondary to the use of these adjunctive diuretics in combination with a loop diuretic warrants additional monitoring to ensure their safety. This limited evidence emphasizes the need for further high-quality trials investigating the efficacy, safety profile and clinical outcomes of such therapeutic interventions for patients with respiratory failure requiring diuretics to control fluid balance.

ARTICLE HIGHLIGHTS

Research background

Diuretics are essential to maintain fluid balance in patients admitted to intensive care units (ICUs). However, resistance to loop-diuretics is common and diuretic combinations are often used in order to mitigate this resistance.

Research motivation

As opposed to patients with heart failure where combinations of different classes of diuretics have been extensively studied and are now recommended, the body of evidence regarding diuretic combinations in ICU patients with hypoxemic respiratory failure is scarce.

Research objectives

This study systematically reviewed the efficacy and safety of common diuretics combinations in ICU patients with respiratory failure when compared to loop-diuretics in monotherapy.

Research methods

A systematic review and meta-analysis were performed. A pooled analysis of the mean difference for the 24-h urine output and the 24-h fluid balance between loop-diuretics in monotherapy and common diuretics combinations (thiazides, carbonic anhydrase inhibitors and mineralocorticoid antagonists) was performed. Descriptive statistics were used to report the occurrence of safety events, such as electrolyte disturbances, hypotension and acute kidney injury.

Research results

From 6510 citations, nine studies totalling 440 patients were included. When compared to loop diuretics alone, the addition of a second diuretic is associated with an improved negative fluid balance at 24 h mean differences (MD) of -1.06 L [95% confidence interval (CI): -1.46; -0.65], mainly driven by the combination of a thiazide plus furosemide [MD: -1.25 L (95%CI: -1.68; -0.82)]. The heterogeneity on the report of clinical and safety endpoints was high, but electrolytes anomalies were frequent and confirms the need for additional monitoring when prescribing such combinations.

Research conclusions

Larger trials are required to confirm the efficacy and safety of diuretic combinations in this population. However, based on limited evidence the combination of thiazide plus loop-diuretics is associated with an increase in urine output and negative fluid balance.

Research perspectives

The study has highlighted the paucity of data on the optimal strategy to optimise fluid balance in patients with respiratory failure and relative diuretics resistance.

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FOOTNOTES

Author contributions: Côté JM, Goulamhoussen N, McMahon BA and Murray PT designed the research study and methodology; Côté JM and Goulamhoussen N performed the research and analyzed the data; Côté JM wrote the draft manuscript; all authors reviewed and approved the final manuscript.

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Country/Territory of origin: Canada

ORCID number: Jean Maxime Côté 0000-0002-3487-2670; Nadir Goulamhoussen 0000-0002-7589-389X; Blaithin A McMahon 0000-0001-8585-2787; Patrick T Murray 0000-0002-0165-6672.

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REFERENCES

1 **Bouchard J**, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL; Program to Improve Care in Acute Renal Disease (PICARD) Study Group. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* 2009; **76**: 422-427 [PMID: 19436332 DOI: 10.1038/ki.2009.159]
2 **Grams ME**, Estrella MM, Coresh J, Brower RG, Liu KD; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. Fluid balance, diuretic use, and mortality in acute kidney injury. *Clin J Am Soc Nephrol* 2011; **6**: 966-973 [PMID: 21393482 DOI: 10.2215/CJN.08781010]
3 **Claure-Del Granado R**, Mehta RL. Fluid overload in the ICU: evaluation and management. *BMC Nephrol* 2016; **17**: 109 [PMID: 27484681 DOI: 10.1186/s12882-016-0323-6]
4 **Liu KD**, Thompson BT, Ancukiewicz M, Steingrub JS, Douglas IS, Matthay MA, Wright P, Peterson MW, Rock P, Hyzy RC, Anzueto A, Truwit JD; National Institutes of Health National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit Care Med* 2011; **39**: 2665-2671 [PMID: 21785346 DOI: 10.1097/CCM.0b013e318228234b]
5 **Sakr Y**, Vincent JL, Reinhart K, Groeneveld J, Michalopoulos A, Sprung CL, Artigas A, Ranieri VM; Sepsis Occurence in Acutely Ill Patients Investigators. High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. *Chest* 2005; **128**: 3098-3108 [PMID: 16304249 DOI: 10.1378/chest.128.5.3098]
6 **Schuller D**, Mitchell JP, Calandrino FS, Schuster DP. Fluid balance during pulmonary edema. Is fluid gain a marker or a cause of poor outcome? *Chest* 1991; **100**: 1068-1075 [PMID: 1914560 DOI: 10.1378/chest.100.4.1068]
7 **National Heart**, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. , Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; **354**: 2564-2575 [PMID: 16714767 DOI: 10.1056/NEJMoa062200]
8 **McCoy IE**, Chertow GM, Chang TI. Patterns of diuretic use in the intensive care unit. *PLoS One* 2019; **14**: e0217911 [PMID: 31150512 DOI: 10.1371/journal.pone.0217911]
9 **Neuberg GW**, Miller AB, O'Connor CM, Belkin RN, Carson PE, Cropp AB, Frid DJ, Nye RG, Pressler ML, Wertheimer JH, Packer M; PRAISE Investigators. Prospective Randomized Amlodipine Survival Evaluation. Diuretic resistance predicts mortality in patients with advanced heart failure. *Am Heart J* 2002; **144**: 31-38 [PMID: 12094185 DOI: 10.1067/mhj.2002.123144]
10 **Rosenberg J**, Gustafsson F, Galatius S, Hildebrandt PR. Combination therapy with metolazone and loop diuretics in outpatients with refractory heart failure: an observational study and review of the literature. *Cardiovasc Drugs Ther* 2005; **19**: 301-306 [PMID: 16189620 DOI: 10.1007/s10557-005-3350-2]
11 **Brisco-Bacik MA**, Ter Maaten JM, Houser SR, Vedage NA, Rao V, Ahmad T, Wilson FP, Testani JM. Outcomes Associated With a Strategy of Adjuvant Metolazone or High-Dose Loop Diuretics in Acute Decompensated Heart Failure: A Propensity Analysis. *J Am Heart Assoc* 2018; **7**: e009149 [PMID: 30371181 DOI: 10.1161/JAHA.118.009149]
12 **Cox ZL**, Hung R, Lenihan DJ, Testani JM. Diuretic Strategies for Loop Diuretic Resistance in Acute Heart Failure: The 3T Trial. *JACC Heart Fail* 2020; **8**: 157-168 [PMID: 31838029 DOI: 10.1016/j.jchf.2019.09.012]
13 **Felker GM**, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic Therapy for Patients With Heart Failure: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2020; **75**: 1178-1195 [PMID: 32164892 DOI: 10.1016/j.jacc.2019.12.059]
14 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017; **136**: e137-e161 [PMID: 28455343 DOI: 10.1161/CIR.0000000000000509]

15 **Ponikowski P**, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; **18**: 891-975 [PMID: 27207191 DOI: 10.1002/ejhf.592]

16 **Côté JM**, Bouchard J, Murray PT, Beaubien-Souligny W. Diuretic strategies in patients with resistance to loop-diuretics in the intensive care unit: A retrospective study from the MIMIC-III database. *J Crit Care* 2021; **65**: 282-291 [PMID: 34298494 DOI: 10.1016/j.jcrc.2021.06.009]

17 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009; **62**: e1-34 [PMID: 19631507 DOI: 10.1016/j.jclinepi.2009.06.006]

18 **Sterne JAC**, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898 [PMID: 31462531 DOI: 10.1136/bmj.l4898]

19 **Sterne JA**, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355**: i4919 [PMID: 27733354 DOI: 10.1136/bmj.i4919]

20 **Wan X**, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; **14**: 135 [PMID: 25524443 DOI: 10.1186/1471-2288-14-135]

21 **Apte Y**, Bellomo R, Warrillow S, Goldsmith D, Gillies M, McGain F. Pilot randomised double-blind controlled trial of high-dose spironolactone in critically ill patients receiving a frusemide infusion. *Crit Care Resusc* 2008; **10**: 306-311 [PMID: 19049481]

22 **Bihari S**, Holt AW, Prakash S, Bersten AD. Addition of indapamide to frusemide increases natriuresis and creatinine clearance, but not diuresis, in fluid overloaded ICU patients. *J Crit Care* 2016; **33**: 200-206 [PMID: 26948252 DOI: 10.1016/j.jcrc.2016.01.017]

23 **Michaud CJ**, Mintus KC. Intravenous Chlorothiazide Versus Enteral Metolazone to Augment Loop Diuretic Therapy in the Intensive Care Unit. *Ann Pharmacother* 2017; **51**: 286-292 [PMID: 28228057 DOI: 10.1177/1060028016683971]

24 **Heming N**, Faisy C, Urien S. Population pharmacodynamic model of bicarbonate response to acetazolamide in mechanically ventilated chronic obstructive pulmonary disease patients. *Crit Care* 2011; **15**: R213 [PMID: 21917139 DOI: 10.1186/cc10448]

25 **Imiela T**, Budaj A. Acetazolamide as Add-on Diuretic Therapy in Exacerbations of Chronic Heart Failure: a Pilot Study. *Clin Drug Investig* 2017; **37**: 1175-1181 [PMID: 28965280 DOI: 10.1007/s40261-017-0577-1]

26 **Vánky F**, Broquist M, Svedjeholm R. Addition of a thiazide: an effective remedy for furosemide resistance after cardiac operations. *Ann Thorac Surg* 1997; **63**: 993-997 [PMID: 9124977 DOI: 10.1016/s0003-4975(96)01217-9]

27 **Bohn BC**, Hadgu RM, Pope HE, Shuster JE. Oral Metolazone Versus Intravenous Chlorothiazide as an Adjunct to Loop Diuretics for Diuresis in Acute Decompensated Heart Failure With Reduced Ejection Fraction. *Hosp Pharm* 2019; **54**: 351-357 [PMID: 31762481 DOI: 10.1177/0018578718795855]

28 **Ng TM**, Konopka E, Hyderi AF, Hshieh S, Tsuji Y, Kim BJ, Han SY, Phan DH, Jeng AI, Lou M, Elkayam U. Comparison of bumetanide- and metolazone-based diuretic regimens to furosemide in acute heart failure. *J Cardiovasc Pharmacol Ther* 2013; **18**: 345-353 [PMID: 23538300 DOI: 10.1177/1074248413482755]

29 **Shulenberger CE**, Jiang A, Devabhakthuni S, Ivaturi V, Liu T, Reed BN. Efficacy and Safety of Intravenous Chlorothiazide *vs* Oral Metolazone in Patients with Acute Decompensated Heart Failure and Loop Diuretic Resistance. *Pharmacotherapy* 2016; **36**: 852-860 [PMID: 27393709 DOI: 10.1002/phar.1798]

30 **Bihari S**, Peake SL, Prakash S, Saxena M, Campbell V, Bersten A. Sodium balance, not fluid balance, is associated with respiratory dysfunction in mechanically ventilated patients: a prospective, multicentre study. *Crit Care Resusc* 2015; **17**: 23-28 [PMID: 25702758]

31 **Bihari S**, Baldwin CE, Bersten AD. Fluid balance does not predict estimated sodium balance in critically ill mechanically ventilated patients. *Crit Care Resusc* 2013; **15**: 89-96 [PMID: 23931039]

32 **Hodson DZ**, Griffin M, Mahoney D, Raghavendra P, Ahmad T, Turner J, Wilson FP, Tang WHW, Rao VS, Collins SP, Mullens W, Testani JM. Natriuretic Response Is Highly Variable and Associated With 6-Month Survival: Insights From the ROSE-AHF Trial. *JACC Heart Fail* 2019; **7**: 383-391 [PMID: 31047017 DOI: 10.1016/j.jchf.2019.01.007]

33 **Mullens W**, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WHW, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion - a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019; **21**: 137-155 [PMID: 30600580 DOI: 10.1002/ejhf.1369]

34 **STARRT-AKI Investigators**; Canadian Critical Care Trials Group; Australian and New Zealand Intensive Care Society Clinical Trials Group; United Kingdom Critical Care Research Group; Canadian Nephrology Trials Network; Irish Critical Care Trials Group, Bagshaw SM, Wald R, Adhikari NKJ, Bellomo R, da Costa BR, Dreyfuss D, Du B, Gallagher MP, Gaudry S, Hoste EA, Lamontagne F, Joannidis M, Landoni G, Liu KD, McAuley DF, McGuinness SP, Neyra JA, Nichol AD, Ostermann M, Palevsky PM, Pettilä V, Quenot JP, Qiu H, Rochwerg B, Schneider AG, Smith OM, Thomé F, Thorpe KE, Vaara S, Weir M, Wang AY, Young P, Zarbock A. Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury. *N Engl J Med* 2020; **383**: 240-251 [PMID: 32668114 DOI: 10.1056/NEJMoa2000741]

35 **McMahon BA**, Chawla LS. The furosemide stress test: current use and future potential. *Ren Fail* 2021; **43**: 830-839 [PMID: 33971784 DOI: 10.1080/0886022X.2021.1906701]

36 **Hoorn EJ**, Ellison DH. Diuretic Resistance. *Am J Kidney Dis* 2017; **69**: 136-142 [PMID: 27814935 DOI: 10.1053/j.ajkd.2016.08.027]

37 **Loon NR**, Wilcox CS, Unwin RJ. Mechanism of impaired natriuretic response to furosemide during prolonged therapy. *Kidney Int* 1989; **36**: 682-689 [PMID: 2811065 DOI: 10.1038/ki.1989.246]

38 **Gulsvik R**, Skjørten I, Undhjem K, Holø L, Frostad A, Saure EW, Lejlic V, Humerfelt S, Hansen G, Bruun Wyller T. Acetazolamide improves oxygenation in patients with respiratory failure and metabolic alkalosis. *Clin Respir J* 2013; **7**: 390-396 [PMID: 23578004 DOI: 10.1111/crj.12025]

39 **Faisy C**, Mokline A, Sanchez O, Tadié JM, Fagon JY. Effectiveness of acetazolamide for reversal of metabolic alkalosis in weaning COPD patients from mechanical ventilation. *Intensive Care Med* 2010; **36**: 859-863 [PMID: 20217045 DOI: 10.1007/s00134-010-1795-7]

40 **Berthelsen P**, Gøthgen I, Husum B, Jacobsen E. Oxygen uptake and carbon dioxide elimination after acetazolamide in the critically ill. *Intensive Care Med* 1985; **11**: 26-29 [PMID: 3918091 DOI: 10.1007/BF00256061]

41 **European Association for the Study of the Liver**. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010; **53**: 397-417 [PMID: 20633946 DOI: 10.1016/j.jhep.2010.05.004]

42 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **62**: e147-e239 [PMID: 23747642 DOI: 10.1016/j.jacc.2013.05.019]

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CASE REPORT

Ball-shaped right atrial mass in renal cell carcinoma: A case report

Sohil Pothiawala, Savan deSilva, Kunzang Norbu

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Sohil Pothiawala, Department of Emergency Medicine, Woodlands Health, Singapore 768024, Singapore

Savan deSilva, Kunzang Norbu, Department of Emergency Medicine, Sengkang General Hospital, Singapore 544886, Singapore

Corresponding author: Sohil Pothiawala, MBBS, MD, Doctor, Department of Emergency Medicine, Woodlands Health, Yishun Central 2, Tower E, Level 5, Yishun Community Hospital, Singapore 768024, Singapore. drsohilpothiawala@yahoo.com

Abstract

BACKGROUND

Renal cell carcinoma (RCC) is an aggressive tumor, with an incidental discovery in most patients. Classic presentation is rare, and it has a high frequency of local and distant metastasis at the time of detection.

CASE SUMMARY

We present a rare case of a 58-year-old man with a ball-shaped thrombus in the right atrium at the time of first incidental identification of RCC in the emergency department. Cardiac metastasis, especially thrombus in the right atrium, is rare. It could either be a bland thrombus or a tumor thrombus, and physicians should consider this potentially fatal complication of RCC early at the time of initial presentation.

CONCLUSION

Ball-shaped lesions in the right atrium are rare, and bland thrombus should be differentiated from tumor thrombus secondary to intracardiac metastasis.

Key Words: Renal cell carcinoma; Metastasis; Tumor thrombus; Bland thrombus; Right atrium; Case report

Core Tip: The classic presentation of renal cell carcinoma is rare, and patients can present with atypical symptoms and local or distant metastasis at the time of initial detection. Cardiac metastasis, especially thrombus in the right atrium, is rare and emergency physicians should consider it early at the time of presentation. Detection of a ball-shaped lesion in the right atrium is rare, and the patient should undergo appropriate evaluation with the aim to differentiate bland thrombus from a tumor thrombus secondary to intracardiac metastasis, as it aids in therapeutic management and prognosis.

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INTRODUCTION

Renal cell carcinoma (RCC) is an aggressive tumor constituting about 3% of all adult malignancies, with a peak incidence in the sixth and seventh decades of life. The classic triad of flank pain, abdominal mass and hematuria is seen in 10% of the cases. Most cases have an incidental discovery[1,2] with local or distant metastases in 25% of the cases at the time of detection. About 10% of these patients have tumor extension into the renal vein and inferior vena cava[3], while only 1% of the total cases have the tumor extending into the right atrium[4]. We present a rare case of a 58-year-old man with a right atrial ball thrombus secondary to metastasis at the time of first incidental identification of RCC in the emergency department (ED).

CASE PRESENTATION

Chief complaints

A 58-year-old man presented to the ED with complaints of breathlessness and reduced effort tolerance for 1 wk.

History of present illness

A 58-year-old man presented to the ED with complaints of breathlessness and reduced effort tolerance for 1 wk. He denied chest pain, orthopnea or paroxysmal nocturnal dyspnea. He also noted a 10 kg weight loss over the last 2 mo. He went to a family physician where he was found to have hematuria and proteinuria on urine examination, and hence referred to the ED. He denied hematuria, lower urinary tract symptoms or fever.

History of past illness

He had no past medical history and was not on any long-term medication.

Physical examination

On presentation, his vital signs were stable but he appeared pale and had bilateral pitting lower limb edema up to the knees. Abdominal examination revealed a left sided large, palpable abdominal mass, but there was no rectal bleeding or melena. Examination of respiratory, cardiac and neurological systems was normal.

Laboratory examinations

His electrocardiogram showed normal sinus rhythm with T-wave inversions and ST-segment flattening in all leads, along with deep T inversions in leads V2-V4. Bedside ultrasound showed a large heterogeneous mass arising from the left kidney suspicious of RCC. Bedside echocardiogram showed a ball-like structure in the right atrium (Figure 1), oscillating between the right atrium and right ventricle intermittently during cardiac cycles, suspicious for a tumor thrombus. There was no pericardial effusion but the right ventricle appeared larger than the left ventricle, suggestive of signs of right heart strain. Blood investigations showed hemoglobin 7.3 g/dL, elevated serum creatinine 155 mol/L (1.75 mg/dL) and N-terminal pro-B type natriuretic peptide 7325 pg/mL. The remaining blood tests, including liver panel, troponin-T, prothrombin time/activated partial thromboplastin time and severe acute respiratory syndrome coronavirus 2 polymerase chain reaction, were normal.

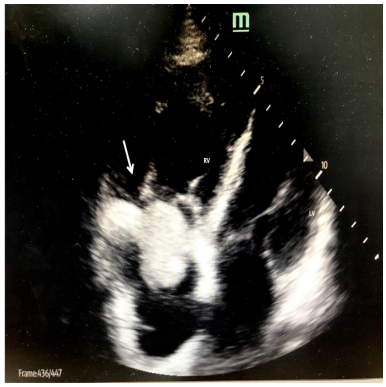

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Figure 1 Bedside ultrasound showing ball-shaped thrombus in the right atrium (arrow).

Imaging examinations

Chest X-ray revealed mild pulmonary venous congestion. Computed tomography (CT) of the abdomen and pelvis (Figure 2) revealed a 13.9 cm × 15.8 cm × 16 cm irregular, heterogeneous left renal mass, suspicious of RCC, with extension of tumor into left renal vein and inferior vena cava (IVC) and metastasis to the liver. CT pulmonary-angiogram showed extensive right pulmonary embolism (Figure 3) with evidence of right heart strain and pulmonary arterial hypertension, as well as pulmonary metastasis (Figure 4). A thrombus was noted in the enlarged right ventricle and right atrial appendage.

MULTIDISCIPLINARY EXPERT CONSULTATION

The patient was commenced on subcutaneous enoxaparin 80 mg and admitted to a high dependency unit. Histopathology after imaging-guided biopsy of the left renal tumor revealed clear cell RCC. After discussion at the multidisciplinary tumor board meeting, he was not scheduled for cytoreductive nephrectomy and thrombectomy in view of metastatic burden.

FINAL DIAGNOSIS

He was diagnosed to have left RCC with ball-shaped thrombus in the right atrium, with associated right pulmonary embolism as well as pulmonary metastasis.

TREATMENT

He was treated with enoxaparin 80 mg twice daily and tyrosine kinase inhibitor (TKI) pazopanib 800 mg once daily.

OUTCOME AND FOLLOW-UP

He was discharged and scheduled for outpatient follow-up with a hematologist and oncologist (Figure 5).

DISCUSSION

RCC can present as a solitary metastatic lesion or as a widespread systemic disease, but cardiac metastasis from RCC is extremely rare. The incidence of a thrombus in the right atrium is 0.75%, which is significantly lower than that that of a thrombus in the left atrium[5]. Thrombus in the right atrium is usually located at the atrial appendage or atrial wall. A ball thrombus in the right atrium is even rarer [5].

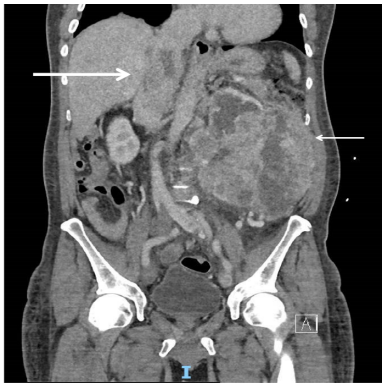

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Figure 2 Computerized tomography scan of abdomen and pelvis showing left renal cell carcinoma (thin arrow) invading in to the hepatic portion of inferior vena cava (thick arrow).

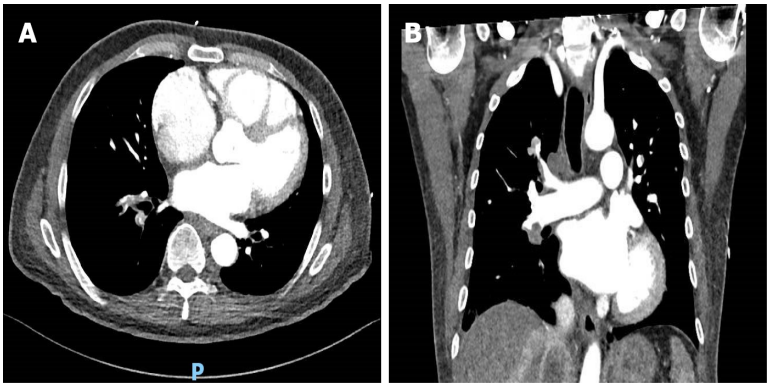

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Figure 3 Large filling-defects in the right segmental and subsegmental branches and right lobar and interlobar arteries suggestive of right-sided pulmonary embolism. A: Right segmental and subsegmental branches; B: Right lobar and interlobar arteries suggestive of right-sided pulmonary embolism.

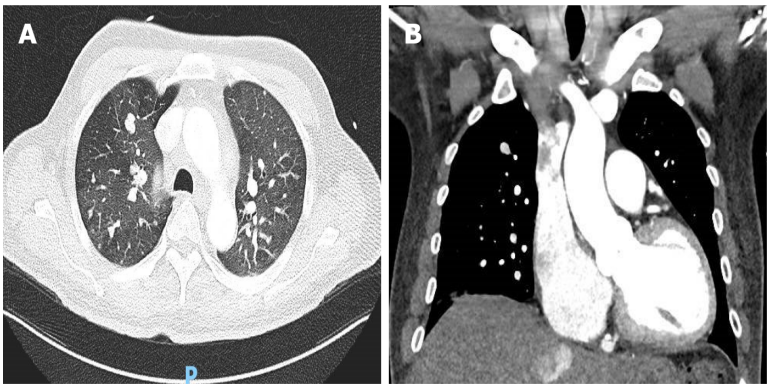

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Figure 4 Multiple pulmonary nodules of varying sizes in the lungs suggestive of pulmonary metastasis. A: Multiple bilateral pulmonary nodules; B: Prominent right sided pulmonary metastasis.

The ball-shaped lesion in our patient's right atrium could either have been a bland thrombus or a tumor thrombus that spread along the IVC. In patients with malignancy, bland thrombus is usually a venous thrombus. Pathogenesis of ball thrombus is still unclear and it can be difficult to make a diagnosis. The challenge is to correctly differentiate bland thrombus from a tumor thrombus secondary to intracardiac metastasis, as it aids in appropriate therapeutic management as well as prognosis. On perfusion magnetic resonance imaging (MRI), heterogeneous enhancement of this ball-shaped lesion

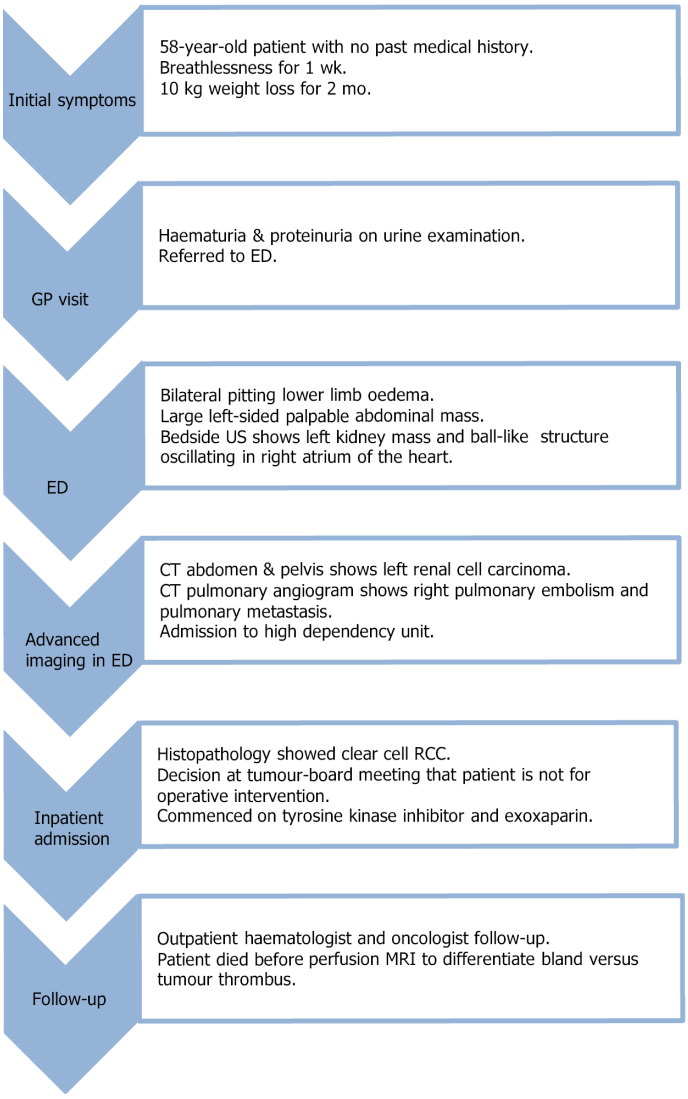

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Figure 5 Timeline following case report guidelines. ED: Emergency department; CT: Computerized tomography; RCC: Renal cell carcinoma; MRI: Magnetic resonance imaging.

and presence of blood products within it suggests a tumor thrombus secondary to RCC metastases. On the contrary, a bland thrombus shows unrestricted diffusion and complete nulling of the mass on MR perfusion imaging[6]. Bland thrombus may resolve after thrombolytic and anticoagulant therapy, unlike tumor thrombus. Our patient unfortunately died before further evaluation could be conducted.

Combining cytoreductive nephrectomy and/or metastasectomy with chemotherapy helps in palliation. The possible surgical option for metastatic RCC extending into the right atrium and causing pulmonary embolism, in this patient, was cardiopulmonary bypass with deep hypothermic circulatory arrest, which is a safe and efficient method for removal of the tumor and thrombus[7]. Manual repositioning of the tumor thrombus out of the right atrium into the IVC on the beating heart is also a safe approach with low risk of tumor thrombembolization[8]. In recent times, the progression free survival has improved due to advances in chemotherapy, immunotherapy and TKI[9]. The overall long-term prognosis of patients with metastatic RCC is poor, with a median survival of 6-12 mo.

CONCLUSION

The classic presentation of RCC is rare, and patients can present with atypical symptoms and local or distant metastasis at the time of initial detection. Cardiac metastasis, especially thrombus in the right atrium, is rare and emergency physicians should consider it early at the time of presentation. Detection of a ball-shaped lesion in the right atrium is rare, and the patient should undergo appropriate evaluation with an aim to differentiate bland thrombus from a tumor thrombus secondary to intracardiac metastasis, as it aids in therapeutic management and prognosis.

FOOTNOTES

Author contributions: Pothiawala S lead conceptualization and wrote the original draft, reviewed and edited the draft; de Silva S and Norbu K wrote the original draft, reviewed and edited the draft.

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ORCID number: Sohil Pothiawala 0000-0002-4789-4326; Savan deSilva 0000-0002-3518-1740; Kunzang Norbu 0000-0002-2475-9578.

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REFERENCES

1 **Sountoulides P**, Metaxa L, Cindolo L. Atypical presentations and rare metastatic sites of renal cell carcinoma: a review of case reports. *J Med Case Rep* 2011; **5**: 429 [PMID: 21888643 DOI: 10.1186/1752-1947-5-429]
2 **Doshi D**, Saab M, Singh N. Atypical presentation of renal cell carcinoma: a case report. *J Med Case Rep* 2007; **1**: 26 [PMID: 17553142 DOI: 10.1186/1752-1947-1-26]
3 **Hunsaker RP**, Stone JR. Images in clinical medicine. Renal-cell carcinoma extending into the vena cava and right side of the heart. *N Engl J Med* 2001; **345**: 1676 [PMID: 11759646 DOI: 10.1056/NEJMicm980108]
4 **Lu HT**, Chong JL, Othman N, Vendargon S, Omar S. An uncommon and insidious presentation of renal cell carcinoma with tumor extending into the inferior vena cava and right atrium: a case report. *J Med Case Rep* 2016; **10**: 109 [PMID: 27142514 DOI: 10.1186/s13256-016-0888-5]
5 **Zhang B**, Tian ZW, Zhang J, Yuan KM, Yu H. Calcified ball thrombus in the right atrium: A case report. *Iran J Radiol* 2020; **17**: e95169 [DOI: 10.5812/iranjradiol.95169]
6 **Elgendy A**. Intracardiac metastasis from known renal cell cancer. Available from: https://radiopaedia.org/cases/intracardiac-metastasis-from-known-renal-cell-cancer
7 **Posacioglu H**, Ayik MF, Zeytunlu M, Amanvermez D, Engin C, Apaydin AZ. Management of renal cell carcinoma with intracardiac extension. *J Card Surg* 2008; **23**: 754-758 [PMID: 19017006 DOI: 10.1111/j.1540-8191.2008.00664.x]
8 **Schneider M**, Hadaschik B, Hallscheidt P, Jakobi H, Fritz M, Motsch J, Pahernik S, Hohenfellner M. Manual repositioning of intra-atrial kidney cancer tumor thrombus: a technique reducing the need for cardiopulmonary bypass. *Urology* 2013; **81**: 909-914 [PMID: 23414691 DOI: 10.1016/j.urology.2012.10.064]
9 **Barata PC**, Rini BI. Treatment of renal cell carcinoma: Current status and future directions. *CA Cancer J Clin* 2017; **67**: 507-524 [PMID: 28961310 DOI: 10.3322/caac.21411]

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LETTER TO THE EDITOR

Ideal scoring system for acute pancreatitis: Quest for the Holy Grail

Deven Juneja

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Deven Juneja, Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket, New Delhi 110017, India

Corresponding author: Deven Juneja, DNB, FCCP, MBBS, Director, Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket, 1, Press Enclave Road, Saket, New Delhi 110017, India. devenjuneja@gmail.com

Abstract

Clinical scoring systems are required to predict complications, severity, need for intensive care unit admission, and mortality in patients with acute pancreatitis. Over the years, many scores have been developed, tested, and compared for their efficacy and accuracy. An ideal score should be rapid, reliable, and validated in different patient populations and geographical areas and should not lose relevance over time. A combination of scores or serial monitoring of a single score may increase their efficacy.

Key Words: Acute pancreatitis; Scoring systems; Sequential organ failure assessment score

Core Tip: A score which is rapid, reproducible, reliable, and validated across different patient populations is ideally required to predict outcomes in acute pancreatitis. As most of the scores have similar efficacy, the choice of score in a particular center may depend on ease of computation and application. Sequential organ failure assessment score has been validated in various patient populations, is easy to compute and apply, and has withstood the test of time. Hence, it may be a good option, to predict outcomes in patients with acute pancreatitis.

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TO THE EDITOR

We read with interest the retrospective analysis of 653 patients with acute pancreatitis

(AP) by Teng *et al*[1], in which they compared the efficacy of six clinical scores to predict outcomes. The authors concluded that even though both sequential organ failure assessment (SOFA) and 48-h Ranson's score could accurately predict the severity, need for intensive care unit (ICU) admission, and mortality in patients with AP, SOFA score had more favourable statistics.

Scoring systems are commonly employed to assess the need for ICU, to compare groups of patients, and to predict complications and outcomes. Many a time, these scoring systems are developed and tested in particular patient populations like patients with sepsis, AP, and chronic liver disease. Some scoring systems can be applied to general ICU patients. Many scores can be computed at the time of admission but certain others have to be calculated 24-48 h after admission. With improvements in healthcare standards and availability of modern healthcare equipment, patient outcomes may also improve over time, making older scores lose relevance. Hence, these scores need to be tested and compared for their efficacy and accuracy in different patient populations, different geographical areas and over different time periods.

Severe AP is associated with high morbidity and mortality and hence, early recognition of patients at risk of developing complications and poor outcomes is required to institute early aggressive care, and improve outcomes. Many scores have been specifically developed for predicting outcomes of patients with AP, and these include Ranson's, Glasgow, Pancreatitis outcome prediction (POP), bedside index of severity in acute pancreatitis, and Harmless AP scores. These have been compared with each other and also with other scores designed for general ICU patients like Acute Physiology and Chronic Health Assessment (APACHE), simplified acute physiology score (SAPS), and SOFA scores. However, no single score has been found to be an ideal score, able to accurately identify the patients at risk and predict outcomes in different clinical conditions. Hence, newer scores are being developed and tested against the existing scores[2]. But before these scores are routinely used, they need to be meticulously tested in varied patient populations, over a period of time.

In a similar prospective cohort study conducted in ICU patients, we compared ten scores: APACHE II and III, SAPS II, mortality probability models II, SOFA score, Logistic Organ Dysfunction System, Multiple Organ Dysfunction Score, Ranson, modified Glasgow, and POP[3]. As with the analysis of Teng *et al*[1], we also could not identify a single ideal score but SOFA score had the best statistics in predicting severity and mortality in patients with AP. SOFA score > 8 had a sensitivity and specificity of 87% and 90%, respectively, in predicting 30-d mortality[3]. Our study is more than a decade old but SOFA score still seems to be efficacious in predicting outcomes of patients with AP.

SOFA score was originally developed to describe organ failure in patients with sepsis and was termed "Sepsis-related Organ Failure Assessment"[4]. Subsequently its utility in other patient populations have been tested and validated. It has been compared to other severity of illness scores and has shown good accuracy to predict outcomes in varied patient populations. Expanding the role of SOFA score, different modifications have been suggested to improve its accuracy in specific patient populations like pSOFA for paediatric patients, CLIF-SOFA for chronic liver disease, SOFA-HM for haematological malignancies, and qSOFA and lactic acid SOFA for patients in emergency rooms[5]. Even the latest sepsis definitions recommend using SOFA score for diagnosis of sepsis and septic shock [6].

Now, in the age of artificial intelligence (AI), machine learning algorithms have been developed to predict severity, complications, recurrence, mortality, and even timing for surgery in patients with AP, with good accuracy[7]. However, the quality of the studies assessing the accuracy of AI remains low and there is a dearth of studies comparing AI with these commonly applied clinical scores. Hence, more studies need to be done before we routinely start using AI in our daily routine clinical practice. Till then, SOFA score, which is easy to compute and apply, seems to be the most reasonable choice.

FOOTNOTES

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ORCID number: Deven Juneja 0000-0002-8841-5678.

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REFERENCES

1 **Teng TZJ**, Tan JKT, Baey S, Gunasekaran SK, Junnarkar SP, Low JK, Huey CWT, Shelat VG. Sequential organ failure assessment score is superior to other prognostic indices in acute pancreatitis. *World J Crit Care Med* 2021; **10**: 355-368 [PMID: 34888161 DOI: 10.5492/wjccm.v10.i6.355]

2 **Rasch S**, Pichlmeier EM, Phillip V, Mayr U, Schmid RM, Huber W, Lahmer T. Prediction of Outcome in Acute Pancreatitis by the qSOFA and the New ERAP Score. *Dig Dis Sci* 2021 [PMID: 33770328 DOI: 10.1007/s10620-021-06945-z]

3 **Juneja D**, Gopal PB, Ravula M. Scoring systems in acute pancreatitis: which one to use in intensive care units? *J Crit Care* 2010; **25**: 358.e9-358.e15 [PMID: 20149591 DOI: 10.1016/j.jcrc.2009.12.010]

4 **Vincent JL**, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22**: 707-710 [PMID: 8844239 DOI: 10.1007/BF01709751]

5 **Kashyap R**, Sherani KM, Dutt T, Gnanapandithan K, Sagar M, Vallabhajosyula S, Vakil AP, Surani S. Current Utility of Sequential Organ Failure Assessment Score: A Literature Review and Future Directions. *Open Respir Med J* 2021; **15**: 1-6 [PMID: 34249175 DOI: 10.2174/1874306402115010001]

6 **Singer M**, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 801-810 [PMID: 26903338 DOI: 10.1001/jama.2016.0287]

7 **Zhou Y**, Ge YT, Shi XL, Wu KY, Chen WW, Ding YB, Xiao WM, Wang D, Lu GT, Hu LH. Machine learning predictive models for acute pancreatitis: A systematic review. *Int J Med Inform* 2022; **157**: 104641 [PMID: 34785488 DOI: 10.1016/j.ijmedinf.2021.104641]

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Peer Reviewer of *World Journal of Critical Care Medicine*, Zhong-Heng Zhang, Doctor, MD, MSc, Chief Physician, Doctor, Professor, Department of Emergency Medicine, Sir Run Run Shaw Hospital, Hangzhou 310016, Zhejiang Province, China. zh_zhang1984@zju.edu.cn

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REVIEW

Effects of nutrients on immunomodulation in patients with severe COVID-19: Current knowledge

Bruna Teixeira da Costa, Glauber Rocha Lima Araújo, Ronaldo Teixeira da Silva Júnior, Luana Kauany de Sá Santos, Vinícius Lima de Souza Gonçalves, Daniel Bastos Alves Lima, Beatriz Rocha Cuzzuol, Jonathan Santos Apolonio, Lorena Sousa de Carvalho, Hanna Santos Marques, Camilo Santana Silva, Isadora de Souza Barcelos, Márcio Vasconcelos Oliveira, Fabrício Freire de Melo

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Vinícius Lima de Souza Gonçalves, Hanna Santos Marques, Campus Vitória da Conquista, Universidade Estadual do Sudoeste da Bahia, Vitória da Conquista 45083-900, Bahia, Brazil

Corresponding author: Fabrício Freire de Melo, MSc, PhD, Postdoc, Professor, Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Rua Hormindo Barros, 58, Quadra 17, Lote 58, Vitória da Conquista 45029-094, Bahia, Brazil. freiremelo@yahoo.com.br

Abstract

Recent research has demonstrated that critically ill patients with coronavirus disease 2019 (COVID-19) show significant immune system dysregulation. Due to that, some nutrients that influence immunomodulation have been suggested as a form of treatment against the infection. This review collected the information on the impact of vitamins on the prognosis of COVID-19, with the intention of facilitating treatment and prevention of the disease risk status in patients. The collected information was obtained using the PubMed electronic database by searching for articles that relate COVID-19 and the mechanisms/effects of the nutrients: Proteins, glucose, lipids, vitamin B12, vitamin D, calcium, iron, copper, zinc, and magnesium, including prospective, retrospective, and support articles. The findings reveal an optimal response related mainly to omega-3, eicosapentaenoic acid, docosahexaenoic acid, calcium, and iron that might represent benefits in the treatment of critically ill patients. However, nutrient supplementation should be done with caution due to the limited availability of randomized controlled studies.

Key Words: COVID-19; Immunomodulation; Patient care; Vitamins; Nutrients; Micronutrients

Core Tip: Immunomodulation has a considerable influence on the response to severe acute respiratory syndrome coronavirus 2 infection. Therefore, the medical team must acknowledge different resources to improve the immune system. In the current situation of prevalence coronavirus disease 2019, knowing the potential risks and benefits of nutritional supplementation can improve patients' response and avoid severe conditions, facilitating the process of healing. For that purpose, this article brings nutrients which might help and those which worsen the immunological regulation and other body functions, pursuing to mitigate the response against the virus.

Citation: Costa BTD, Araújo GRL, da Silva Júnior RT, Santos LKS, Lima de Souza Gonçalves V, Lima DBA, Cuzzuol BR, Santos Apolonio J, de Carvalho LS, Marques HS, Silva CS, Barcelos IS, Oliveira MV, Freire de Melo F. Effects of nutrients on immunomodulation in patients with severe COVID-19: Current knowledge. *World J Crit Care Med* 2022; 11(4): 201-218
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INTRODUCTION

Among nutrition studies, some emphasize the importance of vitamins, trace elements, and long-chain fatty acids in supporting the immune system, keeping it able to protect against infections such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1-3]. Therefore, the analysis of micronutrient supplementation is necessary to consider the effective optimization of the immune function and its use as adjuvant treatment in some cases[1].

Inadequate and insufficient intake of iron, zinc, vitamins B, C, and E can affect the immunological function of the organism and allows the presence of high levels of free radicals favoring oxidative stress [4]. Importantly, according to ESPEN expert statements and practice guidelines for the nutritional management of individuals with SARS-CoV-2 infection[5], oral nutritional supplements (ONS) should be preferred over enteral (EN) and parenteral nutrition, whenever possible to meet the patient's needs. EN should be considered in polymorbid medical inpatients and elderly patients with a reasonable prognosis when ONS are not possible. ONS must provide at least 400 kcal/d, including 30 g or more of protein per day, for at least 1 mo[5].

On the other hand, a diet rich in vitamin C and zinc improves neutrophil phagocytosis, monocytic activity, and immune cell locomotion, and vitamin D is related to the mediation of interleukins (ILs) essential for immune defense, acting in the induction of antimicrobial peptides in macrophages[5]. The strong qualitative T-cell response is crucial against SARS-CoV-2, and lymphopenia is associated with elevated mortality[6,7]. Both CD4+ and CD8+ T-cell responses are present in infection, although the latter is inefficient[6]. Elevated IL-2 associated with decreased IFNγ levels have been observed in these cells, increasing the severity and chronic course of the disease[8].

Successful immune regulation of innate and adaptive immunity is a predictor for avoiding severe responses to SARS-CoV-2 infection[6]. Critically ill infected patients showed increased neutrophil counts, tissue damage, activation of the coagulation cascade, and decreased hemoglobin and lymphocyte values[6,9], which are associated with a drop in monocyte HLA-DR expression, and demonstrated acquired immunosuppression[6]; nutrition has a role in their management.

Some nutrients such as carbohydrates, proteins, omega 3, vitamin B12, vitamin D, iron, copper, calcium, zinc, and magnesium are the focus of this article for being directly linked to the host immune response in coronavirus disease 2019 (COVID-19) cases. Apart from these, conjugated linoleic acid and vitamins A and E regulate cytokine production as well as the proliferation and differentiation of specific leukocyte populations, in addition to acting on immunoglobulin production and lymphocyte differentiation[10-12]. In this review, we summarize the mechanisms of immunomodulation promoted by micro- and macro-nutrients in COVID-19.

METHODOLOGICAL REVIEW

This methodological review was conducted by two investigators, working independently with the guidance and support of a research advisor. Both prospective or retrospective trials and support articles were identified using The United States National Library of Medicine (PubMed). Between October 4, 2021 and February 15, 2022, we searched the relevant articles published in English using the following specific descriptors: COVID-19; SARS-CoV-2; immune system; immune response; vitamin B12; cobalamin; macronutrients; micronutrients; carbohydrate; protein; lipid; intensive care; vitamin D; iron; copper; zinc; magnesium and calcium; severe; nutrition; therapy; critically ill patients; coronavirus;

immunomodulation; pro-resolving mediators; and inflammation. The descriptors were used alone and/or in combination in the PubMed database. No restriction was made as to the date of publication of the articles, nor was a target age range defined. Articles not written in English and not addressing these topics in the title and/or abstract were excluded. Original articles describing prospective, retrospective, and cross-sectional studies were included, as well as secondary research, such as systematic and narrative reviews. Guidelines were also included. Commentaries, editor letters, book chapters, and manuals were not included. Finally, 3316 articles were identified, of which 122 were included in this minireview.

INFLUENCE OF MACRONUTRIENTS ON COVID-19 SEVERITY

Proteins and glucose

The dietary factor that leads to the weakening of immune functions is the failure of macro- and micronutrient intake. In addition, clinical studies have shown that malnutrition, weight imbalance, and fragility and dysbiosis of the gut microbiota are the main factors involved in the deterioration of immune functions in infected patients[13].

The use of immunonutrients aims to increase the production of less potent inflammatory mediators and reduce those highly inflammatory, besides minimizing the production of free radicals and modulating the generalized inflammatory response[14]. For diabetic patients, this formulation is suggested, as it is a supplement already used. Once a product is removed from the formula, fruit is added to reach the caloric goal and improve palatability. Protein is the most important macronutrient for maintaining immune function and preserving muscle mass[1].

Proteins are types of macromolecules made of amino acids (AA) that perform various important functions for the body, for example, acting as antibodies, enzymes, messengers, transporters, and structural components in the body[15,16]. Some studies indicate that protein supplementation stimulates the immune system, which specifically improves infectious disease surveillance[17].

Studies with hydrolyzed proteins have shown that they are able to reduce the inflammatory state and stimulate IgA function and production. Also, arginine and glutamine are both non-essential amino acids that enhance the action of the immune system. The former is associated with macrophages in the generation of nitric oxide, and the latter provides energy for immune cell utilization[18].

Proteins show antiviral activities against enveloped and non-enveloped viruses. They inhibit virus entry into the cell by adhering to cell receptors[19]. Viruses need some enzymes, including DNA or RNA polymerases, reverse transcriptase, and integrase for replication, and some evidence suggests that proteins can inhibit the activity of these enzymes and eventually prevent virus replication[20,21].

On the other hand, increased consumption of saturated fats, refined carbohydrates, and alcohol, and low levels of fiber, unsaturated fats, micronutrients, and antioxidants significantly impair adaptive immunity while increasing innate immunity, which leads to chronic inflammation and severe damage to the host defense against viral pathogens[1]. These dietary patterns might have a detrimental effect on immune responses and are involved in the development of several inflammatory diseases[22]. Excessive macronutrient intake contributes to the propensity to acquire pneumonia, which is the most common high-risk complication of COVID-19[23].

The high mortality from COVID-19 in obese people points to an important role in nutrition[24]. Food can influence cytokine gene expression levels and thus modulate inflammation and oxidative stress[25]. Cytokines such as tumor necrosis factor (TNF)-alpha and IL-6 when produced excessively have been related to dysregulation of the inflammatory response and stimulation of cytokine storms[26]. Furthermore, increased adipose tissue contributes to greater leptin production, which is related to macrophage activation and proliferation, while reduced adiponectin levels decrease the synthesis of anti-inflammatory compounds. In addition, there is an increase in the release of non-esterified fatty acids into the bloodstream, which also leads to the perpetuation of the chronic inflammatory process [27]. Health-related consequences in populations affected by economic outages, quarantines, and curfews due to SARS-CoV-2 infection include psychological distress[28-30], which is associated with an increase in carbohydrate and lipid intake[31] and a decrease in physical exercise[32], resulting in weight gain and increased rates of overweight and obesity. Adipose tissue, besides storing energy, is responsible for producing certain substrates that, in excess, can stimulate a state of constant oxidative stress and contribute to the severity of clinical manifestations during SARS-CoV-2 infection.

Some comorbidities have emerged as risk factors for the severe development of COVID-19, including type 2 diabetes, increased body weight, hypertension, and dyslipidemia. In this sense, increased glucose concentrations may be responsible for the reported poor outcome. A recent study reported that type 2 diabetes was associated with a higher mortality rate due to COVID-19, although the mortality rate was lower with better controlled blood glucose[33]. Furthermore, diabetes mellitus (DM) can impair the adaptive inflammatory response by delaying T-cell activation, as well as negatively impact neutrophil chemotaxis and contribute to cytokine storm, leading to dysregulation of the immune response, susceptibility to infection, and an increased chance of severe clinical manifestation during SARS-CoV-2 infection[34]. On the other hand, DM was related to the overexpression of angiotensin-converting

enzymes in some organs such as the heart, lungs, liver, and pancreas, increasing the severity of the cases and leading to organ failure during infection[35]. Consequently, diabetes was significantly associated with the development of acute respiratory distress syndrome, with a hazard ratio of 2.3[36].

The few articles available that mention supportive care in COVID-19 recommend that nutritional status should be assessed in all infected patients on hospital admission[1,5,37] and that patients at nutritional risk should receive nutritional support as early as possible, especially through increasing the protein intake by ONS[5,37].

Moreover, studies, including SPEN statements[5], highlight that even patients with COVID-19 who are not at risk of malnutrition should maintain an adequate intake, especially regarding adequate amounts of protein (1.5g/d) and calories (25-30 kcal/d), as well as oral supplementation with whey protein (20g/d) and intravenous solutions of multivitamins, multiminerals, and trace elements (goal: satisfaction of recommended dietary intake on admission). The choice of whey proteins is based on their anabolic and antioxidant properties combined with high digestibility[38,39]. Its potential clinical benefits have been highlighted in cancer cachexia[40] and were recently demonstrated in a randomized controlled trial of malnourished patients with advanced cancer[41]. Whey proteins also have immunomodulatory properties[42] and potential antiviral activity[43]. Furthermore, whey protein supplementation has been associated with improved immune recovery in HIV patients during the first 3 mo of antiretroviral treatment[44].

Figure 1 provides a summary of mechanisms of action of proteins and other nutrients in targeting SARS-CoV-2 infection.

Lipid profile and omega-3

Decreased or absent lipids in nutritional support can cause essential fatty acid deficiency, especially in preterm infants, and result in insufficient synthesis of omega-3 fatty acids, docosahexaenoic acid (DHA), and omega-6 fatty acid arachidonic acid (ARA)[45]. Lipids also play an important role in the delivery of fat-soluble vitamins such as vitamins A, D, E, and K[46]. Physiological processes such as metabolism, immune response, oxidative stress, blood clotting, organ function, and wound healing have a direct association with fatty acid availability[46,47]. However, this process needs to be well balanced, given that excess lipids can cause undesirable consequences. The excess of linoleic acid (LA) may be associated with exacerbation of inflammation, manifested mainly by increased levels of CRP, although other biomarkers such as IL-6, adiponectin, and adhesion molecules have not shown significant changes related to higher levels of LA consumption[48]. For this, studies have evaluated the impact of the use of substances able to reduce the expression of cytokines that contribute to the gravity of the infection and the enhancement of the inflammatory state in SARS-CoV-2 infection[49].

Omega-6 polyunsaturated fatty acids (PUFAs) can metabolize LA and further desaturate and form ARA, the main PUFA in cell membranes involved in inflammation in humans[50]. Omega-6 PUFAs may influence inflammation due to the fatty acid composition of the cell membrane phospholipids, which modulates cellular responses and cellular function[50,51]. Membrane phospholipids produce second messengers, such as diacylglycerols, endocannabinoids, and platelet activating factor, that act on biological activity[52]. These second messengers also modulate gene expression and physiological and metabolic responses, affecting the immune and inflammatory response, disease severity, and clinical outcome[53]. Moreover, ARA composes peripheral blood mononuclear cells, such as lymphocytes, neutrophils, and monocytes[52]. ARA also acts as a substrate for the enzymes cyclooxygenase, lipoxygenase, and cytochrome P450, constituting eicosanoid mediators such as leukotriene B4 (LTB4) and prostaglandin E2, which induces pro-inflammatory cytokines and IL-6[53,54]. LTB4 promotes leukocyte chemotaxis, adhesion, and degranulation, increases vascular permeability, and produces inflammatory mediators, leading to a pro-inflammatory effect[51,54]. ARA metabolism also results in the production of lipoxin A4 (LXA4) and lipoxin B4 (LXB4)[55,56]. LXA4 is an anti-inflammatory and pro-resolution mediator that acts by inhibiting inflammatory cell recruitment, cytokine production, and NADPH oxidase function, and restoring normal physiological function in damaged tissue, which leads to decreased inflammation[57,58]. Studies suggest that LXA4 can suppress leukocyte-mediated injury and promote chemotaxis of monocytes, and phagocytosis of apoptotic neutrophils[59]. LXB4 is generated by mucosal tissues in the upper respiratory tract and lower airways, and acts by regulating neutrophil activation[60].

In contrast, PUFAs, such as omega-3, are lipid compounds with potent anti-inflammatory activity, responsible for the homeostasis of the organism and regulation of various biological functions. It can be produced in small quantities by the human organism; however, it is possible to obtain this nutrient through foods such as fish, nuts, and soy oil, and the intake of 250 to 2000 mg/d is recommended for adults and 200 to 250 mg/d for children[61]. Lipid and carbohydrate requirements are adapted using the energy ratio of fat and carbohydrates between 30:70 in patients without respiratory impairment and 50:50 in patients on mechanical ventilation[5]. Linolenic acid, eicosapentaenoic acid (EPA), and DHA correspond to the representatives of this group of essential fatty acids, and their metabolism results in substances such as protectins and resolvins that regulate platelet coagulation and the inflammatory process[62].

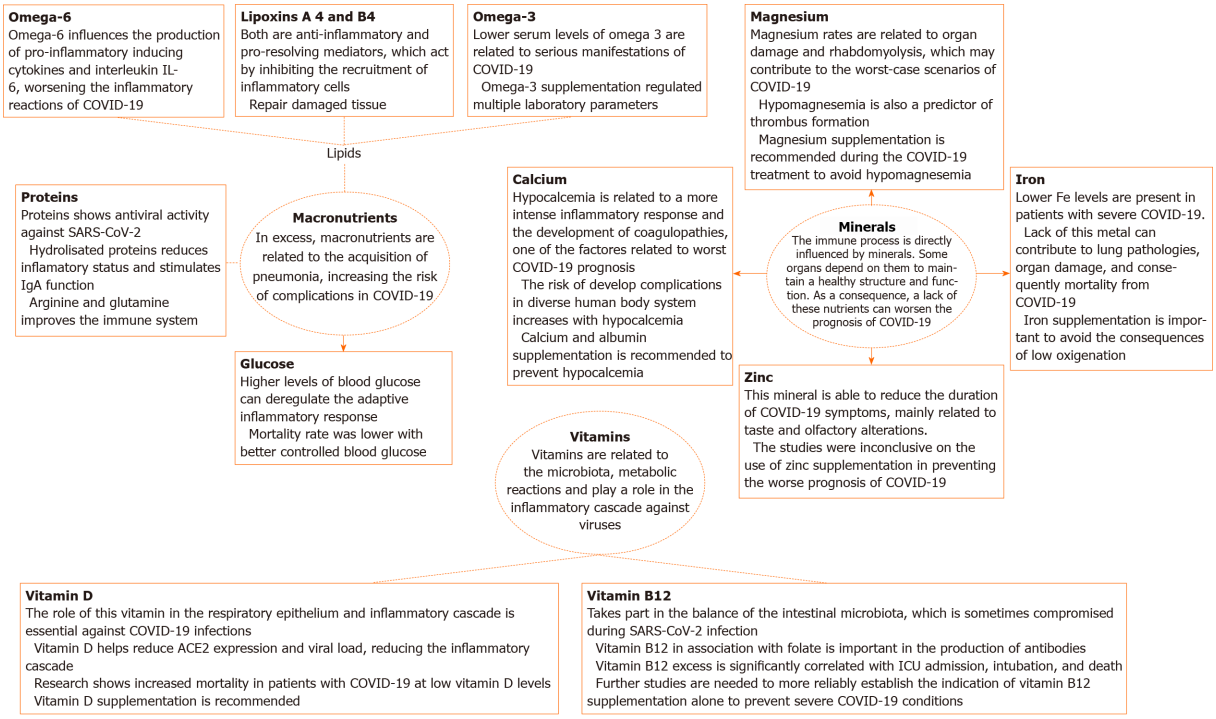

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Figure 1 Summary of nutrients' mechanisms of action in targeting coronavirus disease infection.

EPA and DHA sources have shown potential anti-inflammatory activity, in addition to promoting immune function and improving liver metabolism[63]. Studies have shown that resolvins are able to reduce the inflammatory response by decreasing neutrophil invasion and reducing the synthesis of pro-inflammatory cytokines *via* inhibition of nuclear factor kappa B (NF-κB), in addition to promoting monocyte recruitment and increasing phagocytosis of apoptotic neutrophils and macrophage clearance [46,64]. Resolvins are specialized pro-resolving lipid mediators (SPMs), endogenous lipid mediators that include protectin, maresins, and lipoxins (LXs). SPMs are involved in the pathophysiology of respiratory diseases, such as COVID-19, and play a role in signaling events during the inflammatory process[65-67]. Studies have also shown their potential in tissue repair, regression of inflammation by increasing anti-inflammatory mediators such as IL-10, and regulating the adaptive immune response[67, 68]. Several studies using animal disease models have shown the potential of SPMs to decrease lung inflammation and tissue damage, and to be able to disrupt the cytokine storm. Furthermore, SPMs do not act as an immunosuppressive agent[65,66,69,70]. Thus, regarding COVID-19, SPMs may in the near future be used to treat inflammation with the active precursors 18-HEPE, 17-HDHA, and 14-HDHA[66, 69,71]. Furthermore, omega-3 PUFAs have been linked to reduced expression of cyclooxygenase 2 and decreased levels of pro-inflammatory cytokines such as IL-6, IL-8, and IL-1 beta and free radicals[72].

PUFAs are responsible for altering the composition of cell membranes, modulating cell signaling, and influencing immune responses[73,74]. They are present in the cell membrane, taking part in the formation of the phospholipids and assisting in the maintenance of both cell structure and functionality. Thereby, alterations in the composition and homeostasis of these compounds are able to influence cellular responses[75]. Thus, studies have shown that, due to their lipophilic capacity, PUFAs can bind to the cell membrane, altering the permeability of this structure, interfering with the virus' binding to the angiotensin-converting enzyme 2 (ACE2) receptor, and also interrupting its action as a receptor[76]. In addition, omega-3 PUFAs could contribute to alterations in the structure of the lipid rafts that carry the ACE2, being able to modify the ability of the virus to bind to its receptor and reduce replication rates [77]. This lipid could directly regulate and alter the amount, size, and the proteins expressed in the rafts by modulating the binding between the virus and its receptors[78]. Finally, the viral spike protein, which is responsible for interacting with ACE 2 and allowing entry into the cell, could be inactivated by PUFAs when they bind, thus blocking infection[79].

During cases of infection, adequate management of the patient's nutritional status must be performed, since systemic inflammation is capable of increasing the demand for nutrients and propitiating a picture of malnutrition that may worsen the clinical picture generated by COVID-19[80]. As a result of the aforementioned, lipid nutritional support emerges as a possible element in medical nutrition therapy for critically ill patients with COVID-19[73,74]. Studies have shown that there is a possible association between omega-3 levels in the body and reduced fatal outcomes caused by COVID-19[79]. A cross-sectional study observed a possible relationship between low omega-3 PUFA levels in

the body and clinical manifestations of COVID-19. However, there is a need for further research that evaluates a larger population and standardizes the levels of this lipid as a possible predictor of risk in the bloodstream during infection[80]. Of note, patients admitted to intensive care units (ICUs) with respiratory distress syndrome had improved oxygenation and reduced length of stay after administration of this lipid[81,82]. Similarly, a randomized clinical trial with 101 patients reported that during omega-3 PUFA supplementation, there was regulation of some laboratory parameters such as normalization of arterial pH, bicarbonate level, and base excesses, as well as improvement in renal function[83].

INFLUENCE OF MICRONUTRIENTS ON COVID-19 SEVERITY

Vitamin B12

Vitamin B12, also known as cobalamin, is a micronutrient obtained mainly through the consumption of animal source foods and absorbed in the gastrointestinal tract through metabolic pathways involving substances such as hydrochloric acid, pepsin, and intrinsic factor. It is a micronutrient with well-established functions in red blood cell synthesis, cell growth, the nervous system, and DNA synthesis. The active forms of cobalamin are hydroxocobalamin and methylcobalamin, which are closely linked to folic acid and adenosylcobalamin[84,85]. In addition, studies suggest that vitamin B12 plays an important role in the immune system by assisting in balancing the gut microbiota, which is sometimes compromised during SARS-CoV-2 infection[4]. Yet, cobalamin modulates the immune system by exerting influence on T lymphocytes, participating in their differentiation and proliferation and, thus, being important in maintaining the ratio between cytotoxic and helper T cells, in addition to influencing the activity of natural killer cells. By playing a role in cell division, vitamin B12 can have a direct influence on the rapid proliferation of B lymphocytes. Furthermore, vitamin B12 in association with folate is important in the production of antibodies[86]. Considering that vitamin B12 participates in metabolic reactions involving carbon-1, with interactions occurring with folate metabolism, in individuals with low levels of vitamin B12, 5-methyl-tetrahydrofolate (THF), produced by an irreversible reaction, results in an inactive form of folate. 5-methyl-THF can result in secondary folate deficiency, impairing purine and thymidine synthesis. This results in changes in DNA and RNA synthesis and, consequently, in the secretion of immunoglobulins[87].

Thus, insufficiency or deficiency of micronutrients such as vitamin B12 may affect the host immune response against viral infections and inflammatory activity, as well as influence the clinical outcomes of patients with COVID-19 in both immunological, microbiological, and hematological forms[88,89]. A single-center study[90] noted that patients who died from SARS-CoV-2 infection had less vitamin B12 when compared to those hospitalized in ICUs, but no significant differences were observed between them. Another study that evaluated serum micronutrient levels and disease severity in COVID-19 patients reported that some of these substances, such as cobalamin, were reduced in these individuals [91]. On the other hand, some patients may also have increased B12 levels, especially those who were intubated and deceased, with excess vitamin B12 being significantly correlated with a worse prognosis, such as ICU admission, intubation, and death[92]. Similarly, this increase was also observed in patients with poor clinical outcomes in another study[92,93]. The liver is responsible for cobalamin storage and damage to this organ in hospitalized patients may be the cause for the high levels of this vitamin found in certain individuals. However, despite the high plasma concentration of cobalamin, these patients may have neurological and hematological conditions, which are common in patients with low concentrations of the micronutrient. There are two possible pathways for the occurrence of this paradoxical effect: Tissue lysis reduces the intracellular concentration of cobalamin and increases the plasma concentration; thus, the high concentration ends up interfering in the transport of the substance and, consequently, in the intracellular uptake[94].

Given this scenario, studies linked to vitamin B12 supplementation are scarce and show inconclusive results. In this sense, some authors advocate supplementation associated with other micronutrients, making it difficult to analyze their results in isolation. In non-COVID-19 situations, vitamin B12 deficiency is classically treated with parenteral injection therapy of 1000 μg for 1 to 2 wk, followed by monthly administration. Intramuscular injections are uncomfortable and painful in children, as well as expensive. Thus, oral preparations are being investigated[95]. In a study, children over 6 years were treated with a daily pill containing thiamine 250 mg, pyridoxine 250 mg, and cyanocobalamin 1000 μg for 3 mo, and those under 6 years old with an ampoule of 1000 μg of vitamin B12. This treatment was effective for vitamin B12 nutritional deficiency[96]. Another study that evaluated 47 individuals aged 1 mo to 17 years with serum vitamin B12 levels less than 200 pg/mL treated for 120 d with 1000 μg of this oral vitamin showed improvement in cobalamin levels. However, despite the high dose, reduced results were achieved in older children, indicating the need for dose adjustment according to weight[97]. Yet, patients ≥ 6 or ≥ 18 years who reported gastrointestinal abnormalities or restricted diet received 1000 μg of oral vitamin B12 or 1000 μg intramuscularly in nine injections for 3 mo and both administrations restored the cobalamin levels of all patients[98].

A study performed joint supplementation of magnesium and vitamins B12 and D3 in individuals aged over 50 years with COVID-19 and observed less need for supplemental oxygen and ICU admission [99]. Therefore, these findings suggest the potential role of vitamin B12 in limiting disorders and complications related to SARS-CoV-2 infection, and further studies are needed to more reliably establish whether vitamin B12 alone is able to show statistically significant results in these patients[100,101].

Vitamin D

Although the level of vitamin D has been widely studied in patients infected with SARS-CoV-2, other previous studies have evaluated the role of this vitamin in patients with acute respiratory infections (ARI), mainly in the upper airways[102,103].

The role of vitamin D in bone health, through calcium and phosphorus maintenance, is well established[104], but its role in respiratory infections appears to be related to the production of antimicrobial peptides in the respiratory epithelium and in the response of the inflammatory cascade against the virus[105-107]. In addition, vitamin D helps maintain cell junctions and gaps, decreasing the cytokine storm caused by the infection[108], and inhibiting type 1 T helper cell response and T cell induction[109]. Furthermore, vitamin D deficiency causes deprivation in macrophage production and performance, interfering with the innate immune response and favoring the establishment of infection [110]. Thus, although the levels of this macronutrient do not represent a great impact in reducing the risk of contracting the disease, studies show that there is a great impact on the modulation of the innate and adaptive immune response and, consequently, on the severity of the disease[111].

The pathophysiology of SARS-CoV-2 infection is favored by high expression of ACE2, a receptor through which the virus enters cells of the lung epithelium and other organs, triggering activation of the pro-inflammatory cascade and viral replication[112]. Increased storage of the inactive form of vitamin D (calciferol) increases the risk of virus infection because it stimulates ACE2 production[110]. However, as this is one of the factors for the manifestation of more critical forms of COVID-19, at the experimental level, vitamin D helps to reduce ACE2 expression and viral load by reducing the inflammatory cascade [111,112].

Despite such evidence, studies involving this vitamin and the prognosis of patients with COVID-19 are inconclusive, and most of them are observational or retrospective studies with a small, usually single-center sample. Therefore, the medical recommendation for vitamin D supplementation is based on the observation of increased mortality from COVID-19 in those with low vitamin D levels, even with adjustment for patient age[111]. Studies indicate that vitamin supplementation is relevant only in patients who are vitamin-deficient or at risk for immune system deficiency, such as patients with chronic diseases[113]. In a study that looked at different doses of vitamin D in patients with COVID-19, the recommendation for people at risk of influenza and/or COVID-19 was supplementation of 10000 IU/d of vitamin D3 for a few weeks and then 5000 IU/d, without describing the variation for the patients' age group. The ultimate goal would be to rapidly increase 25(OH)D concentrations and reach concentrations between 40-60 ng/mL (100-150 nmol/L). For the treatment of patients with COVID-19, higher doses, depending on the reference protocol, may be useful[108].

There are studies that have shown lower vitamin D levels in critically ill patients with COVID-19[78, 114] and in addition, a 15% reduction in the number of severe COVID-19 cases with normal vitamin D status was found in a population[115]. However, after removing confounding variables, the results are still inconclusive. Other studies that have found increased mortality from infection in countries with vitamin D deficient populations, such as Italy, point to overlapping risk factors related to old age, obesity, and diabetes[104].

Meanwhile, high level supplementation may be recommended for patients at risk. A randomized controlled trial indicates that high doses of vitamin D supplementation are a successful treatment for high-risk elderly patients, and that this type of treatment would not pose risks to patients. Still, it is clear that further prospective, randomized, controlled, large-scale studies on vitamin D supplementation related to mortality and severity of COVID-19 are needed to conclude[113].

Calcium

Hypocalcemia is quite common in viral diseases, which overcomes the fact that studies report its presence in more than 60% of patients hospitalized for SARS-CoV-2 infection[116]. The calcium ion is involved in two important parts of the development of COVID-19. It is of paramount importance for the life cycle of the virus, but it is also related to the inflammatory response and its regulation[117].

Some hypotheses are raised to explain this condition. Among them, we can mention some degree of malnutrition that causes hypovitaminosis D and hypoalbuminemia in COVID-19, given that the calcium ion is primarily linked to albumin, the high degree of inflammation in the infected patient, as well as a consequence of this, alterations in the receptors and in the hormonal axis of calcium, which causes it to be mobilized from the bones. Furthermore, it is possible to mention the fact that patients with hypocalcemia have fewer lymphocytes and higher levels of D-dimer, justifying the more intense inflammatory response, as well as greater chances of developing coagulopathies. Regarding lymphopenia, it can be justified by mechanisms of bone marrow suppression that may have been caused by the virus and/or by direct destruction of these lymphocytes, due to all the toxic substances that are produced during the SARS-CoV-2 infection, mainly the cytokines[118]. D-dimer is related to the cytokine storm

Table 1 Role of micro- and macro-nutrients in the immune system

Micro-/macro-nutrient	Clinical outcomes	Affected cells and cytokines	Immunological outcomes	Ref.
Proteins	Whey protein has antiviral properties; supplementation facilitates the patients' recovery in viral infections	DNA or RNA polymerases, reverse transcriptase, integrase, *etc.*	Antiviral activities against enveloped and non-enveloped viruses; inhibit the entrance of the virus into the cell; inhibit the virus enzymes activity; prevent virus replication	Siqueiros *et al*[19], 2014; Nejati *et al*[20], 2021; Ng *et al*[21], 2001; Ng *et al*[43], 2015; Olsen *et al*[44], 2014
Lipids/omega-3	Improvement of oxygenation and reduced length of stay after omega-3 administration; normalization of blood pH, reducing base excess; improves renal function	IL-6, IL-8, IL-1beta, free radicals	Altering the composition of cell membranes and modulating cell signaling; decrease the pro-inflammatory response by reducing the levels of proinflammatory cytokines IL-6, IL-8, IL-1beta, and free radicals	Hawryłkowicz *et al*[62], 2021; Romano *et al*[73], 2020; McClave *et al*[74], 2016; Vivar-Sierra *et al* [79], 2021; Asher *et al*[81], 2021; Doaei *et al*[83], 2021
Vitamin B12	Combined supplementation resulted in lower necessity of oxygen and ICU admission; increased levels of B12 are correlated to higher risk of ICU admission, intubation, and death	T and B lymphocytes, NK cells; antibodies	Cell differentiation and proliferation; maintenance of the ratio between T helper and cytotoxic cells; influence on NK cell activity; in association with folate and production of antibodies	Gombart *et al*[2], 2020; Chaari *et al*[86], 2021; Ersöz *et al*[92], 2021; Tan *et al*[99], 2020
Vitamin D	Increased mortality in patients with low vitamin D levels; high dose supplementation is related to successful treatment of high risk elderly patients	Antimicrobial peptides; T cells, macrophages	Production of antimicrobial peptides in the respiratory epithelium; helps maintain cell junctions and gaps; decreasing the cytokine storm; inhibiting type 1 T helper cell response and T cell induction; its deficiency causes deprivation in the production and performance of macrophages	Dankers *et al*[105], 2016; Gombart *et al*[106], 2005; Greiller and Martineau [107], 2015; Grant *et al* [108], 2020; Cantorna *et al* [109], 2015; Ilie *et al*[110], 2020; Rhodes *et al*[111], 2021; Annweiler *et al*[113], 2020
Calcium	Calcium associated with albumin is capable of decreasing metabolic dysfunctions and organ damage during the COVID-19 infection	Cytotoxic T lymphocytes; IL-1, IL-6	Hypocalcemia as a result of hypoalbuminemia; increased pro-inflammatory cytokines IL-1 and IL-6 interfere with calcium metabolism; lower levels of lymphocyte counts related to higher levels of D-dimer in critically ill patients	Alemzadeh *et al*[116], 2021; Alsagaff *et al*[126], 2021; Mendez *et al*[127], 2021
Iron	Maintaining adequate levels of iron is related to lower levels of respiratory failure	T cells, B cells, macrophages	Chelation/deficiency: Enhances IFN-γ signaling and STAT1 activation which may stabilize the TH1 phenotype in early TH polarization; activates the transcription factors hypoxia-inducible factor (HIF)-1α and nuclear factor (NF)-IL6 in macrophages. Supplementation/overload: in TH1 cells, stimulates the production of GM-CS, and reduces expression of the T-box transcription factor T-BET; inhibits ICAM1 and MHC-II expression in macrophages, impairing TH1 immunity; in B cells, counteracts the Ig class switch towards IgG; may promote TH2 polarization	Tojo *et al*[131], 2021; Sonnweber *et al*[133], 2020; Akhtar *et al*[138], 2021; Nairz and Weiss [164], 2020
Copper	There is still no evidence to support the supplementation of copper in COVID-19 patients	Macrophages, neutrophils, NK cells; IL-2	Participates in the functioning of innate immune cells (*e.g.*, it accumulates in macrophage phagolysosomes to combat pathogens); has intrinsic antimicrobial properties; acts in defense against reactive oxygen species; has a role in IL-2 production and response; maintains intracellular antioxidant balance; has a role in differentiation and proliferation of T cells	Zhou *et al*[130], 2020; Zeng *et al*[140], 2021; Rani *et al*[143], 2021
Zinc	Currently there is no evidence of interferences of this element regarding severe cases	Th1 cells; IL-2, IL-1β, IL-6, IL-8	Acute zinc deficiency promotes the adhesion of monocytes to endothelial cells *in vitro* and reduces the production of TH1 profile cytokines including IFN-γ, IL-2, and TNF-α; it has the potential to inhibit the inflammatory process by stimulating the release of IL-1-β depending on the transcription factor NF-κB; low levels of zinc are associated with an increase in IL-6, IL-8, and TNF-α which contributes to inflammation	Gammoh *et al*[144], 2017; Elalfy *et al*[153], 2021; Thomas *et al*[154], 2021; Abdelmaksoud *et al*[155], 2021; Mariani *et al* [165], 2006
Magnesium	This nutrient is capable of reducing the necessity of oxygen and intensive care unit admission	Natural killer cells, CD8 killer T cells, monocytes, macrophages, leukocytes	Reduction of immune cell toxicity; cytokine storm favoring; decreased anti-oxidant and anti-inflammatory action, energy depletion, muscle catabolism, and prothrombotic conditions	Tang *et al*[159], 2020; DiNicolantonio and O'keefe[160], 2021; van Niekerk *et al*[161], 2018; Zhu *et al*[162], 2021; Iotti *et al*[163], 2020; Nairz and Weiss[164], 2020

that is caused in more severe cases of infection. This is because this intense immune reaction activates the coagulation cascade, favoring the occurrence of thrombotic events. As D-dimer is involved in blood clotting events, its detection in examinations is favorable to attest to a possible state of thrombosis in the patient, which increases the chances of pulmonary complications and thromboembolism[118]. However, the increase in unsaturated lipids can also contribute to hypocalcemia, due to the link established with the ion[116,119,120].

Given this and studies that have evaluated calcemia in hospitalized patients, it was possible to establish an important risk factor between low calcium levels and increased risk of developing serious diseases, complications in the cardiovascular system, nervous system, and muscle, and mortality[116, 120,121].

In regard to the viral life cycle, much has been studied about the role of calcium. SARS-CoV-2 needs to release its genetic material inside the host cell and to do so, it needs to penetrate the host cell membrane and fuse its membrane with the viral membrane[122].

The key and initial point lies with the spike (S) protein, which is composed of two subunits, S1 and S2, containing a region called fusion peptide (FP) that is crucial in the cell invasion process, along with the help of calcium, which binds to two negatively charged FP residues located in the S2 subunit to allow viral fusion. In this sense, calcium acts directly on the proteins responsible for mediating fusion, playing an activating role and increasing the binding of the S protein to host cells, favoring viral penetration[122-124]. Importantly, PF interacts with the host cell membrane, changing its structure and allowing membrane fusion[124].

Despite the use of calcium in the process of virus entry into the host cell, what may account for the hypocalcemia is the lack of the viral envelope protein E that alters intracellular calcium metabolism, favoring the increase of IL-1B. This cytokine is responsible for regulating the expression of a calcium-sensitive receptor. With the action of the cytokine, the set point of calcium suppression by PTH is reduced. Thus, even though calcium is in lesser amounts, it is able to decrease PTH secretion and corroborate an even greater decrease in serum calcium[117].

Early use of calcium and albumin supplementation is reported to lead to reduced toxicity from free fatty acids, which are then carried by albumin, and to decrease the degree of mitochondrial metabolic dysfunction and organ damage[125,126]. Also, a meta-analysis of 199298 patients demonstrated that the use of calcium channel blockers (CCBs) in hypertensive patients reduced mortality rates in hypertensive patients with COVID-19. This may be explained by the action of CCBs blocking the virus replication cycle through ion-dependent pathways, although the use of CCBs has not been shown to interfere with the severity of disease presentation[126]. Some studies, which used a smaller sample of patients, are against the use of CCBs in the treatment of patients with COVID-19 and found an increased risk of respiratory failure, intubation, and death in patients taking this medication[127].

Further studies are needed, but vitamin D supplementation is hypothesized to prevent hypocalcemia, severe disease, and other complications[120,128].

Iron

Hemoglobin, iron, and saturated transferrin levels were lower in patients with COVID-19 compared to individuals without the disease, while ferritin levels were higher in SARS-CoV-2 infected patients[129]. Correspondingly, Zhou *et al*[130] reported that serum hepcidin and ferritin levels contribute independently to the severity of COVID-19. Another study points out that the relationship between iron levels and disease severity is U-shaped, considering that patients with mild respiratory failure had significantly lower serum iron levels compared to individuals without respiratory failure, while no significant differences in iron levels were observed between the group without respiratory failure and those with severe respiratory failure[131]. Hippchen *et al*[132] identified an iron concentration < 6 μmol/L as the best cut-off point to predict hospitalization of patients with COVID-19. Furthermore, it has been reported that alterations in iron metabolism can persist for a few months after the initiation of COVID-19 and are associated with pulmonary pathologies[133]. Low serum iron has also been associated with mortality from COVID-19[134].

In order to decrease viral replication, the innate immune system stimulates the reduction of iron bioavailability, so hepcidin levels tend to increase and block ferroportin activity, which results in cellular accumulation of the metal, mainly inside macrophages, hepatocytes, and enterocytes[135]. The increase in intracellular iron stimulates the expression of inflammatory cytokines, such as IL-6, IL-8, and TNF-α, which worsen the accumulation of iron in cells, generating a cycle that contributes to the "cytokine storm" in patients with COVID-19[133].

In general, adequate levels of iron are obtained through diet. However, supplementation of this mineral can be used in patients with challenges in meeting dietary requirements[136]. The usual dosage for therapeutic iron supplementation is 325 mg (equivalent to 65 mg of elemental iron), three times a day[137]. Iron supplementation therapy has been considered a more promising approach than transfusion to promote erythropoiesis in pregnant women and cancer patients with anemia and COVID-19[138].

Copper

Skalny *et al*[139] reported that the copper/zinc ratio, besides being increased in patients with COVID-19 compared to healthy individuals, presents a gradual increase according to the severity of the cases and was considered as a predictor of lower O_2 saturation. A cohort of 306 patients with COVID-19 in Wuhan also identified an increase in copper levels in severe cases compared to non-severe patients[140]. On the other hand, Hackler *et al*[141] reported that patients surviving COVID-19 had higher mean serum copper levels compared to non-surviving patients. Arrieta *et al*[142], in turn, carried out a study with patients with severe COVID-19 on parental nutrition and supplemented with zinc, revealing that serum copper concentrations were lower in critically ill participants. However, it should be considered that copper and zinc are competitively absorbed in the small intestine, which may justify the reduction of copper in these patients[143].

SARS-CoV-2 infection involves the induction of an inducible transcription factor (NF-κB), responsible for triggering an inflammatory process. Copper, in turn, acts by preventing inflammatory events, through several mechanisms, such as the generation of reactive oxygen species, which act in the destruction of viral morphology and genomes[143]. Despite a favorable theoretical approach to complementary therapy with copper supplementation, there is still no evidence to support its use in cases of patients with COVID-19[142].

Zinc

Zinc plays an important role in modulating the immune system, including roles in antiviral and antibacterial responses[144]. Zinc is essential for the recruitment of neutrophil granulocytes and chemotaxis process and positively influences NK cells, phagocytosis, oxidative burst generation, and CD4+ and CD8+ T cells[145]. It has already been clarified that acute zinc deficiency has the potential to interfere with both innate immunity and T cell-mediated immunity by impairing those defenses, whereas chronic deficiency of that metal is associated with an increase in pro-inflammatory cytokines[146]. In addition, previous studies have already suggested the use of zinc in order to reduce the duration of acute respiratory tract viral infections and to prevent symptoms[147].

A possible therapeutic role of the mineral in respiratory tract infections was the demonstration that zinc gluconate supplementation inhibits the NF-κB-dependent transcription of inflammatory genes, contributing to a reduction of neutrophilic infiltration and TNF-α release in the airways[148]. In that context, it was hypothesized that zinc could inhibit SARS-CoV-2 viral replication since it inhibits RNA-dependent RNA polymerase (RdRp) activity *in vitro* by inhibiting SARS-CoV-2 RdRp elongation and binding of model[149,150]. Furthermore, it is possible that zinc has the potential to restrict SARS-CoV-2 access in host cells by inhibiting ACE2 activity[151,152]. Therefore, during the COVID-19 pandemic, the possibility of reducing infection severity through zinc administration led scientists to research this metal. Among these studies, a non-randomized clinical trial including 113 patients compared the use of combined nitazoxanide, ribavirin, ivermectin, and zinc along with routine supportive treatment and the results showed that the combination effectively cleared SARS-CoV-2 from the nasopharynx faster than supportive therapy; however, patients experienced some side effects such as gastrointestinal disturbances[153]. In contrast, a randomized clinical trial including 214 patients looked at whether high-dose zinc, high-dose ascorbic acid, or both substances were able to reduce the severity or duration of symptoms caused by SARS-CoV-2 infection compared to standard care. The results of the study concluded that there was no significant difference between groups and that treatment with zinc, ascorbic acid, or both did not interfere with the symptoms of the disease[154]. In addition, a prospective clinical trial with 134 patients analyzed the serum zinc levels of patients positive for COVID-19 at various severity levels, with and without olfactory alterations, in order to assess the therapeutic potential of zinc supplementation. The authors concluded that there were no significant differences between the subgroups regarding severity, recovery time, or the presence or absence of olfactory and taste dysfunction. However, olfactory and taste functions recovered more quickly in patients who underwent zinc therapy ($P < 0.001$)[155]. Zinc supplementation offers numerous benefits for different comorbidities; however, its dosage may vary with the patient's age and the specific pathophysiology of the disease[156]. The recommended pharmacological dosage of zinc for adults is greater than 40 mg/d and generally ranges from 220 mg/d to 660 mg/d of zinc chelate, which is equivalent to 50 mg to 150 mg of elemental zinc[157]. Finally, the clinical data obtained to date are not sufficient to support zinc supplementation in outpatients and hospitalized patients with COVID-19[154,158].

Magnesium

Magnesium ion is one of the most relevant elements in the homeostasis of several body systems such as the respiratory, neurological, cardiovascular, and digestive systems. It has anti-oxidant and anti-inflammatory functions and integrates several biochemical and metabolic reactions, such as transport of other ions and activation of vitamin D, and it is involved in energy metabolism[159]; considering the role of magnesium in body homeostasis, this element is involved in the context of the organic disorders caused by COVID-19.

When there is a cytokine storm and an increase in the generalized inflammatory status, there is a functional imbalance between the cells of the immune system and higher energy depletion[160,161].

A good part of the population already has low serum magnesium levels and, with the infection, food intake is reduced in more critical cases. As a result, the organism uses other means of obtaining this ion which, along with phosphate, is removed from its natural reservoirs, mainly the musculoskeletal system, catabolizing it[159,161].

Besides the muscle tissue involved, which may evolve to kidney injury and rhabdomyolysis, low magnesium levels may favor the development of respiratory complications by integrating membrane proteins involved in energy metabolism. Nevertheless, hypomagnesemia can contribute to endothelial dysfunction, favoring, as the calcium mentioned above, prothrombotic situations[159,160].

To date, little is known about magnesium homeostasis during COVID-19, as it is not a commonly assessed parameter, even though many patients have low Mg levels during the disease. However, in addition to all the inflammatory and metabolic issues involved with hypomagnesemia, SARS-CoV-2 has magnesium in its structure. In this sense, the virus would need the ion to remain structurally and functionally active[162-165].

The use of magnesium, vitamin D, and vitamin B12 supplementation was positive in the development of COVID-19 in patients over 50 years old, reducing the number of patients who required supplemental oxygen or ICU admission. The doses used were 1000 IU of cholecalciferol, 150 mg of magnesium oxide, and 500 μg of methylcobalamin, for a period less than or equal to 14 d[99].

To summarize the influence of nutrients on the immune system, Table 1 brings the macro- and micronutrients above cited, relating it to the modulation in cells and cytokines and to clinical outcomes.

CONCLUSION

The relationship between COVID-19 and nutrients is controversial. The expression of pro-inflammatory compounds and the individual's dysregulated immune response are the main causes of modulation in critically ill patients infected with the virus. In view of this, correct modulation is essential to avoid mild or exaggerated responses. The macro- and micro-nutrients mentioned are directly involved in the basic structure of the immune system, participating in the development of cells, cytokines, and antibodies. Some nutrients such as vitamin B12 and copper are contradictory as to the beneficial effects of their bioavailability, and their overstocking is predictive of a worse prognosis. The lack of studies with this isolated micronutrient requires further analysis to guide medical professionals in prescribing vitamin B12 supplementation. Furthermore, supplementation of vitamin D, calcium, iron, and magnesium is beneficial, especially in patients with comorbidities, whose risk of developing the most severe forms of the disease is greater. The action of these elements, promoting anti-inflammatory and antioxidant functions, is essential to control the aggressive COVID-19 response. Vitamin D, calcium, and magnesium supplementation is important for patients at risk and with deficiency. In addition, early use of calcium associated with albumin has shown benefits in preventing toxicity and organ damages that can lead to severe cases of COVID-19. Those findings are alien to what is found in ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection, which points that vitamins D and B, zinc, iron, and omega-3 PUFAs should be considered in COVID-19 patients for nutritional support. It is also suggested that the daily supply of these micronutrients should be ensured in malnourished patients with SARS-CoV-2 infection.

Regarding the high consumption of proteins, carbohydrates, and lipids, there is influence of the excess of these in the diets of prehospital patients, considering the connection with the acquisition of pneumonia. Moreover, these nutrients influence the function of adipose tissue by stimulating the inflammatory response, worsening the patient's condition. Meanwhile, omega 3 PUFA supplementation is recommended to improve oxygenation, contributing additionally to the regulation of laboratory tests and renal function. However, further randomized controlled trials are needed to complement and confirm the information on the influence of vitamins and other nutrients on immunomodulation of the COVID-19 response, in order to determine which nutrients are beneficially administered and select the correct doses for the treatment of critically ill patients.

FOOTNOTES

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Country/Territory of origin: Brazil

ORCID number: Bruna Teixeira da Costa 0000-0003-4227-0060; Glauber Rocha Lima Araújo 0000-0002-5195-3632; Ronaldo Teixeira da Silva Júnior 0000-0003-0835-4092; Luana Kauany de Sá Santos 0000-0003-4618-1129; Vinícius Lima de Souza Gonçalves 0000-0002-6445-9318; Daniel Bastos Alves Lima 0000-0002-8273-7502; Beatriz Rocha Cuzzuol 0000-0002-1456-2982; Jonathan Santos Apolonio 0000-0002-9463-8114; Lorena Sousa de Carvalho 0000-0003-1876-9240; Hanna Santos Marques 0000-0001-5741-1570; Camilo Santana Silva 0000-0002-2919-0149; Isadora de Souza Barcelos 0000-0002-6868-2840; Márcio Vasconcelos Oliveira 0000-0002-8959-0478; Fabrício Freire de Melo 0000-0002-5680-2753.

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REFERENCES

1 **Zhang L**, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. *J Med Virol* 2020; **92**: 479-490 [PMID: 32052466 DOI: 10.1002/jmv.25707]
2 **Gombart AF**, Pierre A, Maggini S. A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection. *Nutrients* 2020; **12** [PMID: 31963293 DOI: 10.3390/nu12010236]
3 **Calder PC**, Carr AC, Gombart AF, Eggersdorfer M. Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections. *Nutrients* 2020; **12** [PMID: 32340216 DOI: 10.3390/nu12041181]
4 **Kumar P**, Kumar M, Bedi O, Gupta M, Kumar S, Jaiswal G, Rahi V, Yedke NG, Bijalwan A, Sharma S, Jamwal S. Role of vitamins and minerals as immunity boosters in COVID-19. *Inflammopharmacology* 2021; **29**: 1001-1016 [PMID: 34110533 DOI: 10.1007/s10787-021-00826-7]
5 **Singer P**, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, Hiesmayr M, Mayer K, Montejo JC, Pichard C, Preiser JC, van Zanten ARH, Oczkowski S, Szczeklik W, Bischoff SC. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr* 2019; **38**: 48-79 [PMID: 30348463 DOI: 10.1016/j.clnu.2018.08.037]
6 **Fantacone ML**, Lowry MB, Uesugi SL, Michels AJ, Choi J, Leonard SW, Gombart SK, Gombart JS, Bobe G, Gombart AF. The Effect of a Multivitamin and Mineral Supplement on Immune Function in Healthy Older Adults: A Double-Blind, Randomized, Controlled Trial. *Nutrients* 2020; **12** [PMID: 32823974 DOI: 10.3390/nu12082447]
7 **Payen D**, Cravat M, Maadadi H, Didelot C, Prosic L, Dupuis C, Losser MR, De Carvalho Bittencourt M. A Longitudinal Study of Immune Cells in Severe COVID-19 Patients. *Front Immunol* 2020; **11**: 580250 [PMID: 33178207 DOI: 10.3389/fimmu.2020.580250]
8 **Kared H**, Redd AD, Bloch EM, Bonny TS, Sumatoh H, Kairi F, Carbajo D, Abel B, Newell EW, Bettinotti MP, Benner SE, Patel EU, Littlefield K, Laeyendecker O, Shoham S, Sullivan D, Casadevall A, Pekosz A, Nardin A, Fehlings M, Tobian AA, Quinn TC. SARS-CoV-2-specific CD8+ T cell responses in convalescent COVID-19 individuals. *J Clin Invest* 2021; **131** [PMID: 33427749 DOI: 10.1172/JCI145476]
9 **Sattler A**, Angermair S, Stockmann H, Heim KM, Khadzhynov D, Treskatsch S, Halleck F, Kreis ME, Kotsch K. SARS-CoV-2-specific T cell responses and correlations with COVID-19 patient predisposition. *J Clin Invest* 2020; **130**: 6477-6489 [PMID: 32833687 DOI: 10.1172/JCI140965]
10 **Secchi M**, Bazzigaluppi E, Brigatti C, Marzinotto I, Tresoldi C, Rovere-Querini P, Poli A, Castagna A, Scarlatti G, Zangrillo A, Ciceri F, Piemonti L, Lampasona V. COVID-19 survival associates with the immunoglobulin response to the SARS-CoV-2 spike receptor binding domain. *J Clin Invest* 2020; **130**: 6366-6378 [PMID: 32991329 DOI: 10.1172/JCI142804]
11 **Bassaganya-Riera J**, Hontecillas R. CLA and n-3 PUFA differentially modulate clinical activity and colonic PPAR-responsive gene expression in a pig model of experimental IBD. *Clin Nutr* 2006; **25**: 454-465 [PMID: 16698153 DOI: 10.1016/j.clnu.2005.12.008]
12 **Bendich A**. Physiological role of antioxidants in the immune system. *J Dairy Sci* 1993; **76**: 2789-2794 [PMID: 8227682 DOI: 10.3168/jds.S0022-0302(93)77617-1]
13 **Rocha J**, Basra T, El Kurdi B, Venegas-Borsellino C. Effects of Potential Micro- and Macro-nutrients in Combatting COVID-19. *Curr Surg Rep* 2021; **9**: 24 [PMID: 34484977 DOI: 10.1007/s40137-021-00301-w]
14 **Fernandes AC**, Bezerra OMPA. Terapia nutricional na doença pulmonar obstrutivacrônica e suas complicações nutricionais. *J Bras Pneumol* 2006; **32**: 461-471 [DOI: 10.1590/S1806-37132006000500014]
15 **Mente A**, Chalcraft K, Ak H, Davis AD, Lonn E, Miller R, Potter MA, Yusuf S, Anand SS, McQueen MJ. The Relationship Between Trimethylamine-N-Oxide and Prevalent Cardiovascular Disease in a Multiethnic Population Living in Canada. *Can J Cardiol* 2015; **31**: 1189-1194 [PMID: 26239008 DOI: 10.1016/j.cjca.2015.06.016]
16 **Banerjee A**, Kulcsar K, Misra V, Frieman M, Mossman K. Bats and Coronaviruses. *Viruses* 2019; **11** [PMID: 30634396 DOI: 10.3390/v11010041]
17 **Martinon F**, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. *Mol Cell* 2002; **10**: 417-426 [PMID: 12191486 DOI: 10.1016/s1097-2765(02)00599-3]
18 **Childs CE**, Calder PC, Miles EA. Diet and Immune Function. *Nutrients* 2019; **11** [PMID: 31426423 DOI: 10.3390/nu11081933]
19 **Siqueiros-Cendón T**, Arévalo-Gallegos S, Iglesias-Figueroa BF, García-Montoya IA, Salazar-Martínez J, Rascón-Cruz

Q. Immunomodulatory effects of lactoferrin. *Acta Pharmacol Sin* 2014; **35**: 557-566 [PMID: 24786230 DOI: 10.1038/aps.2013.200]

20 **Nejati M**, Dehghan P, Hashempour-Baltork F, Alizadeh AM, Farshi P, Khosravi-Darani K. Potential Dietary Interventions for COVID-19 Infection Based on the Gut-Immune Axis: An Update Review on Bioactive Component of Macronutrients. *Int J Prev Med* 2021; **12**: 105 [PMID: 34729139 DOI: 10.4103/ijpvm.IJPVM_493_20]

21 **Ng TB**, Lam TL, Au TK, Ye XY, Wan CC. Inhibition of human immunodeficiency virus type 1 reverse transcriptase, protease and integrase by bovine milk proteins. *Life Sci* 2001; **69**: 2217-2223 [PMID: 11669464 DOI: 10.1016/s0024-3205(01)01311-x]

22 **Thorburn AN**, Macia L, Mackay CR. Diet, metabolites, and "western-lifestyle" inflammatory diseases. *Immunity* 2014; **40**: 833-842 [PMID: 24950203 DOI: 10.1016/j.immuni.2014.05.014]

23 **Chemudupati M**, Kenney AD, Smith AC, Fillinger RJ, Zhang L, Zani A, Liu SL, Anderson MZ, Sharma A, Yount JS. Butyrate Reprograms Expression of Specific Interferon-Stimulated Genes. *J Virol* 2020; **94** [PMID: 32461320 DOI: 10.1128/JVI.00326-20]

24 **Simonnet A**, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, Labreuche J, Mathieu D, Pattou F, Jourdain M; LICORN and the Lille COVID-19 and Obesity study group. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. *Obesity (Silver Spring)* 2020; **28**: 1195-1199 [PMID: 32271993 DOI: 10.1002/oby.22831]

25 **Di Renzo L**, Gualtieri P, Romano L, Marrone G, Noce A, Pujia A, Perrone MA, Aiello V, Colica C, De Lorenzo A. Role of Personalized Nutrition in Chronic-Degenerative Diseases. *Nutrients* 2019; **11** [PMID: 31344895 DOI: 10.3390/nu11081707]

26 **Yang Y**, Wang L, Liu J, Fu S, Zhou L, Wang Y. Obesity or increased body mass index and the risk of severe outcomes in patients with COVID-19: A protocol for systematic review and meta-analysis. *Medicine (Baltimore)* 2022; **101**: e28499 [PMID: 35029905 DOI: 10.1097/MD.0000000000028499]

27 **de Heredia FP**, Gómez-Martínez S, Marcos A. Obesity, inflammation and the immune system. *Proc Nutr Soc* 2012; **71**: 332-338 [PMID: 22429824 DOI: 10.1017/S0029665112000092]

28 **Wu T**, Jia X, Shi H, Niu J, Yin X, Xie J, Wang X. Prevalence of mental health problems during the COVID-19 pandemic: A systematic review and meta-analysis. *J Affect Disord* 2021; **281**: 91-98 [PMID: 33310451 DOI: 10.1016/j.jad.2020.11.117]

29 **Lei L**, Huang X, Zhang S, Yang J, Yang L, Xu M. Comparison of Prevalence and Associated Factors of Anxiety and Depression Among People Affected by *vs* People Unaffected by Quarantine During the COVID-19 Epidemic in Southwestern China. *Med Sci Monit* 2020; **26**: e924609 [PMID: 32335579 DOI: 10.12659/MSM.924609]

30 **Qiu J**, Shen B, Zhao M, Wang Z, Xie B, Xu Y. A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: implications and policy recommendations. *Gen Psychiatr* 2020; **33**: e100213 [PMID: 32215365 DOI: 10.1136/gpsych-2020-100213]

31 **Isasi CR**, Parrinello CM, Jung MM, Carnethon MR, Birnbaum-Weitzman O, Espinoza RA, Penedo FJ, Perreira KM, Schneiderman N, Sotres-Alvarez D, Van Horn L, Gallo LC. Psychosocial stress is associated with obesity and diet quality in Hispanic/Latino adults. *Ann Epidemiol* 2015; **25**: 84-89 [PMID: 25487969 DOI: 10.1016/j.annepidem.2014.11.002]

32 **Rodríguez MÁ**, Crespo I, Olmedillas H. Exercising in times of COVID-19: what do experts recommend doing within four walls? *Rev Esp Cardiol (Engl Ed)* 2020; **73**: 527-529 [DOI: 10.1016/j.rec.2020.04.001]

33 **Zhu L**, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, Lei F, Wang H, Xie J, Wang W, Li H, Zhang P, Song X, Chen X, Xiang M, Zhang C, Bai L, Xiang D, Chen MM, Liu Y, Yan Y, Liu M, Mao W, Zou J, Liu L, Chen G, Luo P, Xiao B, Zhang Z, Lu Z, Wang J, Lu H, Xia X, Wang D, Liao X, Peng G, Ye P, Yang J, Yuan Y, Huang X, Guo J, Zhang BH. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab* 2020; **31**: 1068-1077.e3 [PMID: 32369736 DOI: 10.1016/j.cmet.2020.04.021]

34 **Muniyappa R**, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. *Am J Physiol Endocrinol Metab* 2020; **318**: E736-E741 [PMID: 32228322 DOI: 10.1152/ajpendo.00124.2020]

35 **Katsiki N**, Gómez-Huelgas R, Mikhailidis DP, Pérez-Martínez P. Narrative review on clinical considerations for patients with diabetes and COVID-19: More questions than answers. *Int J Clin Pract* 2021; **75**: e14833 [PMID: 34510676 DOI: 10.1111/ijcp.14833]

36 **Wu C**, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020; **180**: 934-943 [PMID: 32167524 DOI: 10.1001/jamainternmed.2020.0994]

37 **Jin YH**, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, Fang C, Huang D, Huang LQ, Huang Q, Han Y, Hu B, Hu F, Li BH, Li YR, Liang K, Lin LK, Luo LS, Ma J, Ma LL, Peng ZY, Pan YB, Pan ZY, Ren XQ, Sun HM, Wang Y, Wang YY, Weng H, Wei CJ, Wu DF, Xia J, Xiong Y, Xu HB, Yao XM, Yuan YF, Ye TS, Zhang XC, Zhang YW, Zhang YG, Zhang HM, Zhao Y, Zhao MJ, Zi H, Zeng XT, Wang XH; , for the Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team, Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care (CPAM). A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res* 2020; **7**: 4 [PMID: 32029004 DOI: 10.1186/s40779-020-0233-6]

38 **McPherson RA**, Hardy G. Clinical and nutritional benefits of cysteine-enriched protein supplements. *Curr Opin Clin Nutr Metab Care* 2011; **14**: 562-568 [PMID: 21986479 DOI: 10.1097/MCO.0b013e32834c1780]

39 **Rondanelli M**, Faliva MA, Gasparri C, Peroni G, Spadaccini D, Maugeri R, Nichetti M, Infantino V, Perna S. Current opinion on dietary advice in order to preserve fat-free mass during a low-calorie diet. *Nutrition* 2020; **72**: 110667 [PMID: 31962189 DOI: 10.1016/j.nut.2019.110667]

40 **Teixeira FJ**, Santos HO, Howell SL, Pimentel GD. Whey protein in cancer therapy: A narrative review. *Pharmacol Res* 2019; **144**: 245-256 [PMID: 31005617 DOI: 10.1016/j.phrs.2019.04.019]

41 **Cereda E**, Turri A, Klersy C, Cappello S, Ferrari A, Filippi AR, Brugnatelli S, Caraccia M, Chiellino S, Borioli V,

Monaco T, Stella GM, Arcaini L, Benazzo M, Grugnetti G, Pedrazzoli P, Caccialanza R. Whey protein isolate supplementation improves body composition, muscle strength, and treatment tolerance in malnourished advanced cancer patients undergoing chemotherapy. *Cancer Med* 2019; **8**: 6923-6932 [PMID: 31568698 DOI: 10.1002/cam4.2517]

42 **Cross ML**, Gill HS. Immunomodulatory properties of milk. *Br J Nutr* 2000; **84** Suppl 1: S81-S89 [PMID: 11242451 DOI: 10.1017/s0007114500002294]

43 **Ng TB**, Cheung RC, Wong JH, Wang Y, Ip DT, Wan DC, Xia J. Antiviral activities of whey proteins. *Appl Microbiol Biotechnol* 2015; **99**: 6997-7008 [PMID: 26198883 DOI: 10.1007/s00253-015-6818-4]

44 **Olsen MF**, Abdissa A, Kæstel P, Tesfaye M, Yilma D, Girma T Wells J CK, Ritz C, Mølgaard C, Michaelsen KF, Zerfu D, Brage S, B Andersen A, Friis H. Effects of nutritional supplementation for HIV patients starting antiretroviral treatment: randomized controlled trial in Ethiopia. *BMJ* 2014; **348**: g3187 [DOI: 10.1136/bmj.g3187]

45 **Paulsrud JR**, Pensler L, Whitten CF, Stewart S, Holman RT. Essential fatty acid deficiency in infants induced by fat-free intravenous feeding. *Am J Clin Nutr* 1972; **25**: 897-904 [PMID: 4626563 DOI: 10.1093/ajcn/25.9.897]

46 **Calder PC**, Adolph M, Deutz NE, Grau T, Innes JK, Klek S, Lev S, Mayer K, Michael-Titus AT, Pradelli L, Puder M, Vlaardingerbroek H, Singer P. Lipids in the intensive care unit: Recommendations from the ESPEN Expert Group. *Clin Nutr* 2018; **37**: 1-18 [PMID: 28935438 DOI: 10.1016/j.clnu.2017.08.032]

47 **Calder PC**. Functional Roles of Fatty Acids and Their Effects on Human Health. *JPEN J Parenter Enteral Nutr* 2015; **39**: 18S-32S [PMID: 26177664 DOI: 10.1177/0148607115595980]

48 **Su H**, Liu R, Chang M, Huang J, Wang X. Dietary linoleic acid intake and blood inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. *Food Funct* 2017; **8**: 3091-3103 [PMID: 28752873 DOI: 10.1039/c7fo00433h]

49 **Talasaz AH**, Sadeghipour P, Aghakouchakzadeh M, Dreyfus I, Kakavand H, Ariannejad H, Gupta A, Madhavan MV, Van Tassell BW, Jimenez D, Monreal M, Vaduganathan M, Fanikos J, Dixon DL, Piazza G, Parikh SA, Bhatt DL, Lip GYH, Stone GW, Krumholz HM, Libby P, Goldhaber SZ, Bikdeli B. Investigating Lipid-Modulating Agents for Prevention or Treatment of COVID-19: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2021; **78**: 1635-1654 [PMID: 34649702 DOI: 10.1016/j.jacc.2021.08.021]

50 **Innes JK**, Calder PC. Omega-6 fatty acids and inflammation. *Prostaglandins Leukot Essent Fatty Acids* 2018; **132**: 41-48 [PMID: 29610056 DOI: 10.1016/j.plefa.2018.03.004]

51 **Calder PC**. Fatty acids and inflammation: the cutting edge between food and pharma. *Eur J Pharmacol* 2011; **668** Suppl 1: S50-S58 [PMID: 21816146 DOI: 10.1016/j.ejphar.2011.05.085]

52 **Saini RK**, Keum YS. Omega-3 and omega-6 polyunsaturated fatty acids: Dietary sources, metabolism, and significance - A review. *Life Sci* 2018; **203**: 255-267 [PMID: 29715470 DOI: 10.1016/j.lfs.2018.04.049]

53 **D'Angelo S**, Motti ML, Meccariello R. ω-3 and ω-6 Polyunsaturated Fatty Acids, Obesity and Cancer. *Nutrients* 2020; **12** [PMID: 32927614 DOI: 10.3390/nu12092751]

54 **DiNicolantonio JJ**, O'Keefe JH. Importance of maintaining a low omega-6/omega-3 ratio for reducing inflammation. *Open Heart* 2018; **5**: e000946 [PMID: 30564378 DOI: 10.1136/openhrt-2018-000946]

55 **Martinez RM**, Fattori V, Saito P, Melo CBP, Borghi SM, Pinto IC, Bussmann AJC, Baracat MM, Georgetti SR, Verri WA Jr, Casagrande R. Lipoxin A4 inhibits UV radiation-induced skin inflammation and oxidative stress in mice. *J Dermatol Sci* 2018 [PMID: 29731194 DOI: 10.1016/j.jdermsci.2018.04.014]

56 **Luo CL**, Li QQ, Chen XP, Zhang XM, Li LL, Li BX, Zhao ZQ, Tao LY. Lipoxin A4 attenuates brain damage and downregulates the production of pro-inflammatory cytokines and phosphorylated mitogen-activated protein kinases in a mouse model of traumatic brain injury. *Brain Res* 2013; **1502**: 1-10 [PMID: 23370001 DOI: 10.1016/j.brainres.2013.01.037]

57 **Pirault J**, Bäck M. Lipoxin and Resolvin Receptors Transducing the Resolution of Inflammation in Cardiovascular Disease. *Front Pharmacol* 2018; **9**: 1273 [PMID: 30487747 DOI: 10.3389/fphar.2018.01273]

58 **Serhan CN**, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat Rev Immunol* 2008; **8**: 349-361 [PMID: 18437155 DOI: 10.1038/nri2294]

59 **Liu X**, Wang X, Duan X, Poorun D, Xu J, Zhang S, Gan L, He M, Zhu K, Ming Z, Hu F, Chen H. Lipoxin A4 and its analog suppress inflammation by modulating HMGB1 translocation and expression in psoriasis. *Sci Rep* 2017; **7**: 7100 [PMID: 28769106 DOI: 10.1038/s41598-017-07485-1]

60 **Karra L**, Haworth O, Priluck R, Levy BD, Levi-Schaffer F. Lipoxin B_4 promotes the resolution of allergic inflammation in the upper and lower airways of mice. *Mucosal Immunol* 2015; **8**: 852-862 [PMID: 25465102 DOI: 10.1038/mi.2014.116]

61 **Jeyakumar SM**, Vajreswari A. Pharmaconutrition strategy to resolve SARS-CoV-2-induced inflammatory cytokine storm in non-alcoholic fatty liver disease: Omega-3 Long-chain polyunsaturated fatty acids. *World J Clin Cases* 2021; **9**: 9333-9349 [PMID: 34877270]

62 **Hawryłkowicz V**, Lietz-Kijak D, Kaźmierczak-Siedlecka K, Sołek-Pastuszka J, Stachowska L, Folwarski M, Parczewski M, Stachowska E. Patient Nutrition and Probiotic Therapy in COVID-19: What Do We Know in 2021? *Nutrients* 2021; **13** [PMID: 34684384 DOI: 10.3390/nu13103385]

63 **Harvey SE**, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, Bellingan G, Leonard R, Mythen MG, Rowan KM; CALORIES Trial Investigators. Trial of the route of early nutritional support in critically ill adults. *N Engl J Med* 2014; **371**: 1673-1684 [PMID: 25271389 DOI: 10.1056/NEJMoa1409860]

64 **Serhan CN**, Petasis NA. Resolvins and protectins in inflammation resolution. *Chem Rev* 2011; **111**: 5922-5943 [PMID: 21766791 DOI: 10.1021/cr100396c]

65 **Regidor PA**, Santos FG, Rizo JM, Egea FM. Pro resolving inflammatory effects of the lipid mediators of omega 3 fatty acids and its implication in SARS COVID-19. *Med Hypotheses* 2020; **145**: 110340 [PMID: 33069094]

66 **Russell CD**, Schwarze J. The role of pro-resolution lipid mediators in infectious disease. *Immunology* 2014; **141**: 166-173 [PMID: 24400794 DOI: 10.1111/imm.12206]

67 **Yang A**, Wu Y, Yu G, Wang H. Role of specialized pro-resolving lipid mediators in pulmonary inflammation diseases:

mechanisms and development. *Respir Res* 2021; **22**: 204 [PMID: 34261470 DOI: 10.1186/s12931-021-01792-y]

68 **Balta MG**, Papathanasiou E, Christopoulos PF. Specialized Pro-Resolving Mediators as Potential Regulators of Inflammatory Macrophage Responses in COVID-19. *Front Immunol* 2021; **12**: 632238 [PMID: 33717168 DOI: 10.3389/fimmu.2021.632238]

69 **Regidor PA**, De La Rosa X, Santos FG, Rizo JM, Gracia Banzo R, Silva RS. Acute severe SARS COVID-19 patients produce pro-resolving lipids mediators and eicosanoids. *Eur Rev Med Pharmacol Sci* 2021; **25**: 6782-6796 [PMID: 34787883 DOI: 10.26355/eurrev_202111_27123]

70 **Wang Q**, Zheng X, Cheng Y, Zhang YL, Wen HX, Tao Z, Li H, Hao Y, Gao Y, Yang LM, Smith FG, Huang CJ, Jin SW. Resolvin D1 stimulates alveolar fluid clearance through alveolar epithelial sodium channel, Na,K-ATPase *via* ALX/cAMP/PI3K pathway in lipopolysaccharide-induced acute lung injury. *J Immunol* 2014; **192**: 3765-3777 [PMID: 24646745 DOI: 10.4049/jimmunol.1302421]

71 **Fullerton JN**, Gilroy DW. Resolution of inflammation: a new therapeutic frontier. *Nat Rev Drug Discov* 2016; **15**: 551-567 [PMID: 27020098 DOI: 10.1038/nrd.2016.39]

72 **Saeed H**, Osama H, Abdelrahman MA, Madney YM, Harb HS, Abdelrahim MEA, Ali F. Vitamins and other immune-supportive elements as cofactors for passing the COVID-19 pandemic. *Beni Suef Univ J Basic Appl Sci* 2021; **10**: 71 [PMID: 34729372 DOI: 10.1186/s43088-021-00163-2]

73 **Romano L**, Bilotta F, Dauri M, Macheda S, Pujia A, De Santis GL, Tarsitano MG, Merra G, Di Renzo L, Esposito E, De Lorenzo A. Short Report - Medical nutrition therapy for critically ill patients with COVID-19. *Eur Rev Med Pharmacol Sci* 2020; **24**: 4035-4039 [PMID: 32329880 DOI: 10.26355/eurrev_202004_20874]

74 **McClave SA**, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, McCarthy MS, Davanos E, Rice TW, Cresci GA, Gervasio JM, Sacks GS, Roberts PR, Compher C; Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2016; **40**: 159-211 [PMID: 26773077 DOI: 10.1177/0148607115621863]

75 **Zakrzewska K**, Oszajca K, Zep W, Piekarska A, Sidorkiewicz M. The Impact of Short-Term Shark Liver Oil Supplementation on the Fatty Acid Composition of Erythrocyte Membranes. *Nutrients* 2021; **13** [PMID: 34684329 DOI: 10.3390/nu13103329]

76 **Goc A**, Niedzwiecki A, Rath M. Polyunsaturated ω-3 fatty acids inhibit ACE2-controlled SARS-CoV-2 binding and cellular entry. *Sci Rep* 2021; **11**: 5207 [PMID: 33664446 DOI: 10.1038/s41598-021-84850-1]

77 **Ling V**, Zabetakis I. The Role of an Anti-Inflammatory Diet in Conjunction to COVID-19. *Diseases* 2021; **9** [PMID: 34842636 DOI: 10.3390/diseases9040076]

78 **Weill P**, Plissonneau C, Legrand P, Rioux V, Thibault R. May omega-3 fatty acid dietary supplementation help reduce severe complications in Covid-19 patients? *Biochimie* 2020; **179**: 275-280 [PMID: 32920170 DOI: 10.1016/j.biochi.2020.09.003]

79 **Vivar-Sierra A**, Araiza-Macías MJ, Hernández-Contreras JP, Vergara-Castañeda A, Ramírez-Vélez G, Pinto-Almazán R, Salazar JR, Loza-Mejía MA. In Silico Study of Polyunsaturated Fatty Acids as Potential SARS-CoV-2 Spike Protein Closed Conformation Stabilizers: Epidemiological and Computational Approaches. *Molecules* 2021; **26** [PMID: 33573088 DOI: 10.3390/molecules26030711]

80 **Clemente-Suárez VJ**, Ramos-Campo DJ, Mielgo-Ayuso J, Dalamitros AA, Nikolaidis PA, Hormeño-Holgado A, Tornero-Aguilera JF. Nutrition in the Actual COVID-19 Pandemic. A Narrative Review. *Nutrients* 2021; **13** [PMID: 34205138 DOI: 10.3390/nu13061924]

81 **Asher A**, Tintle NL, Myers M, Lockshon L, Bacareza H, Harris WS. Blood omega-3 fatty acids and death from COVID-19: A pilot study. *Prostaglandins Leukot Essent Fatty Acids* 2021; **166**: 102250 [PMID: 33516093 DOI: 10.1016/j.plefa.2021.102250]

82 **Zapata B R**, Müller JM, Vásquez JE, Ravera F, Lago G, Cañón E, Castañeda D, Pradenas M, Ramírez-Santana M. Omega-3 Index and Clinical Outcomes of Severe COVID-19: Preliminary Results of a Cross-Sectional Study. *Int J Environ Res Public Health* 2021; **18** [PMID: 34360016 DOI: 10.3390]

83 **Doaei S**, Gholami S, Rastgoo S, Gholamalizadeh M, Bourbour F, Bagheri SE, Samipoor F, Akbari ME, Shadnoush M, Ghorat F, Mosavi Jarrahi SA, Ashouri Mirsadeghi N, Hajipour A, Joola P, Moslem A, Goodarzi MO. The effect of omega-3 fatty acid supplementation on clinical and biochemical parameters of critically ill patients with COVID-19: a randomized clinical trial. *J Transl Med* 2021; **19**: 128 [PMID: 33781275 DOI: 10.1186/s12967-021-02795-5]

84 **Rizzo G**, Laganà AS, Rapisarda AM, La Ferrera GM, Buscema M, Rossetti P, Nigro A, Muscia V, Valenti G, Sapia F, Sarpietro G, Zigarelli M, Vitale SG. Vitamin B12 among Vegetarians: Status, Assessment and Supplementation. *Nutrients* 2016; **8** [PMID: 27916823 DOI: 10.3390/nu8120767]

85 **Shakoor H**, Feehan J, Mikkelsen K, Al Dhaheri AS, Ali HI, Platat C, Ismail LC, Stojanovska L, Apostolopoulos V. Be well: A potential role for vitamin B in COVID-19. *Maturitas* 2021; **144**: 108-111 [PMID: 32829981 DOI: 10.1016/j.maturitas.2020.08.007]

86 **Chaari A**, Bendriss G, Zakaria D, McVeigh C. Importance of Dietary Changes During the Coronavirus Pandemic: How to Upgrade Your Immune Response. *Front Public Health* 2020; **8**: 476 [PMID: 32984253 DOI: 10.3389/fpubh.2020.00476]

87 **Maggini S**, Wintergerst ES, Beveridge S, Hornig DH. Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. *Br J Nutr* 2007; **98** Suppl 1: S29-S35 [PMID: 17922955 DOI: 10.1017/S0007114507832971]

88 **Im JH**, Je YS, Baek J, Chung MH, Kwon HY, Lee JS. Nutritional status of patients with COVID-19. *Int J Infect Dis* 2020; **100**: 390-393 [PMID: 32795605 DOI: 10.1016/j.ijid.2020.08.018]

89 **Wee AKH**. COVID-19's toll on the elderly and those with diabetes mellitus - Is vitamin B12 deficiency an accomplice? *Med Hypotheses* 2021; **146**: 110374 [PMID: 33257090 DOI: 10.1016/j.mehy.2020.110374]

90 **Shakeri H**, Azimian A, Ghasemzadeh-Moghaddam H, Safdari M, Haresabadi M, Daneshmand T, Namdar Ahmadabad H. Evaluation of the relationship between serum levels of zinc, vitamin B12, vitamin D, and clinical outcomes in patients

with COVID-19. *J Med Virol* 2022; **94**: 141-146 [PMID: 34406674 DOI: 10.1002/jmv.27277]

91 **Beigmohammadi MT**, Bitarafan S, Abdollahi A, Amoozadeh L, Salahshour F, Mahmoodi Ali Abadi M, Soltani D, Motallebnejad ZA. The association between serum levels of micronutrients and the severity of disease in patients with COVID-19. *Nutrition* 2021; **91-92**: 111400 [PMID: 34388583 DOI: 10.1016/j.nut.2021.111400]

92 **Ersöz A**, Yılmaz TE. The association between micronutrient and hemogram values and prognostic factors in COVID-19 patients: A single-center experience from Turkey. *Int J Clin Pract* 2021; **75**: e14078 [PMID: 33555131 DOI: 10.1111/ijcp.14078]

93 **Itelman E**, Wasserstrum Y, Segev A, Avaky C, Negru L, Cohen D, Turpashvili N, Anani S, Zilber E, Lasman N, Athamna A, Segal O, Halevy T, Sabiner Y, Donin Y, Abraham L, Berdugo E, Zarka A, Greidinger D, Agbaria M, Kitany N, Katorza E, Shenhav-Saltzman G, Segal G. Clinical Characterization of 162 COVID-19 patients in Israel: Preliminary Report from a Large Tertiary Center. *Isr Med Assoc J* 2020; **22**: 271-274 [PMID: 32378815]

94 **Ermens AA**, Vlasveld LT, Lindemans J. Significance of elevated cobalamin (vitamin B12) levels in blood. *Clin Biochem* 2003; **36**: 585-590 [PMID: 14636871 DOI: 10.1016/j.clinbiochem.2003.08.004]

95 **Stabler SP**. Clinical practice. Vitamin B12 deficiency. *N Engl J Med* 2013; **368**: 149-160 [PMID: 23301732 DOI: 10.1056/NEJMcp1113996]

96 **Sezer RG**, Bozaykut A, Akoğlu HA, Özdemir GN. The Efficacy of Oral Vitamin B12 Replacement for Nutritional Vitamin B12 Deficiency. *J Pediatr Hematol Oncol* 2018; **40**: e69-e72 [PMID: 29189512 DOI: 10.1097/MPH.0000000000001037]

97 **Bahadir A**, Reis PG, Erduran E. Oral vitamin B12 treatment is effective for children with nutritional vitamin B12 deficiency. *J Paediatr Child Health* 2014; **50**: 721-725 [PMID: 24944005 DOI: 10.1111/jpc.12652]

98 **Castelli MC**, Friedman K, Sherry J, Brazzillo K, Genoble L, Bhargava P, Riley MG. Comparing the efficacy and tolerability of a new daily oral vitamin B12 formulation and intermittent intramuscular vitamin B12 in normalizing low cobalamin levels: a randomized, open-label, parallel-group study. *Clin Ther* 2011; **33**: 358-371.e2 [PMID: 21600388 DOI: 10.1016/j.clinthera.2011.03.003]

99 **Tan CW**, Ho LP, Kalimuddin S, Cherng BPZ, Teh YE, Thien SY, Wong HM, Tern PJW, Chandran M, Chay JWM, Nagarajan C, Sultana R, Low JGH, Ng HJ. Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19). *Nutrition* 2020; **79-80**: 111017 [PMID: 33039952 DOI: 10.1016/j.nut.2020.111017]

100 **Junaid K**, Ejaz H, Abdalla AE, Abosalif KOA, Ullah MI, Yasmeen H, Younas S, Hamam SSM, Rehman A. Effective Immune Functions of Micronutrients against SARS-CoV-2. *Nutrients* 2020; **12** [PMID: 33003648 DOI: 10.3390/nu12102992]

101 **Jovic TH**, Ali SR, Ibrahim N, Jessop ZM, Tarassoli SP, Dobbs TD, Holford P, Thornton CA, Whitaker IS. Could Vitamins Help in the Fight Against COVID-19? *Nutrients* 2020; **12** [PMID: 32842513 DOI: 10.3390/nu12092550]

102 **Bergman P**. The link between vitamin D and COVID-19: distinguishing facts from fiction. *J Intern Med* 2021; **289**: 131-133 [PMID: 32652766 DOI: 10.1111/joim.13158]

103 **Hyppönen E**, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. *Am J Clin Nutr* 2007; **85**: 860-868 [PMID: 17344510 DOI: 10.1093/ajcn/85.3.860]

104 **Mitchell F**. Vitamin-D and COVID-19: do deficient risk a poorer outcome? *Lancet Diabetes Endocrinol* 2020; **8**: 570 [PMID: 32445630 DOI: 10.1016/S2213-8587(20)30183-2]

105 **Dankers W**, Colin EM, van Hamburg JP, Lubberts E. Vitamin D in Autoimmunity: Molecular Mechanisms and Therapeutic Potential. *Front Immunol* 2016; **7**: 697 [PMID: 28163705 DOI: 10.3389/fimmu.2016.00697]

106 **Gombart AF**, Borregaard N, Koeffler HP. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. *FASEB J* 2005; **19**: 1067-1077 [PMID: 15985530 DOI: 10.1096/fj.04-3284com]

107 **Greiller CL**, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. *Nutrients* 2015; **7**: 4240-4270 [PMID: 26035247 DOI: 10.3390/nu7064240]

108 **Grant WB**, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients* 2020; **12** [PMID: 32252338 DOI: 10.3390/nu12040988]

109 **Cantorna MT**, Snyder L, Lin YD, Yang L. Vitamin D and 1,25(OH)2D regulation of T cells. *Nutrients* 2015; **7**: 3011-3021 [PMID: 25912039 DOI: 10.3390/nu7043011]

110 **Ilie PC**, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin Exp Res* 2020; **32**: 1195-1198 [PMID: 32377965 DOI: 10.1007/s40520-020-01570-8]

111 **Rhodes JM**, Subramanian S, Laird E, Griffin G, Kenny RA. Perspective: Vitamin D deficiency and COVID-19 severity - plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2 and thrombosis. *J Intern Med* 2021; **289**: 97-115 [PMID: 32613681 DOI: 10.1111/joim.13149]

112 **Kumar R**, Rathi H, Haq A, Wimalawansa SJ, Sharma A. Putative roles of vitamin D in modulating immune response and immunopathology associated with COVID-19. *Virus Res* 2021; **292**: 198235 [PMID: 33232783 DOI: 10.1016/j.virusres.2020.198235]

113 **Annweiler C**, Beaudenon M, Gautier J, Simon R, Dubée V, Gonsard J, Parot-Schinkel E; COVIT-TRIAL study group. COvid-19 and high-dose VITamin D supplementation TRIAL in high-risk older patients (COVIT-TRIAL): study protocol for a randomized controlled trial. *Trials* 2020; **21**: 1031 [PMID: 33371905 DOI: 10.1186/s13063-020-04928-5]

114 **Munshi R**, Hussein MH, Toraih EA, Elshazli RM, Jardak C, Sultana N, Youssef MR, Omar M, Attia AS, Fawzy MS, Killackey M, Kandil E, Duchesne J. Vitamin D insufficiency as a potential culprit in critical COVID-19 patients. *J Med Virol* 2021; **93**: 733-740 [PMID: 32716073 DOI: 10.1002/jmv.26360]

115 **Ali N**. Role of vitamin D in preventing of COVID-19 infection, progression and severity. *J Infect Public Health* 2020; **13**: 1373-1380 [PMID: 32605780 DOI: 10.1016/j.jiph.2020.06.021]

116 **Alemzadeh E**, Alemzadeh E, Ziaee M, Abedi A, Salehiniya H. The effect of low serum calcium level on the severity and mortality of Covid patients: A systematic review and meta-analysis. *Immun Inflamm Dis* 2021; **9**: 1219-1228 [PMID:

34534417 DOI: 10.1002/iid3.528]
117 **Torres B**, Alcubilla P, González-Cordón A, Inciarte A, Chumbita M, Cardozo C, Meira F, Giménez M, de Hollanda A, Soriano A; COVID19 Hospital Clínic Infectious Diseases Research Group. Impact of low serum calcium at hospital admission on SARS-CoV-2 infection outcome. *Int J Infect Dis* 2021; **104**: 164-168 [PMID: 33278624 DOI: 10.1016/j.ijid.2020.11.207]
118 **Paliogiannis P**, Mangoni AA, Dettori P, Nasrallah GK, Pintus G, Zinellu A. D-Dimer Concentrations and COVID-19 Severity: A Systematic Review and Meta-Analysis. *Front Public Health* 2020; **8**: 432 [PMID: 32903841 DOI: 10.3389/fpubh.2020.00432]
119 **di Filippo L**, Allora A, Locatelli M, Rovere Querini P, Frara S, Banfi G, Giustina A. Hypocalcemia in COVID-19 is associated with low vitamin D levels and impaired compensatory PTH response. *Endocrine* 2021; **74**: 219-225 [PMID: 34586582 DOI: 10.1007/s12020-021-02882-z]
120 **di Filippo L**, Doga M, Frara S, Giustina A. Hypocalcemia in COVID-19: Prevalence, clinical significance and therapeutic implications. *Rev Endocr Metab Disord* 2021 [PMID: 33846867 DOI: 10.1007/s11154-021-09655-z]
121 **Osman W**, Al Fahdi F, Al Salmi I, Al Khalili H, Gokhale A, Khamis F. Serum Calcium and Vitamin D levels: Correlation with severity of COVID-19 in hospitalized patients in Royal Hospital, Oman. *Int J Infect Dis* 2021; **107**: 153-163 [PMID: 33892191 DOI: 10.1016/j.ijid.2021.04.050]
122 **Khelashvili G**, Plante A, Doktorova M, Weinstein H. Ca2+-dependent mechanism of membrane insertion and destabilization by the SARS-CoV-2 fusion peptide. *Biophys J* 2021; **120**: 1105-1119 [PMID: 33631204 DOI: 10.1016/j.bpj.2021.02.023]
123 **Dakal TC**. SARS-CoV-2 attachment to host cells is possibly mediated *via* RGD-integrin interaction in a calcium-dependent manner and suggests pulmonary EDTA chelation therapy as a novel treatment for COVID 19. *Immunobiology* 2021; **226**: 152021 [PMID: 33232865 DOI: 10.1016/j.imbio.2020.152021]
124 **Lai AL**, Freed JH. SARS-CoV-2 Fusion Peptide has a Greater Membrane Perturbating Effect than SARS-CoV with Highly Specific Dependence on Ca2. *J Mol Biol* 2021; **433**: 166946 [PMID: 33744314 DOI: 10.1016/j.jmb.2021.166946]
125 **Berlansky S**, Sallinger M, Grabmayr H, Humer C, Bernhard A, Fahrner M, Frischauf I. Calcium Signals during SARS-CoV-2 Infection: Assessing the Potential of Emerging Therapies. *Cells* 2022; **11** [PMID: 35053369 DOI: 10.3390/cells11020253]
126 **Alsagaff MY**, Mulia EPB, Maghfirah I, Luke K, Nugraha D, Rachmi DA, Septianda I, A'yun MQ. Association of calcium channel blocker use with clinical outcome of COVID-19: A meta-analysis. *Diabetes Metab Syndr* 2021; **15**: 102210 [PMID: 34298269 DOI: 10.1016/j.dsx.2021.102210]
127 **Mendez SR**, Frank RC, Stevenson EK, Chung M, Silverman MG. Dihydropyridine Calcium Channel Blockers and the Risk of Severe COVID-19. *Chest* 2021; **160**: 89-93 [PMID: 33548220 DOI: 10.1016/j.chest.2021.01.073]
128 **Bennouar S**, Cherif AB, Kessira A, Bennouar DE, Abdi S. Lower plasma calcium associated with COVID-19, but not with disease severity: a two-centre retrospective cohort study. *Journal of the American College of Nutrition* 2021; **40**: 104-110 [PMID: 33434117 DOI: 10.1080/07315724.2020.1856013]
129 **Bastin A**, Shiri H, Zanganeh S, Fooladi S, Momeni Moghaddam MA, Mehrabani M, Nematollahi MH. Iron Chelator or Iron Supplement Consumption in COVID-19? *Biol Trace Elem Res* 2021 [PMID: 34825316 DOI: 10.1007/s12011-021-03048-8]
130 **Zhou C**, Chen Y, Ji Y, He X, Xue D. Increased Serum Levels of Hepcidin and Ferritin Are Associated with Severity of COVID-19. *Med Sci Monit* 2020; **26**: e926178 [PMID: 32978363 DOI: 10.12659/MSM.926178]
131 **Tojo K**, Sugawara Y, Oi Y, Ogawa F, Higurashi T, Yoshimura Y, Miyata N, Hayami H, Yamaguchi Y, Ishikawa Y, Takeuchi I, Tachikawa N, Goto T. The U-shaped association of serum iron level with disease severity in adult hospitalized patients with COVID-19. *Sci Rep* 2021; **11**: 13431 [PMID: 34183735 DOI: 10.1038/s41598-021-92921-6]
132 **Hippchen T**, Altamura S, Muckenthaler MU, Merle U. Hypoferremia is Associated With Increased Hospitalization and Oxygen Demand in COVID-19 Patients. *Hemasphere* 2020; **4**: e492 [PMID: 33205000 DOI: 10.1097/HS9.0000000000000492]
133 **Sonnweber T**, Boehm A, Sahanic S, Pizzini A, Aichner M, Sonnweber B, Kurz K, Koppelstätter S, Haschka D, Petzer V, Hilbe R, Theurl M, Lehner D, Nairz M, Puchner B, Luger A, Schwabl C, Bellmann-Weiler R, Wöll E, Widmann G, Tancevski I, Judith-Löffler-Ragg, Weiss G. Persisting alterations of iron homeostasis in COVID-19 are associated with non-resolving lung pathologies and poor patients' performance: a prospective observational cohort study. *Respir Res* 2020; **21**: 276 [PMID: 33087116 DOI: 10.1186/s12931-020-01546-2]
134 **Zhao K**, Huang J, Dai D, Feng Y, Liu L, Nie S. Serum Iron Level as a Potential Predictor of Coronavirus Disease 2019 Severity and Mortality: A Retrospective Study. *Open Forum Infect Dis* 2020; **7**: ofaa250 [PMID: 32661499 DOI: 10.1093/ofid/ofaa250]
135 **Taneri PE**, Gómez-Ochoa SA, Llanaj E, Raguindin PF, Rojas LZ, Roa-Díaz ZM, Salvador D Jr, Groothof D, Minder B, Kopp-Heim D, Hautz WE, Eisenga MF, Franco OH, Glisic M, Muka T. Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. *Eur J Epidemiol* 2020; **35**: 763-773 [PMID: 32816244 DOI: 10.1007/s10654-020-00678-5]
136 **de Faria Coelho-Ravagnani C**, Corgosinho FC, Sanches FFZ, Prado CMM, Laviano A, Mota JF. Dietary recommendations during the COVID-19 pandemic. *Nutr Rev* 2021; **79**: 382-393 [PMID: 32653930 DOI: 10.1093/nutrit/nuaa067]
137 **Lopez A**, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet* 2016; **387**: 907-916 [PMID: 26314490 DOI: 10.1016/S0140-6736(15)60865-0]
138 **Akhtar S**, Das JK, Ismail T, Wahid M, Saeed W, Bhutta ZA. Nutritional perspectives for the prevention and mitigation of COVID-19. *Nutr Rev* 2021; **79**: 289-300 [PMID: 33570583 DOI: 10.1093/nutrit/nuaa063]
139 **Skalny AV**, Timashev PS, Aschner M, Aaseth J, Chernova LN, Belyaev VE, Grabeklis AR, Notova SV, Lobinski R, Tsatsakis A, Svistunov AA, Fomin VV, Tinkov AA, Glybochko PV. Serum Zinc, Copper, and Other Biometals Are Associated with COVID-19 Severity Markers. *Metabolites* 2021; **11** [PMID: 33920813 DOI: 10.3390/metabo11040244]
140 **Zeng HL**, Yang Q, Yuan P, Wang X, Cheng L. Associations of essential and toxic metals/metalloids in whole blood with

both disease severity and mortality in patients with COVID-19. *FASEB J* 2021; **35**: e21392 [PMID: 33577131 DOI: 10.1096/fj.202002346RR]

141 **Hackler J**, Heller RA, Sun Q, Schwarzer M, Diegmann J, Bachmann M, Moghaddam A, Schomburg L. Relation of Serum Copper Status to Survival in COVID-19. *Nutrients* 2021; **13** [PMID: 34072977 DOI: 10.3390/nu13061898]

142 **Arrieta F**, Martinez-Vaello V, Bengoa N, Jiménez-Mendiguchia L, Rosillo M, de Pablo A, Voguel C, Martinez-Barros H, Pintor R, Belanger-Quintana A, Mateo R, Candela A, Botella-Carretero JI. Serum zinc and copper in people with COVID-19 and zinc supplementation in parenteral nutrition. *Nutrition* 2021; **91-92**: 111467 [PMID: 34592694 DOI: 10.1016/j.nut.2021.111467]

143 **Rani I**, Goyal A, Bhatnagar M, Manhas S, Goel P, Pal A, Prasad R. Potential molecular mechanisms of zinc- and copper-mediated antiviral activity on COVID-19. *Nutr Res* 2021; **92**: 109-128 [PMID: 34284268 DOI: 10.1016/j.nutres.2021.05.008]

144 **Gammoh NZ**, Rink L. Zinc in Infection and Inflammation. *Nutrients* 2017; **9** [PMID: 28629136 DOI: 10.3390/nu9060624]

145 **Shakoor H**, Feehan J, Al Dhaheri AS, Ali HI, Platat C, Ismail LC, Apostolopoulos V, Stojanovska L. Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19? *Maturitas* 2021; **143**: 1-9 [PMID: 33308613 DOI: 10.1016/j.maturitas.2020.08.003]

146 **Bonaventura P**, Benedetti G, Albarède F, Miossec P. Zinc and its role in immunity and inflammation. *Autoimmun Rev* 2015; **14**: 277-285 [PMID: 25462582 DOI: 10.1016/j.autrev.2014.11.008]

147 **Hunter J**, Arentz S, Goldenberg J, Yang G, Beardsley J, Myers SP, Mertz D, Leeder S. Zinc for the prevention or treatment of acute viral respiratory tract infections in adults: a rapid systematic review and meta-analysis of randomised controlled trials. *BMJ Open* 2021; **11**: e047474 [PMID: 34728441 DOI: 10.1136/bmjopen-2020-047474]

148 **Morgan CI**, Ledford JR, Zhou P, Page K. Zinc supplementation alters airway inflammation and airway hyperresponsiveness to a common allergen. *J Inflamm (Lond)* 2011; **8**: 36 [PMID: 22151973 DOI: 10.1186/1476-9255-8-36]

149 **Karim MM**, Sultana S, Sultana R, Rahman MT. Possible Benefits of Zinc supplement in CVD and COVID-19 Comorbidity. *J Infect Public Health* 2021; **14**: 1686-1692 [PMID: 34649043 DOI: 10.1016/j.jiph.2021.09.022]

150 **te Velthuis AJ**, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity *in vitro* and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog* 2010; **6**: e1001176 [PMID: 21079686 DOI: 10.1371/journal.ppat.1001176]

151 **Bagheri-Hosseinabadi Z**, Pirsadeghi A, Rahnama A, Bahrehmand F, Abbasifard M. Is there any relationship between serum zinc levels and angiotensin-converting enzyme 2 gene expression in patients with coronavirus disease 2019? *Meta Gene* 2022; **31**: 100991 [PMID: 34778004 DOI: 10.1016/j.mgene.2021.100991]

152 **McPherson SW**, Keunen JE, Bird AC, Chew EY, van Kuijk FJ. Investigate Oral Zinc as a Prophylactic Treatment for Those at Risk for COVID-19. *Am J Ophthalmol* 2020; **216**: A5-A6 [PMID: 32505362 DOI: 10.1016/j.ajo.2020.04.028]

153 **Elalfy H**, Besheer T, El-Mesery A, El-Gilany AH, Soliman MA, Alhawarey A, Alegezy M, Elhadidy T, Hewidy AA, Zaghloul H, Neamatallah MAM, Raafat D, El-Emshaty WM, Abo El Kheir NY, El-Bendary M. Effect of a combination of nitazoxanide, ribavirin, and ivermectin plus zinc supplement (MANS.NRIZ study) on the clearance of mild COVID-19. *J Med Virol* 2021; **93**: 3176-3183 [PMID: 33590901 DOI: 10.1002/jmv.26880]

154 **Thomas S**, Patel D, Bittel B, Wolski K, Wang Q, Kumar A, Il'Giovine ZJ, Mehra R, McWilliams C, Nissen SE, Desai MY. Effect of High-Dose Zinc and Ascorbic Acid Supplementation *vs* Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection: The COVID A to Z Randomized Clinical Trial. *JAMA Netw Open* 2021; **4**: e210369 [PMID: 33576820 DOI: 10.1001/jamanetworkopen.2021.0369]

155 **Abdelmaksoud AA**, Ghweil AA, Hassan MH, Rashad A, Khodeary A, Aref ZF, Sayed MAA, Elsamman MK, Bazeed SES. Olfactory Disturbances as Presenting Manifestation Among Egyptian Patients with COVID-19: Possible Role of Zinc. *Biol Trace Elem Res* 2021; **199**: 4101-4108 [PMID: 33409924 DOI: 10.1007/s12011-020-02546-5]

156 **Muhamed PK**, Vadstrup S. Zinc is the most important trace element. *Ugeskr Laeger* 2014; **176** [PMID: 25096007]

157 **Santos HO**, Teixeira FJ, Schoenfeld BJ. Dietary vs. pharmacological doses of zinc: A clinical review. *Clin Nutr* 2020; **39**: 1345-1353 [PMID: 31303527 DOI: 10.1016/j.clnu.2019.06.024]

158 **Carlucci PM**, Ahuja T, Petrilli C, Rajagopalan H, Jones S, Rahimian J. Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients. *J Med Microbiol* 2020; **69**: 1228-1234 [PMID: 32930657 DOI: 10.1099/jmm.0.001250]

159 **Tang CF**, Ding H, Jiao RQ, Wu XX, Kong LD. Possibility of magnesium supplementation for supportive treatment in patients with COVID-19. *Eur J Pharmacol* 2020; **886**: 173546 [PMID: 32931782 DOI: 10.1016/j.ejphar.2020.173546]

160 **DiNicolantonio JJ**, O'Keefe JH. Magnesium and Vitamin D Deficiency as a Potential Cause of Immune Dysfunction, Cytokine Storm and Disseminated Intravascular Coagulation in covid-19 patients. *Mo Med* 2021; **118**: 68-73 [PMID: 33551489]

161 **van Niekerk G**, Mitchell M, Engelbrecht AM. Bone resorption: supporting immunometabolism. *Biol Lett* 2018; **14** [PMID: 29491030 DOI: 10.1098/rsbl.2017.0783]

162 **Zhu L**, Bao X, Bi J, Lin Y, Shan C, Fan X, Bian J, Wang X. Serum magnesium in patients with severe acute respiratory syndrome coronavirus 2 from Wuhan, China. *Magnes Res* 2021; **34**: 103-113 [PMID: 34642156 DOI: 10.1684/mrh.2021.0488]

163 **Iotti S**, Wolf F, Mazur A, Maier JA. The COVID-19 pandemic: is there a role for magnesium? *Magnes Res* 2020; **33**: 21-27 [PMID: 32554340 DOI: 10.1684/mrh.2020.0465]

164 **Nairz M**, Weiss G. Iron in infection and immunity. *Mol Aspects Med* 2020; **75**: 100864 [PMID: 32461004 DOI: 10.1016/j.mam.2020.100864]

165 **Mariani E**, Cattini L, Neri S, Malavolta M, Mocchegiani E, Ravaglia G, Facchini A. Simultaneous evaluation of circulating chemokine and cytokine profiles in elderly subjects by multiplex technology: relationship with zinc status. *Biogerontology* 2006; **7**: 449-459 [PMID: 16967203 DOI: 10.1007/s10522-006-9060-8]

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MINIREVIEWS

Challenges in hyperglycemia management in critically ill patients with COVID-19

Rajesh Kethireddy, Darshan Gandhi, Asim Kichloo, Love Patel

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Rajesh Kethireddy, Love Patel, Division of Hospital Medicine, Abbott Northwestern Hospital, Allina Health, Minneapolis, MN 55407, United States

Darshan Gandhi, Department of Diagnostic Radiology, University of Tennessee Health Science Center, Memphis, TN 38103, United States

Asim Kichloo, Internal Medicine, Central Michigan University School of Medicine, Mt Pleasant, MI 48859, United States

Corresponding author: Darshan Gandhi, MD Assistant Professor, Department of Diagnostic Radiology, University of Tennessee Health Science Center, 920 Madison Ave, Memphis, TN 38103, United States. darshangandhi7@gmail.com

Abstract

Hyperglycemia is commonly associated with adverse outcomes especially in patients requiring intensive care unit stay. Data from the corona virus disease 2019 (COVID-19) pandemic indicates that individuals with diabetes appear to be at similar risk for COVID-19 infection to those without diabetes but are more likely to experience increased morbidity and mortality. The proposed hypothesis for hyperglycemia in COVID-19 include insulin resistance, critical illness hyperglycemia (stress- induced hyperglycemia) secondary to high levels of hormones like cortisol and catecholamines that counteract insulin action, acute cytokine storm and pancreatic cell dysfunction. Diabetic patients are more likely to have severe hyperglycemic complications including diabetic ketoacidosis and hyperosmolar hyperglycemic state. Management of hyperglycemia in COVID-19 is often complicated by use of steroids, prolonged total parenteral or enteral nutrition, frequent acute hyperglycemic events, and restrictions with fluid management due to acute respiratory distress syndrome. While managing hyperglycemia special attention should be paid to mode of insulin delivery, frequency of glucose monitoring based on patient and caregiver safety thereby minimizing exposure and conserving personal protective equipment. In this article we describe the pathophysiology of hyperglycemia, challenges encountered in managing hyperglycemia, and review some potential solutions to address them.

Key Words: Hyperglycemia; COVID-19; Critical care; Diabetes; Diabetic ketoacidosis

Core Tip: Data from the corona virus disease 2019 (COVID-19) pandemic indicates that individuals with diabetes are more likely to experience hyperglycemia related complications including diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome. These patients often require hospitalization to intensive care units. In this article we intend to describe the pathophysiology of hyperglycemia in critically ill patients with COVID-19 infection, challenges encountered in managing hyperglycemia, and review some potential solutions to address them.

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INTRODUCTION

Corona virus disease 2019 (COVID-19) hospitalization rates have varied across different hospitals across the United States and can be as high as 15% among infected patients[1]. One in four patients admitted to the hospital with COVID-19 infection requires intensive care unit (ICU) level of care. Mortality rates vary widely among these patients, sometimes approaching as high as 62%[2]. Intensive care hospitalization rates of COVID-19 patients differ widely across the countries and in the United States range between 5% and 12% of the total positive cases[3]. The median duration of hospital stays among the COVID-19 patients ranges from 16 to 23 d, the median length of ICU stay is 7 to 17 d, and the average time of mechanical ventilation is about 1-12 d[4].

Both Type 1 and type 2 diabetes are frequently identified medical comorbidities in patients with severe COVID-19 infection with poor clinical outcomes[5,6]. Diabetic patients treated with insulin prior to hospitalization also had poor outcomes[7]. Hyperglycemia (fasting blood glucose more than 125 mg/dL) is identified as an independent predictor of increased mortality in hospitalized patients without prior diagnosis of diabetes[8]. It can be concluded from review of currently available literature that new onset hyperglycemia in non-diabetic patients and new onset diabetes in COVID-19 have poor clinical outcomes compared to people with preexisting diabetes and people with euglycemia[9]. A recent systemic review and meta-analysis reported high prevalence of diabetic ketoacidosis (DKA 63.4%), EDKA (euglycemic diabetic ketoacidosis 8.5%), hyperosmolar hyperglycemic state (HHS 1.4%) and combined DKA/HHS (26.8%) among acute diabetes- associated metabolic emergencies in COVID-19 patients. The mortality rate related to diabetes-associated acute metabolic emergencies in COVID-19 patients' range between 7.7% to 32.4%. The major factors associated with worse outcomes in these patients were the need of mechanical ventilation, acute renal failure and dual presence of hyperosmolar state and ketoacidosis[10]. Strict blood glucose control has been shown to have a protective effect with better outcomes in patients with COVID-19 with hyperglycemia. Sardu *et al*[11] reported that use of intravenous insulin infusion to achieve a substantial drop in blood glucose levels was associated with better clinical outcomes in patients hospitalized with COVID-19.

MECHANISM OF HYPERGLYCEMIA IN PATIENTS WITH COVID-19 INFECTION

Infection mediated factors leading to hyperglycemia

Role of inflammatory storm: Critical illness associated stress results in stimulation of the hypothalamic-pituitary-adrenal (HPA) axis. Excess release of various stress hormones (cortisol, growth hormone, catecholamines and glucagon) that follows, causes insulin resistance by decreasing the uptake of glucose in skeletal muscle and induce gluconeogenesis and glycogenolysis in liver contributing to hyperglycemia.

Inflammatory storm associated with hyperglycemia is frequently among COVID-19 patients with preexisting diabetes, prediabetes, and/or obesity. The association between chronic inflammation and hyperglycemia and its effect on complications has been well described in literature[12-14]. This preexisting inflammatory state can further fuel added cytokine release related complications including increasing insulin resistance, acute (stress) hyperglycemia, and can lead to additional complications in patients with diabetes[15-18]. Severe hyperglycemia was frequently associated with elevations of inflammatory biomarkers like high sensitivity C- reactive protein (hsCRP), procalcitonin, interleukin-6 (IL-6), and D-dimers that act as important predictors for a more severe form of disease[19,20].

In the CORONADO study[21], about 11% of the participants had diabetes-related complications at admission in the form of hyperglycemia, and/or ketoacidosis. Ketosis can be explained because of discontinuation of glucose-lowering medications because of anorexia before hospital admission, a direct

effect of COVID-19 cannot be ruled out. The virus binds to ACE2 receptors which are expressed in pancreatic tissue and β-cells[22]. This can lead to dramatic loss of insulin secretion from pancreas which in combination with stress induced cytokine storm could lead to a rapid metabolic deterioration causing DKA or HHS.

Role of pancreatic damage: COVID-19 virus infects and replicates in cells of the human endocrine and exocrine pancreas resulting in morphological, transcriptional, and functional changes, leading to reduced numbers of insulin-secretory granules in β-cells and impaired glucose-stimulated insulin secretion leading to de novo development of diabetes[23]. Several case reports of new-onset diabetes have been reported in COVID-19 patients admitted to hospital[24]. In a population of 453 patients with COVID-19, 94 were identified with new-onset diabetes and these individuals had the greater risk of all-cause mortality compared with patients with known diabetes, hyperglycemia, and normal glucose.

Treatment related factors leading to hyperglycemia

Role of steroids: RECOVERY trial reported that dexamethasone significantly reduced the mortality risk by 17% in hospitalized patients with COVID-19, by 18% in the subsets of patients who required noninvasive oxygen therapy, and by 36% in the subsets of patients who required invasive mechanical ventilation making it standard of treatment in these subsets of patients[25].

The metabolic effects of glucocorticoids on glucose metabolism are seen at numerous stages in the insulin-signaling cascade. Glucocorticoids reduce peripheral glucose uptake at the level of the muscle and adipose tissue[26]. Skeletal muscle is primarily responsible for the insulin-mediated capture of postprandial glucose and corticosteroids can induce insulin resistance by interfering directly with various components of the insulin signaling cascade[26,27]. Corticosteroids increase endogenous glucose production by glycogenolysis and gluconeogenesis[28]. Glucocorticoids also inhibit the production and secretion of insulin from pancreatic β-cells[29-31]. In adipose tissue, steroids are responsible for increased lipolysis and subsequent accumulation of non-esterified fatty acids, which interfere with insulin-induced glucose uptake. The liver plays a major role in the control of glucose metabolism, maintaining fasting euglycemia. The abilities of glucocorticoids to induce hyperglycemia depend on their dose and the duration of exposure[32].

Glycemic variability is highly debated for its potential role in the development of diabetic complications, glucocorticoid therapy represents a powerful trigger for glycemic excursions. Hydrocortisone boluses administered in critically ill patients were associated with a higher glycemic and insulin rate variability across all Acute Physiology and Chronic Health Evaluation (APACHE) II score grades, irrespective of potential confounders, such as type of admission, body mass index, and age as well as a previous diagnosis of diabetes[33].

Role of nutrition: Enteric and parenteral nutrition are frequently used in critically ill patients add rapid or persistent glucose load leading to hyperglycemia[34-37].

Role of other therapies: Other therapies administered often in ICU patients such as catecholamines, vasopressors, glucocorticoids and mineralocorticoids contribute to hyperglycemia mainly by augmenting insulin resistance at peripheral tissues. Immunomodulatory medications were shown to have mixed effects on glycemic control[38-42].

Challenges in glycemic control

Optimal glycemic control in ICU is important for improved patient outcomes[43]. Patients with COVID-19 and hyperglycemia are at higher risk of worse outcomes compared with those with normoglycemia [44]. Acute hyperglycemia is associated with increased production of inflammatory cytokines and oxidative stress[45] frequently called "Inflammatory storm".

Hypoglycemia can produce the same effects as acute hyperglycemia and independently affects mortality[46,47]. Sudden hyperglycemia as result of correcting hypoglycemia also leads to an enhancement of inflammation. Treatment of hypoglycemia should be slow and acute iatrogenic hyperglycemia should be avoided by rightful choice of dextrose delivery[48].

There is enough literature available to indicate that glucose variability can contribute to worse of the prognosis in ICU[47,49-51] even when glucose is kept in normal range[51]. Frequent fluctuations in blood glucose are a known risk factor for oxidative stress and the release of inflammatory cytokines. So, it seems advisable that glucose variability should be avoided[52]. Hyperglycemia interferes with the efficacy of other COVID-19 treatments. Glucocorticoid treatment has been associated with improved clinical outcomes in patients with COVID-19 but can induce and/or worsen hyperglycemia. In this case keeping normoglycemia may be challenging[53]. There is enough evidence that Tocilizumab (TCZ) in hyperglycemic patients failed to attenuate risk of severe outcomes of COVID-19 infection in both diabetic and non-diabetic patients[54].

Patients who are on existing hypoglycemia therapies before hospitalization adds to complexity of glucose management as well. Controlled diabetes before hospitalization as evidenced by low Hemoglobin A1c is favorable in predicting the insulin dosing, avoiding hyperglycemic excursions. Duration of therapeutic effects are shorter with agents like dipeptidyl-peptidase 4 inhibitors (DPP-4i),

sodium-glucose-transporter-2 inhibitors (SGLT-2i), pioglitazone, alpha-glucosidase inhibitors, metformin, and short-acting Glucagon-LikePeptide-1 Receptor Agonists (GLP-1RA) (exenatide and lixisenatide). The duration of effects is longer with agents like long-acting insulins long-acting insulins, GLP-1RA (dulaglutide, exenatide LA, liraglutide and semaglutide)[55]. Their action will add to that of insulin used during the treatment in ICU and must be considered in choosing the insulin dose.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to significantly reduce cardiovascular mortality and heart failure (HF) hospitalizations in patients with Type 2 diabetes mellitus (T2DM). Given these cardiac benefits and the low incidence of adverse events, SGLT2 inhibitors are strongly recommended as a treatment for HF, to slowdown the progression of chronic kidney disease (CKD), to decrease atherosclerosis related cardiac events in patients with T2DM[55-57]. Therefore, it has become a class of drugs widely used in clinical practice. In 2015, the Food and Drug Administration (FDA) warned that treatment with SGLT-2 inhibitors may increase the risk of EDKA [58]. Since then, several scientific papers were published reporting the association between these drugs and EDKA[59-61]. One third of COVID-19 patients reported gastrointestinal symptoms such as diarrhea, loss of appetite, nausea, and vomiting resulting in volume depletion. Persistent glycosuria in a subset of diabetic patients using SLGT2 inhibitors results in worsening of volume depletion. Insulin resistance in COVID-19 patients causes lipolysis leading to ketosis and theoretically can precipitate ketoacidosis[62]. The risk of mortality was four-fold higher in patients with T2D compared to nondiabetic cohorts. Patients receiving incretin-based therapies (GLP□1 receptor agonist and DDP□4 inhibitor) had decreased risk of hospitalization, mortality and respiratory complications compared to those patients not on these medications. A relative decrease in mortality was noted in patients when DDP-4 inhibitors are continued upon admission compared with patients where these were discontinued on admission[63].

Adequate hydration of the diabetic patient with COVID-19 is essential. Hyperhydration can induce ARDS further worsening lung damage. Attention should also be paid to serum Potassium (K+) levels as patients can be at major risk of hypokalemia, likely due to hyperaldosteronism associated with COVID-19 infection. Insulin treatment may worsen hypokalemia if not corrected in time. Spironolactone through its dual action as a mineralocorticoid receptor antagonist and an androgenic inhibitor, can help reducing risk of pulmonary edema and ARDS in COVID-19. Its potassium-sparing action by antagonizing mineralocorticoid receptors helps in minimizing the risk of hypokalemia during insulin treatment[64].

TREATMENT OF HYPERGLYCEMIA

Glycemic targets

There is a paucity of literature on glycemic control among COVID-19 patients hospitalized with hyperglycemia with or without diabetes. The limited literature suggests inadequate glycemia management due to lack of established guidelines regarding the most appropriate management of hyperglycemia in patients infected by COVID-19. Meanwhile, established guidelines in non-COVID patients can be adopted with slight modifications to manage hyperglycemia in critical and noncritical care settings to care of COVID-19 patients during this pandemic. Blood sugar goals in ICU have been an active area of research and debate. Intensive glycemic control (80-110 mg/dL) compared to moderate control (140-180 mg/dL) does not provide significant benefit and can be associated with increased harm [65,66]. In many studies glucose levels above 180 mg/dL were associated with increased risk of hospital complications. However, the lower limit for glycemia target is less well established and values greater than 110 mg/dL are generally recommended to minimize the risks of hypoglycemia[67]. Clinical guidelines recommend maintaining glucose levels between 140 and 180 mg/dL for most critically ill patients[68] and more stringent goals of 110-140 mg/dL may be reasonable for selected patients if they can be achieved without significant hypoglycemia[67-69]. However, blood glucose levels less than 200 mg/dL were also targeted in some patients with very labile and critical forms of disease, particularly since most were also on continuous enteral or parenteral nutrition and thus in a constant postprandial state[70].

Insulin therapy

Insulin is still the best glucose-lowering medication and recommended treatment for critically ill patients with COVID-19. The primary goals of a safe and effective insulin regimen include reducing contact frequency of health care workers with patient, reducing glucose variability, minimize risk of hypoglycemia, and optimal glycemic control[71]. There is no ideal protocol for the management of hyperglycemia in the critically ill patient and there is no clear evidence demonstrating the benefit of one protocol/algorithm *vs* any other. The implementation of any of these algorithms is prone to human errors and their success is greatly dependent on nursing education, clarity, and ease of understanding of instructions. To avoid errors in dosing, some institutions have adopted validated computerized protocols aiming to direct the nursing staff to adjust the insulin infusion rate[72,73]. Most important elements that increase success of any protocol using continuous insulin infusion are the rate adjustment

that considers the current and previous glucose value and the current rate of insulin infusion; rate adjustment that considers the rate of change from the previous reading, and frequency of glucose monitoring.

Hemodynamically unstable patients on vasopressors; those receiving parenteral nutrition, enteral nutrition with frequent rate adjustments; those on high-dose steroids; those in diabetic ketoacidosis or hyperosmolar hyperglycemic state will need intravenous insulin infusion and will need hourly blood glucose monitoring. For hemodynamically stable patients who are not meeting the above criteria; patients with stable insulin requirements (including those on enteral feeding); subcutaneous basal insulin regimens (standard basal-bolus, basal-bolus-correction, or basal-correction) can be used. The blood sugar testing can be every 4-6 h in this cohort of patients.

Once the patient is clinically stable, intravenous insulin can be transitioned to subcutaneous administration. Initial dose of subcutaneous insulin is usually 60-80% of intravenous insulin needed in previous 24 h. Overlap between intravenous and subcutaneous insulin is advised usually for 2-3 h to reduce risk of rebound hyperglycemia[74,75].

The degree of hyperglycemia and insulin resistance were associated with rapid elevations of inflammatory markers (high sensitivity CRP, Interleukin-6, procalcitonin, and D-dimers *etc*.,). Some institutions developed predictive algorithms based on artificial intelligence to predict the glucose values corresponding to changes in inflammatory marker levels. This allows timely dosing of insulin to prevent extreme blood glucose fluctuations[71,76].

The literature related to treatment of corticosteroid induced hyperglycemia is limited. The hyperglycemic effect of dexamethasone lasts up to 48 h and can be treated with addition of long-acting insulin preparations like glargine or detemir whose glucose lowering effect can last longer than 24 h[77,78]. Similarly, hyperglycemic peak of methylprednisolone develops after 4-6 h of administration. Insulin-neutral protamine Hagedorn (NPH) can be used as correctional insulin to target peak blood glucose elevation with methylprednisolone as the timeline of peak blood glucose elevation from methylprednisolone coincide with timeline of peak action of NPH insulin[79]. Therefore, clinicians who choose systemic corticosteroid treatment for their patients with COVID-19 should anticipate the occurrence of hyperglycemia and manage it based on the glycemic profile of the systemic corticosteroid. Addition of NPH insulin in the morning in addition to the existing insulin regimen can help with better glycemic control in setting of steroid use[71].

Protecting healthcare providers

Protecting healthcare providers is also an important part of taking care of COVID-19 patients. Caregivers must use appropriate personal protective equipment (PPE) while facing procurement challenges due to nationwide shortage of PPE. Every attempt should be made to minimize unnecessary contact with patients while not compromising on care. Bundling cares including glucose checks, therapy sessions, patient repositioning can reduce frequent healthcare personnel exposure. Intravenous drips that require frequent titration like insulin can be managed from outside the patient room through long tubing.

Finally, consideration should be given to changing how we measure blood glucose levels in the critically ill patient. For patients on intravenous insulin infusion, blood sugar monitoring recommended every 1-2 h, while those on subcutaneous insulin regimen, monitoring can be spaced every 4-6 h. Patients can also participate in f self-glucose checks through devices approved by FDA[80].

US FDA approved 2 continuous glucose monitors (CGM)--the Optiscanner 5000 and the GlucoScout--for remote glucose monitoring in hospitalized patients, but they are not commonly used. On April 8, 2020, FDA has excised "enforcement discretion" and temporarily sanctioned off label use and put out guidance on the potential use of CGM (Dexcom/Abbott FreeStyle Libre) in the hospital (but not for use in critically ill) during the current pandemic. In addition, studies based on use of CGM technology in hospitalized patients prior to COVID-19 pandemic have shown that several potential circumstances (both patient and management related) in the intensive care unit (*e.g*., MRI, use of vasoactive agents, acidosis, anasarca, dehydration, peripheral edema, hypotension, and dialysis) require careful use of this technology as they can negatively impact the accuracy of blood glucose monitoring. Hybrid models utilizing both point of care blood sugar testing and CGM a few times a day may be indicated in these situations to ensure readings are valid[81]. Published literature regarding the use of CGM in ICU patients with COVID-19 is limited[82].

CONCLUSION

Hyperglycemia is common and is associated with worse outcomes in COVID-19 patients admitted to ICU. The mechanism of hyperglycemia is explained by infection and treatment related factors. Established guidelines can be used as a roadmap but need to be tailored for individual patient needs. Though most current guidelines recommend targeting blood glucose levels < 180 mg/dL in critically ill patients, a target glucose range of 110-180 mg/ dL is acceptable when tailored to individual patient characteristics and clinical situation. Insulin is still the best glucose-lowering medication and should be

a treatment of choice for critically ill patients with COVID-19. Intravenous insulin infusion and subcutaneous basal insulin regimens (standard basal-bolus, basal-bolus-correction, or basal-correction) are the preferred for glycemic control hospitalized patients in critical and noncritical settings respectively. Bundling the glucose checks together with other nursing and therapist activities will minimize patient contact of health care workers and help to conserve PPE. Published literature regarding the use of CGM in ICU patients with COVID-19 is limited.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Rajesh Kethireddy 0000-0001-7501-1618; Darshan Gandhi 0000-0002-7079-450X; Asim Kichloo 0000-0003-4788-8572; Love Patel 0000-0002-6271-6376.

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REFERENCES

1 **COVID-19 statistics**. COVID-19 Weekly Epidemiological Update. [cited 23 March 2021]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports [DOI: 10.46234/ccdcw2020.032]
2 **Garg S**, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, Prill M, Chai SJ, Kirley PD, Alden NB, Kawasaki B, Yousey-Hindes K, Niccolai L, Anderson EJ, Openo KP, Weigel A, Monroe ML, Ryan P, Henderson J, Kim S, Como-Sabetti K, Lynfield R, Sosin D, Torres S, Muse A, Bennett NM, Billing L, Sutton M, West N, Schaffner W, Talbot HK, Aquino C, George A, Budd A, Brammer L, Langley G, Hall AJ, Fry A. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1-30, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 458-464 [PMID: 32298251 DOI: 10.15585/mmwr.mm6915e3]
3 **Muniyappa R**, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. *Am J Physiol Endocrinol Metab* 2020; **318**: E736-E741 [PMID: 32228322 DOI: 10.1152/ajpendo.00124.2020]
4 **Yang JK**, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, Sun GZ, Yang GR, Zhang XL, Wang L, Xu X, Xu XP, Chan JC. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med* 2006; **23**: 623-628 [PMID: 16759303 DOI: 10.1111/j.1464-5491.2006.01861.x]
5 **Rawshani A**, Kjölhede EA, Rawshani A, Sattar N, Eeg-Olofsson K, Adiels M, Ludvigsson J, Lindh M, Gisslén M, Hagberg E, Lappas G, Eliasson B, Rosengren A. Severe COVID-19 in people with type 1 and type 2 diabetes in Sweden: A nationwide retrospective cohort study. *Lancet Reg Health Eur* 2021; **4**: 100105 [PMID: 33969336 DOI: 10.1016/j.lanepe.2021.100105]
6 **Holman N**, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, Barron E, Bakhai C, Khunti K, Wareham NJ, Sattar N, Young B, Valabhji J. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol* 2020; **8**: 823-833 [PMID: 32798471 DOI: 10.1016/S2213-8587(20)30271-0]
7 **Nguyen NN**, Ho DS, Nguyen HS, Ho DKN, Li HY, Lin CY, Chiu HY, Chen YC. Preadmission use of antidiabetic medications and mortality among patients with COVID-19 having type 2 diabetes: A meta-analysis. *Metabolism* 2022; **131**: 155196 [PMID: 35367460 DOI: 10.1016/j.metabol.2022.155196]
8 **Wang S**, Ma P, Zhang S, Song S, Wang Z, Ma Y, Xu J, Wu F, Duan L, Yin Z, Luo H, Xiong N, Xu M, Zeng T, Jin Y. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study. *Diabetologia* 2020; **63**: 2102-2111 [PMID: 32647915 DOI: 10.1007/s00125-020-05209-1]
9 **Singh AK**, Singh R. Hyperglycemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19. *Diabetes Res Clin Pract* 2020; **167**: 108382 [PMID: 32853686 DOI: 10.1016/j.diabres.2020.108382]
10 **Apicella M**, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol* 2020; **8**: 782-792 [PMID: 32687793 DOI:

10.1016/S2213-8587(20)30238-2]
11 **Sardu C**, D'Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, Maggi P, Coppola N, Paolisso G, Marfella R. Outcomes in Patients With Hyperglycemia Affected by COVID-19: Can We Do More on Glycemic Control? *Diabetes Care* 2020; **43**: 1408-1415 [PMID: 32430456 DOI: 10.2337/dc20-0723]
12 **Donath MY**, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol* 2011; **11**: 98-107 [PMID: 21233852 DOI: 10.1038/nri2925]
13 **Esposito K**, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliaro L, Ceriello A, Giugliano D. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation* 2002; **106**: 2067-2072 [PMID: 12379575 DOI: 10.1161/01.cir.0000034509.14906.ae]
14 **Pradhan AD**, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001; **286**: 327-334 [PMID: 11466099 DOI: 10.1001/jama.286.3.327]
15 **Oswald GA**, Smith CC, Betteridge DJ, Yudkin JS. Determinants and importance of stress hyperglycaemia in non-diabetic patients with myocardial infarction. *Br Med J (Clin Res Ed)* 1986; **293**: 917-922 [PMID: 3094714 DOI: 10.1136/bmj.293.6552.917]
16 **Umpierrez GE**, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002; **87**: 978-982 [PMID: 11889147 DOI: 10.1210/jcem.87.3.8341]
17 **Hill MA**, Mantzoros C, Sowers JR. Commentary: COVID-19 in patients with diabetes. *Metabolism* 2020; **107**: 154217 [PMID: 32220611 DOI: 10.1016/j.metabol.2020.154217]
18 **Zhu L**, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, Lei F, Wang H, Xie J, Wang W, Li H, Zhang P, Song X, Chen X, Xiang M, Zhang C, Bai L, Xiang D, Chen MM, Liu Y, Yan Y, Liu M, Mao W, Zou J, Liu L, Chen G, Luo P, Xiao B, Zhang Z, Lu Z, Wang J, Lu H, Xia X, Wang D, Liao X, Peng G, Ye P, Yang J, Yuan Y, Huang X, Guo J, Zhang BH. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab* 2020; **31**: 1068-1077.e3 [PMID: 32369736 DOI: 10.1016/j.cmet.2020.04.021]
19 **Dungan KM**, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet* 2009; **373**: 1798-1807 [PMID: 19465235 DOI: 10.1016/S0140-6736(09)60553-5]
20 **Kim NY**, Ha E, Moon JS, Lee YH, Choi EY. Acute Hyperglycemic Crises with Coronavirus Disease-19: Case Reports. *Diabetes Metab J* 2020; **44**: 349-353 [PMID: 32347027 DOI: 10.4093/dmj.2020.0091]
21 **Cariou B**, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, Amadou C, Arnault G, Baudoux F, Bauduceau B, Borot S, Bourgeon-Ghittori M, Bourron O, Boutoille D, Cazenave-Roblot F, Chaumeil C, Cosson E, Coudol S, Darmon P, Disse E, Ducet-Boiffard A, Gaborit B, Joubert M, Kerlan V, Laviolle B, Marchand L, Meyer L, Potier L, Prevost G, Riveline JP, Robert R, Saulnier PJ, Sultan A, Thébaut JF, Thivolet C, Tramunt B, Vatier C, Roussel R, Gautier JF, Gourdy P; CORONADO investigators. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia* 2020; **63**: 1500-1515 [PMID: 32472191 DOI: 10.1007/s00125-020-05180-x]
22 **Hamming I**, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; **203**: 631-637 [PMID: 15141377 DOI: 10.1002/path.1570]
23 **Müller JA**, Groß R, Conzelmann C, Krüger J, Merle U, Steinhart J, Weil T, Koepke L, Bozzo CP, Read C, Fois G, Eiseler T, Gehrmann J, van Vuuren J, Wessbecher IM, Frick M, Costa IG, Breunig M, Grüner B, Peters L, Schuster M, Liebau S, Seufferlein T, Stenger S, Stenzinger A, MacDonald PE, Kirchhoff F, Sparrer KMJ, Walther P, Lickert H, Barth TFE, Wagner M, Münch J, Heller S, Kleger A. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nat Metab* 2021; **3**: 149-165 [PMID: 33536639 DOI: 10.1038/s42255-021-00347-1]
24 **Li H**, Tian S, Chen T, Cui Z, Shi N, Zhong X, Qiu K, Zhang J, Zeng T, Chen L, Zheng J. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. *Diabetes Obes Metab* 2020; **22**: 1897-1906 [PMID: 32469464 DOI: 10.1111/dom.14099]
25 **RECOVERY Collaborative Group**, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; **384**: 693-704 [PMID: 32678530 DOI: 10.1056/NEJMoa2021436]
26 **Mills E**, Devendra S. Steroid-induced hyperglycaemia in primary care. *London J Prim Care (Abingdon)* 2015; **7**: 103-106 [PMID: 26550039 DOI: 10.1080/17571472.2015.1082344]
27 **van Raalte DH**, Ouwens DM, Diamant M. Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? *Eur J Clin Invest* 2009; **39**: 81-93 [PMID: 19200161 DOI: 10.1111/j.1365-2362.2008.02067.x]
28 **Weinstein SP**, Wilson CM, Pritsker A, Cushman SW. Dexamethasone inhibits insulin-stimulated recruitment of GLUT4 to the cell surface in rat skeletal muscle. *Metabolism* 1998; **47**: 3-6 [PMID: 9440469 DOI: 10.1016/s0026-0495(98)90184-6]
29 **Vegiopoulos A**, Herzig S. Glucocorticoids, metabolism and metabolic diseases. *Mol Cell Endocrinol* 2007; **275**: 43-61 [PMID: 17624658 DOI: 10.1016/j.mce.2007.05.015]
30 **Boden G**, Shulman GI. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction. *Eur J Clin Invest* 2002; **32** Suppl 3: 14-23 [PMID: 12028371 DOI: 10.1046/j.1365-2362.32.s3.3.x]
31 **Delaunay F**, Khan A, Cintra A, Davani B, Ling ZC, Andersson A, Ostenson CG, Gustafsson J, Efendic S, Okret S. Pancreatic beta cells are important targets for the diabetogenic effects of glucocorticoids. *J Clin Invest* 1997; **100**: 2094-2098 [PMID: 9329975 DOI: 10.1172/JCI119743]
32 **van Raalte DH**, Nofrate V, Bunck MC, van Iersel T, Elassaiss Schaap J, Nässander UK, Heine RJ, Mari A, Dokter WH, Diamant M. Acute and 2-week exposure to prednisolone impair different aspects of beta-cell function in healthy men. *Eur J Endocrinol* 2010; **162**: 729-735 [PMID: 20124412 DOI: 10.1530/EJE-09-1034]
33 **Geer EB**, Islam J, Buettner C. Mechanisms of glucocorticoid-induced insulin resistance: focus on adipose tissue function

and lipid metabolism. *Endocrinol Metab Clin North Am* 2014; **43**: 75-102 [PMID: 24582093 DOI: 10.1016/j.ecl.2013.10.005]

34 **Lin LY**, Lin HC, Lee PC, Ma WY, Lin HD. Hyperglycemia correlates with outcomes in patients receiving total parenteral nutrition. *Am J Med Sci* 2007; **333**: 261-265 [PMID: 17505165 DOI: 10.1097/MAJ.0b013e3180536b26]

35 **Bjerke HS**, Shabot MM. Glucose intolerance in critically ill surgical patients: relationship to total parenteral nutrition and severity of illness. *Am Surg* 1992; **58**: 728-731 [PMID: 1456594]

36 **Ziegler TR**. Parenteral nutrition in the critically ill patient. *N Engl J Med* 2009; **361**: 1088-1097 [PMID: 19741230 DOI: 10.1056/NEJMct0806956]

37 **Laesser CI**, Cumming P, Reber E, Stanga Z, Muka T, Bally L. Management of Glucose Control in Noncritically Ill, Hospitalized Patients Receiving Parenteral and/or Enteral Nutrition: A Systematic Review. *J Clin Med* 2019; **8** [PMID: 31261760 DOI: 10.3390/jcm8070935]

38 **Pretty C**, Chase JG, Lin J, Shaw GM, Le Compte A, Razak N, Parente JD. Impact of glucocorticoids on insulin resistance in the critically ill. *Comput Methods Programs Biomed* 2011; **102**: 172-180 [PMID: 20801543 DOI: 10.1016/j.cmpb.2010.08.004]

39 **Tamez-Pérez HE**, Quintanilla-Flores DL, Rodríguez-Gutiérrez R, González-González JG, Tamez-Peña AL. Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. *World J Diabetes* 2015; **6**: 1073-1081 [PMID: 26240704 DOI: 10.4239/wjd.v6.i8.1073]

40 **Bratusch-Marrain PR**. Insulin-counteracting hormones: their impact on glucose metabolism. *Diabetologia* 1983; **24**: 74-79 [PMID: 6341138 DOI: 10.1007/BF00297384]

41 **Khoury N**, McGill JB. Reduction in insulin sensitivity following administration of the clinically used low-dose pressor, norepinephrine. *Diabetes Metab Res Rev* 2011; **27**: 604-608 [PMID: 21538777 DOI: 10.1002/dmrr.1212]

42 **Halter JB**, Beard JC, Porte D Jr. Islet function and stress hyperglycemia: plasma glucose and epinephrine interaction. *Am J Physiol* 1984; **247**: E47-E52 [PMID: 6377920 DOI: 10.1152/ajpendo.1984.247.1.E47]

43 **van Hooijdonk RT**, Binnekade JM, Bos LD, Horn J, Juffermans NP, Abu-Hanna A, Schultz MJ. Associations between bolus infusion of hydrocortisone, glycemic variability and insulin infusion rate variability in critically Ill patients under moderate glycemic control. *Ann Intensive Care* 2015; **5**: 34 [PMID: 26525053 DOI: 10.1186/s13613-015-0077-5]

44 **Stoudt K**, Chawla S. Don't Sugar Coat It: Glycemic Control in the Intensive Care Unit. *J Intensive Care Med* 2019; **34**: 889-896 [PMID: 30309291 DOI: 10.1177/0885066618801748]

45 **Guo W**, Li M, Dong Y, Zhou H, Zhang Z, Tian C, Qin R, Wang H, Shen Y, Du K, Zhao L, Fan H, Luo S, Hu D. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev* 2020; e3319 [DOI: 10.1002/dmrr.3319]

46 **Ceriello A**, Zarich SW, Testa R. Lowering glucose to prevent adverse cardiovascular outcomes in a critical care setting. *J Am Coll Cardiol* 2009; **53**: S9-13 [PMID: 19179217 DOI: 10.1016/j.jacc.2008.09.054]

47 **Bellaver P**, Schaeffer AF, Dullius DP, Viana MV, Leitão CB, Rech TH. Association of multiple glycemic parameters at intensive care unit admission with mortality and clinical outcomes in critically ill patients. *Sci Rep* 2019; **9**: 18498 [PMID: 31811218 DOI: 10.1038/s41598-019-55080-3]

48 **Borzì V**, Frasson S, Gussoni G, Di Lillo M, Gerloni R, Augello G, Gulli G, Ceriello A, Solerte B, Bonizzoni E, Fontanella A; Research Department of FADOI. Risk factors for hypoglycemia in patients with type 2 diabetes, hospitalized in internal medicine wards: Findings from the FADOI-DIAMOND study. *Diabetes Res Clin Pract* 2016; **115**: 24-30 [PMID: 27242119 DOI: 10.1016/j.diabres.2016.01.020]

49 **Ceriello A**, Novials A, Ortega E, La Sala L, Pujadas G, Testa R, Bonfigli AR, Esposito K, Giugliano D. Evidence that hyperglycemia after recovery from hypoglycemia worsens endothelial function and increases oxidative stress and inflammation in healthy control subjects and subjects with type 1 diabetes. *Diabetes* 2012; **61**: 2993-2997 [PMID: 22891214 DOI: 10.2337/db12-0224]

50 **Kulkarni H**, Bihari S, Prakash S, Huckson S, Chavan S, Mamtani M, Pilcher D. Independent Association of Glucose Variability With Hospital Mortality in Adult Intensive Care Patients: Results From the Australia and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Binational Registry. *Crit Care Explor* 2019; **1**: e0025 [PMID: 32166267 DOI: 10.1097/CCE.0000000000000025]

51 **Takahashi H**, Iwahashi N, Kirigaya J, Kataoka S, Minamimoto Y, Gohbara M, Abe T, Okada K, Matsuzawa Y, Konishi M, Maejima N, Hibi K, Kosuge M, Ebina T, Tamura K, Kimura K. Glycemic variability determined with a continuous glucose monitoring system can predict prognosis after acute coronary syndrome. *Cardiovasc Diabetol* 2018; **17**: 116 [PMID: 30121076 DOI: 10.1186/s12933-018-0761-5]

52 **Ceriello A**, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. *Lancet Diabetes Endocrinol* 2019; **7**: 221-230 [PMID: 30115599 DOI: 10.1016/S2213-8587(18)30136-0]

53 **Berton AM**, Prencipe N, Giordano R, Ghigo E, Grottoli S. Systemic steroids in patients with COVID-19: pros and contras, an endocrinological point of view. *J Endocrinol Invest* 2021; **44**: 873-875 [PMID: 32514902 DOI: 10.1007/s40618-020-01325-2]

54 **Marfella R**, Paolisso P, Sardu C, Bergamaschi L, D'Angelo EC, Barbieri M, Rizzo MR, Messina V, Maggi P, Coppola N, Pizzi C, Biffi M, Viale P, Galié N, Paolisso G. Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients. *Diabetes Metab* 2020; **46**: 403-405 [PMID: 32447102 DOI: 10.1016/j.diabet.2020.05.005]

55 **Prattichizzo F**, La Sala L, Rydén L, Marx N, Ferrini M, Valensi P, Ceriello A. Glucose-lowering therapies in patients with type 2 diabetes and cardiovascular diseases. *Eur J Prev Cardiol* 2019; **26**: 73-80 [PMID: 31766918 DOI: 10.1177/2047487319880040]

56 **Scheen AJ**. Challenging 2019 ESC guidelines for the management of type 2 diabetes. *Diabetes Metab* 2020; **46**: 181-185 [PMID: 31707046 DOI: 10.1016/j.diabet.2019.10.006]

57 **Srinivas N**, Sarnaik MK, Modi S, Pisipati Y, Vaidya S, Syed Gaggatur N, Sange AH, Sange I. Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors: Delving Into the Potential Benefits of Cardiorenal Protection Beyond the Treatment of Type-2 Diabetes Mellitus. *Cureus* 2021; **13**: e16868 [PMID: 34513443 DOI: 10.7759/cureus.16868]

58 **US Food and Drug Administration**. Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may

result in a serious condition of too much acid in the blood [DOI: 10.1037/e378952004-001]
59 **Barski L**, Eshkoli T, Brandstaetter E, Jotkowitz A. Euglycemic diabetic ketoacidosis. *Eur J Intern Med* 2019; **63**: 9-14 [PMID: 30910328 DOI: 10.1016/j.ejim.2019.03.014]
60 **Somagutta MR**, Agadi K, Hange N, Jain MS, Batti E, Emuze BO, Amos-Arowoshegbe EO, Popescu S, Hanan S, Kumar VR, Pormento K. Euglycemic Diabetic Ketoacidosis and Sodium-Glucose Cotransporter-2 Inhibitors: A Focused Review of Pathophysiology, Risk Factors, and Triggers. *Cureus* 2021; **13**: e13665 [PMID: 33824816 DOI: 10.7759/cureus.13665]
61 **Alhemeiri M**, Alseddeeqi E. Euglycemic Diabetic Ketoacidosis after Discontinuing SGLT2 Inhibitor. *Case Rep Endocrinol* 2022; **2022**: 4101975 [PMID: 35282610 DOI: 10.1155/2022/4101975]
62 **Batista DV**, Vieira CAFA, Costa TA, Lima EG. COVID-19-associated euglycemic diabetic ketoacidosis in a patient with type 2 diabetes on SGLT2 inhibitor: a case report. *Diabetol Int* 2021; **12**: 313-316 [PMID: 33133998 DOI: 10.1007/s13340-020-00473-3]
63 **Nyland JE**, Raja-Khan NT, Bettermann K, Haouzi PA, Leslie DL, Kraschnewski JL, Parent LJ, Grigson PS. Diabetes, Drug Treatment, and Mortality in COVID-19: A Multinational Retrospective Cohort Study. *Diabetes* 2021; **70**: 2903-2916 [PMID: 34580086 DOI: 10.2337/db21-0385]
64 **Kotfis K**, Lechowicz K, Drożdżal S, Niedźwiedzka-Rystwej P, Wojdacz TK, Grywalska E, Biernawska J, Wiśniewska M, Parczewski M. COVID-19-The Potential Beneficial Therapeutic Effects of Spironolactone during SARS-CoV-2 Infection. *Pharmaceuticals (Basel)* 2021; **14** [PMID: 33477294 DOI: 10.3390/ph14010071]
65 **Alhazzani W**, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, Oczkowski S, Levy MM, Derde L, Dzierba A, Du B, Aboodi M, Wunsch H, Cecconi M, Koh Y, Chertow DS, Maitland K, Alshamsi F, Belley-Cote E, Greco M, Laundy M, Morgan JS, Kesecioglu J, McGeer A, Mermel L, Mammen MJ, Alexander PE, Arrington A, Centofanti JE, Citerio G, Baw B, Memish ZA, Hammond N, Hayden FG, Evans L, Rhodes A. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Crit Care Med* 2020; **48**: e440-e469 [PMID: 32224769 DOI: 10.1097/CCM.0000000000004363]
66 **NICE-SUGAR Study Investigators**, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive vs conventional glucose control in critically ill patients. *N Engl J Med* 2009; **360**: 1283-1297 [DOI: 10.1056/nejmoa0810625]
67 **Van den Berghe G**, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; **354**: 449-461 [PMID: 16452557 DOI: 10.1056/NEJMoa052521]
68 **Farrokhi F**, Smiley D, Umpierrez GE. Glycemic control in non-diabetic critically ill patients. *Best Pract Res Clin Endocrinol Metab* 2011; **25**: 813-824 [PMID: 21925080 DOI: 10.1016/j.beem.2011.05.004]
69 **Pérez A**, Ramos A, Carreras G. Insulin Therapy in Hospitalized Patients. *Am J Ther* 2020; **27**: e71-e78 [PMID: 31833876 DOI: 10.1097/MJT.0000000000001078]
70 **Krinsley JS**, Preiser JC, Hirsch IB. Safety and efficacy of personalized glycemic control in critically ill patients: A 2-year before and after interventional trial. *Endocr Pract* 2017; **23**: 318-330 [PMID: 27967228 DOI: 10.4158/EP161532.OR]
71 **Gianchandani R**, Esfandiari NH, Ang L, Iyengar J, Knotts S, Choksi P, Pop-Busui R. Managing Hyperglycemia in the COVID-19 Inflammatory Storm. *Diabetes* 2020; **69**: 2048-2053 [PMID: 32778570 DOI: 10.2337/dbi20-0022]
72 **Hamdy O**, Gabbay RA. Early Observation and Mitigation of Challenges in Diabetes Management of COVID-19 Patients in Critical Care Units. *Diabetes Care* 2020; **43**: e81-e82 [PMID: 32444458 DOI: 10.2337/dc20-0944]
73 **Moghissi ES**, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, Inzucchi SE, Ismail-Beigi F, Kirkman MS, Umpierrez GE; American Association of Clinical Endocrinologists; American Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009; **32**: 1119-1131 [PMID: 19429873 DOI: 10.2337/dc09-9029]
74 **Pérez Pérez A**, Conthe Gutiérrez P, Aguilar Diosdado M, Bertomeu Martínez V, Galdos Anuncibay P, García de Casasola G, Gomis de Bárbara R, Palma Gamiz JL, Puig Domingo M, Sánchez Rodríguez A. [Hospital management of hyperglycemia]. *Med Clin (Barc)* 2009; **132**: 465-475 [PMID: 19298976 DOI: 10.1016/j.medcli.2009.02.001]
75 **Furnary AP**, Braithwaite SS. Effects of outcome on in-hospital transition from intravenous insulin infusion to subcutaneous therapy. *Am J Cardiol* 2006; **98**: 557-564 [PMID: 16893717 DOI: 10.1016/j.amjcard.2006.02.065]
76 **Ramos A**, Zapata L, Vera P, Betbese AJ, Pérez A. Transition from intravenous insulin to subcutaneous long-acting insulin in critical care patients on enteral or parenteral nutrition. *Endocrinol Diabetes Nutr* 2017; **64**: 552-556 [PMID: 29179857 DOI: 10.1016/j.endinu.2017.08.005]
77 **Zhou K**, Al-Jaghbeer MJ, Lansang MC. Hyperglycemia management in hospitalized patients with COVID-19. *Cleve Clin J Med* 2020 [DOI: 10.3949/ccjm.87a.ccc012]
78 **Low Wang CC**, Draznin B. Practical approach to management of inpatient hyperglycemia in select patient populations. *Hosp Pract (1995)* 2013; **41**: 45-53 [PMID: 23680736 DOI: 10.3810/hp.2013.04.1025]
79 **Owens DR**, Bolli GB. Beyond the era of NPH insulin--long-acting insulin analogs: chemistry, comparative pharmacology, and clinical application. *Diabetes Technol Ther* 2008; **10**: 333-349 [PMID: 18715209 DOI: 10.1089/dia.2008.0023]
80 **Donner T**, Sarkar S. Insulin - Pharmacology, Therapeutic Regimens, and Principles of Intensive Insulin Therapy. [Updated 23 Feb 2019]. In: Feingold KR, Anawalt B, Boyce A, et al, editors. Endotext [DOI: 10.2337/db18-1054-p]
81 **Trajanoski Z**, Brunner GA, Gfrerer RJ, Wach P, Pieber TR. Accuracy of home blood glucose meters during hypoglycemia. *Diabetes Care* 1996; **19**: 1412-1415 [PMID: 8941473 DOI: 10.2337/diacare.19.12.1412]
82 **Xu H**, Huang S, Qiu C, Liu S, Deng J, Jiao B, Tan X, Ai L, Xiao Y, Belliato M, Yan L. Monitoring and Management of Home-Quarantined Patients With COVID-19 Using a WeChat-Based Telemedicine System: Retrospective Cohort Study. *J Med Internet Res* 2020; **22**: e19514 [PMID: 32568727 DOI: 10.2196/19514]

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MINIREVIEWS

Medicinal nicotine in COVID-19 acute respiratory distress syndrome, the new corticosteroid

Farrukh Ahmad

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Farrukh Ahmad, Department of Internal Medicine, Saint Vincent Hospital, Worcester, MA 01608, United States

Corresponding author: Farrukh Ahmad, MD, Staff Physician, Department of Internal Medicine, Saint Vincent Hospital, 123, Summer Street, Worcester, MA 01608, United States.
farrukh2.ahmad@stvincenthospital.com

Abstract

The cholinergic anti-inflammatory pathway (CAP) refers to the anti-inflammatory effects mediated by the parasympathetic nervous system. Existence of this pathway was first demonstrated when acetylcholinesterase inhibitors showed benefits in animal models of sepsis. CAP functions *via* the vagus nerve. The systemic anti-inflammatory effects of CAP converges on the α7 nicotinic acetylcholine receptor on splenic macrophages, leading to suppression of pro-inflammatory cytokines and simultaneous stimulation of anti-inflammatory cytokines, including interleukin 10. CAP offers a novel mechanism to mitigate inflammation. Electrical vagal nerve stimulation has shown benefits in patients suffering from rheumatoid arthritis. Direct agonists like nicotine and GTS-1 have also demonstrated anti-inflammatory properties in models of sepsis and acute respiratory distress syndrome, as have acetylcholinesterase inhibitors like Galantamine and Physostigmine. Experience with coronavirus disease 2019 (COVID-19) induced acute respiratory distress syndrome indicates that immunomodulators have a protective role in patient outcomes. Dexamethasone is the only medication currently in use that has shown to improve clinical outcomes. This is likely due to the suppression of what is referred to as a cytokine storm, which is implicated in the lethality of viral pneumonia. Nicotine transdermal patch activates CAP and harvests its anti-inflammatory potential by means of an easily administered depot delivery mechanism. It could prove to be a promising, safe and inexpensive additional tool in the currently limited armamentarium at our disposal for management of COVID-19 induced acute hypoxic respiratory failure.

Key Words: COVID-19; Acute respiratory distress syndrome; Medicinal nicotine; Cholinergic anti-inflammatory pathway; Corticosteroid

Core Tip: Cholinergic anti-inflammatory pathway is novel pathway of the inflammatory reflex. Activation of this pathway can suppress maladaptive inflammatory response seen in coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (ARDS). Nicotine is a potent activator of this pathway and may offer benefits in the management of COVID-19 ARDS, *via* immune suppressive effects similar to dexamethasone.

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INTRODUCTION

A dramatic inflammatory response is a common manifestation of severe coronavirus disease 2019 (COVID-19) infection[1]. The purpose of such an inflammatory surge, under normal conditions, is to allow the body to attack, constrain, and kill invading organisms. However, that same inflammatory cascade has negative downstream consequences which can cause direct damage to the host.

Sepsis is the consequence of this hyperactive immune state, most commonly due to a poorly controlled infection or significant tissue injury[2]. The unbalanced immune reaction perpetuates further injury. Neutrophils are recruited and infiltrate the lungs where they undergo apoptosis, further causing tissue damage leading to the development of shock and acute respiratory distress syndrome (ARDS)[3]. These cells and the molecules they release are a potent force designed to neutralise pathogens, but cause significant collateral damage in the process. Another casualty of this inflammatory dysregulation is vasodilatation and microvascular thrombi that lead to poor tissue perfusion, further perpetuating the cycle of destruction. This self-perpetuating cycle of tissue damage and release of pro-inflammatory cytokines[4,5] causes further dysregulation of the immune system.

Cytokine is a term given to molecules that carry out inflammatory responses of the immune system, each having their respective receptors distributed across the body. They orchestrate most, if not all, of the consequences of sepsis. This phenomenon is now dubbed a 'cytokine storm'[6] and has been particularly devastating in the current pandemic of COVID-19 infection[7,8].

In recent years many immune modulators have been administered to mitigate sepsis and shock but with limited success in changing the disease course, morbidity, and mortality outcomes. Tocilizumab was used widely during the initial phase of the COVID-19 pandemic in ICUs across the world. But it failed to demonstrate mortality benefits[9]. The reason could partly be explained by the fact that it has a narrow scope of action, only blocking the interleukin (IL)-6 receptor. Upregulation of alternate pathways of inflammation likely are at play. A mechanism to reduce the global immune response is required to suppress collectively the molecules perpetuating inflammation. Corticosteroids are touted as one of the strongest tools in our arsenal to achieve such a goal. Dexamethasone is the only drug we have at our disposal that has shown mortality benefits during the COVID-19 pandemic[10]. Although corticosteroids are considered to globally suppress inflammation, patients are still succumbing to this coronavirus infection despite high doses administered over several days. Other medications for global suppression of inflammation are needed.

One potential pathway that may hold promise in achieving global suppression of the immune system is the cholinergic anti-inflammatory pathway (CAP). CAP is a component of the inflammatory reflex, mediated by the cholinergic nervous system and augmenting its tone has been shown to decrease inflammation in both human and animal models. The first evidence of the cholinergic system having immunomodulatory properties dates back to 1987. Zabrodskiĭ[11] showed that Armin, an irreversible acetylcholinesterase inhibitor reduces mortality in animal models of sepsis. It was first recognized in humans when patients with Rheumatoid Arthritis and drug-resistant epilepsy underwent Vagal Nerve stimulation to ameliorate their recurrent seizures. After initiation of Vagal Nerve stimulation, patients incidentally reported improvement in joint pains[12].

INFLAMMATORY REFLEX

The inflammatory reflex[13] is a central nervous system mediated reflex arc that modulates the immune system. Like other prototypical reflexes, it has an incoming and outgoing arm. Instead of a sensory input that begets a motor response, this circuit senses inflammation and responds with appropriate inflammatory inhibition to reestablish homeostasis. The afferent arm is activated by the products of sterile or infectious inflammation.

The efferent arm is termed the CAP which, through diverse mechanisms, suppresses inflammation [14]. Both the afferent and efferent limbs of the reflex are transmitted predominantly by the vagus nerves. Tracey KJ team[15,16] has conducted extensive research in the potential therapeutic application of vagal stimulation in modulating the immune system, thereby providing initial major contributions to mapping this pathway (Figure 1)[17,18].

THE AFFERENT LIMB

We are more familiar with the afferent limb of this pathway[19], which plays a role in triggering the mammalian febrile response. Disrupting the afferent arm, for example with a subdiaphragmatic vagotomy, prevented IL-1β induced fever in mice[20]. The afferent limb is activated by pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α) and IL-1β, neuropeptide Y and prostaglandins. Vagal fibers innervating visceral organs like the lungs and gastrointestinal tract demonstrate sensitivity to IL-1β. Furthermore, the nodose ganglion expresses Toll-like receptors[18] which are directly stimulated by pathogen associated molecular patterns such as those found on bacterial cell walls[21]. Area postrema directly expresses proinflammatory cytokine receptors[22]. The afferent limb converges on the nucleus tractus solitarius (NTS), the primary central vagal afferent nucleus. Interneurons connect the NTS to the dorsal motor nucleus of vagus (DMV), which are the primary efferent nuclei of the vagus nerve (Figure 2).

THE EFFERENT LIMB/CAP

The systemic anti-inflammatory effects of CAP are thought to exert its effects *via* the spleen[23,24]. The efferent limb originates at the DMV, the motor nuclei of the vagus nerve. Motor signals are transmitted *via* cholinergic fibers down the vagus nerve to mount an anti-inflammatory response, reestablishing homeostasis. The vagus nerve does not directly innervate the spleen like it does with other visceral organs such as the heart, intestines and liver. So to realize a response from splenic lymphocytes and macrophages, the splenic nerve functions as an intermediary. The efferent pathway is as follows: Cholinergic fibers from the vagus nerve innervate the celiac ganglion; Noradrenergic neurons from the celiac ganglion, *via* the splenic nerve, innervate the spleen, and by releasing norepinephrine stimulate β -2 adrenergic receptors on choline-acetyltransferase positive T cells that reside in the spleen; Activation of the β-2 adrenergic receptors with norepinephrine induces the release of acetylcholine (ACh) from these splenic T cells; ACh then activates α-7 nicotinic acetylcholinergic receptor (α7nAChr) on the splenic macrophages; Activation of α7nAChr causes downstream inhibition of the NF-Kappa β pathway and subsequent suppression of pro-inflammatory cytokines. It also induces the release of anti-inflammatory molecules by activating the JAK2-STAT3 pathway[13,14].

Iatrogenic activation of the efferent limb of the inflammatory reflex, irrespective of the modality, has demonstrated anti-inflammatory effects in diverse pathological conditions[15] (Figure 3).

HARVESTING THE POTENTIAL OF CAP

Augmenting the CAP offers an effective tool in controlling maladaptive inflammatory responses[25,26]. Modulating the cholinergic tone, irrespective of the modality used, has been shown to suppress inflammation[27]. Direct electrical stimulation of the vagus nerve aims to trigger an action potential that consequently activate this pathway downstream. Vagal nerve stimulation has been shown to suppress inflammation and decrease serum levels of TNF, IL-1β and IL-6[28-32]. Pharmacological modalities to increase the activity of CAP have also yielded similar results. Direct agonists of α7nAChr like the pharmacological agent nicotine have demonstrated anti-inflammatory properties[33-39]. Ongoing trials using GTS-1, a specific α7nAChr agonist, are being conducted in human models of sepsis[40,41]. Another feasible pharmacological strategy is to use inhibitors of acetylcholinesterase to delay degradation of ACh and, thus, enhance the tone of this pathway[42-47]. It must be noted that acetylcholinesterase inhibitors require a functional vagal pathway and fail to demonstrate anti-inflammatory effects in vagotomized animals[48].

Practical modalities for bedside manipulation of CAP is limited. Vagal nerve stimulation has limited feasibility for critically ill septic patients. GTS-1, an α7nAChr agonist, is in an experimental phase acetylcholinesterase inhibitors like physostigmine increase cholinergic tone systemically and cause undesirable muscarinic side effects. That currently leaves nicotine as the only feasible and medically available potentiator of CAP as an agonist of α7nAChr. As such, it has demonstrated anti-inflammatory properties in ulcerative colitis and models of human sepsis[33,34].

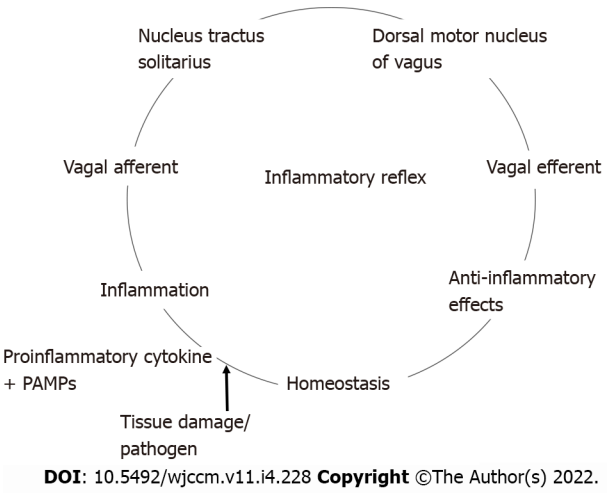

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Figure 1 The inflammatory reflex. The above graphic demonstrates the inflammatory reflex. The afferent limb is activated by pro-inflammatory cytokines like tumor necrosis factor and interleukin 1βor by pathogen-associated molecular patterns *via* Toll-like receptors. The afferent limb connects to the nucleus tractus solitarius (NTS), the primary vagal afferent nuclei. The mammalian febrile response is initiated at the NTS. Interneurons connect NTS to dorsal motor nucleus of vagus (DMV) incoming signals. The DMV is the primary efferent nuclei of the vagus nerve. This efferent signal initiates an anti-inflammatory effect, reestablishing homeostasis. PAMPS: pathogen-associated molecular patterns.

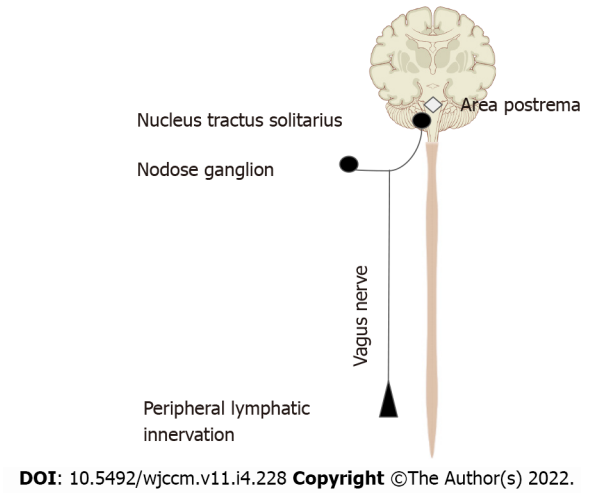

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Figure 2 Afferent limb of the inflammatory reflex. This figure demonstrates the mechanisms by which the vagus nerve senses inflammation. Vagal sensory neurons directly express receptors for various pro-inflammatory cytokines such as, tumor necrosis factor, interleukin 1β, neuropeptide Y and prostaglandins. Vagal fibers innervating the lymphatic system demonstrate sensitivity to interleukin-1β. In addition, the nodose ganglion has been shown to express Toll-like receptors. Area postrema directly expresses proinflammatory cytokine receptors[22]. The signal is transmitted *via* the vagal afferents to the bilateral nucleus tractus solitarius, the primary vagal afferent nucleus[19].

NICOTINE

Humans have been using nicotine since prehistoric times[49], mostly in the form of tobacco. Even though it is widely acknowledged that smoking or chewing tobacco is unequivocally injurious to health, nicotine by itself has not been shown to be harmful. Medicinal nicotine has demonstrated potent anti-inflammatory properties while being safe and possessing a low side-effect profile in short term administration. Nicotine administration in animal models of ARDS and sepsis have shown improved survival with lower serum inflammatory markers and reduced migration of neutrophils[36-38]. Human models of lipopolysaccharide (LPS) induced sepsis show faster resolution of sepsis[33]. Nicotine has also shown anti-inflammatory effects in patients with ulcerative colitis[34,35].

Nicotine patches are well suited as a modality for increasing nicotinic cholinergic receptor activity, and possess the following advantages: Nicotine does not have any underlying muscarinic effects and, therefore, lack concerns of increasing airway secretions that occur with acetylcholinesterase inhibitors like galantamine or physostigmine; Using a nicotine patch achieves therapeutic levels of nicotine in the blood within 4-6 h, offering a rapid drug onset profile[50]; The active drug nicotine has a short half-life of 2 h. Its metabolite, cotinine, has minimal biological activity[51]. This allows for rapid withdrawal of

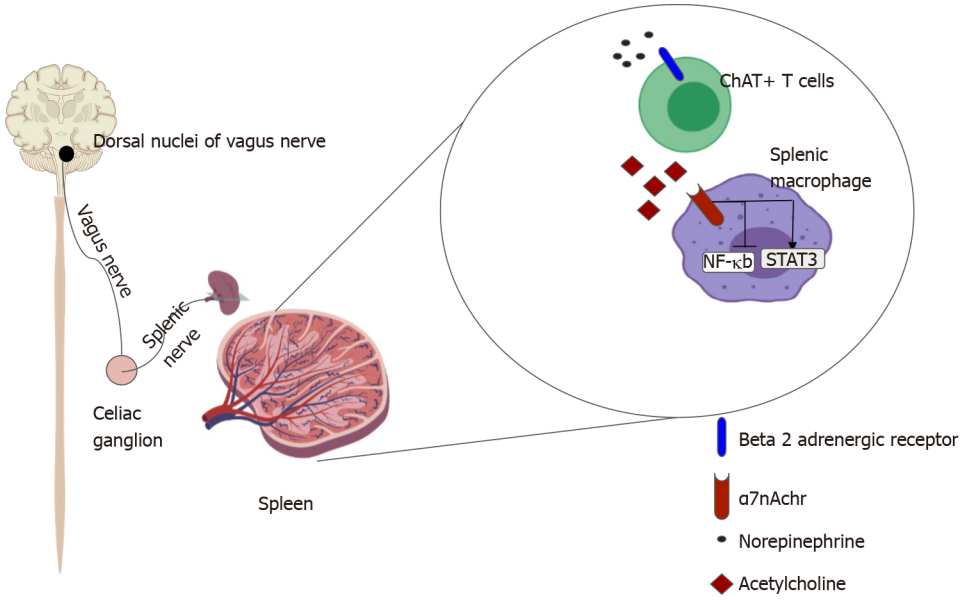

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Figure 3 Efferent limb of the inflammatory reflex. Signal from the dorsal nuclei of vagus is transmitted *via* cholinergic fibers of the vagus nerve to the celiac ganglion. Noradrenergic neurons from the celiac ganglion *via* the splenic nerve innervate the spleen. Choline-acetyltransferase positive T cells that reside in the spleen express β-2 adrenergic receptors. Activation of this receptor causes the release of Acetylcholine which binds to the α-7 nicotinic acetylcholinergic receptor on splenic macrophages causing the inhibition of NF-kappa β pathway and upregulation of STAT3, ultimately suppressing inflammation[16,23].

treatment if necessary. Most acetylcholinesterase inhibitors have a much longer half-life; The depot mechanism of drug delivery for the nicotine patch allows for a rapid onset, prolonged drug delivery during the duration of application, with a quick withdrawal time; The 24-h depot administration avoids repeated administrations and minimized nursing exposure for delivery of the medication; Ease of administration; Nicotine transdermal patches are widely used as clinical medication for nicotine replacement therapy in both the hospital and outpatient settings; There are minimal drug-drug interactions[52].

IN-HOSPITAL SAFETY DATA ON NICOTINE REPLACEMENT THERAPY

The data on the safety of nicotine on non-smoking patients in an inpatient setting is limited.

Safety data on current or former smokers receiving nicotine replacement therapy in ICU settings and hospital settings fail to demonstrate an increase in adverse events[53-58]. Potential side effects of medicinal nicotine administration are few. They may include hypertension and tachyarrhythmias. Rash at the site of the nicotine patch application has been described. Patients with end stage renal disease have a decreased rate of nicotine metabolism so the safety profile for patients on dialysis is uncertain[59, 60].

CONCLUSION

The current ongoing pandemic of severe acute respiratory syndrome coronavirus 2 proves a new challenge for the medical community. Owing to the tremendous ingenuity and grit demonstrated by teams across the globe, we now have several promising vaccines which demonstrate remarkable efficacy. However, we are yet to develop a similarly promising tool for management of severe infection which is still very prevalent. Consequently, patients continue to succumb in ICUs across the world to the COVID-19 acute hypoxic respiratory failure and septic shock. Several touted treatment modalities during this pandemic have emerged only to quickly fall out of favour due to lack of documented benefit, including Hydroxychloroquine, Tocilizumab, and transfusion of convalescent plasma. Management for COVID-19 pneumonia, at present, comprises two parallel approaches. Remdesivir or other upcoming potential antivirals, to control viral replication and immunomodulators like dexamethasone to control the maladaptive immune response. Dexamethasone has shown utility in reducing mortality in patients with COVID-19 induced acute hypoxic respiratory failure. However, despite its use early in the course of the disease, many still deteriorate, requiring increased levels of oxygen support or even mechanical ventilation. Patients continue to die even with dexamethasone as

part of their pharmacological regimen. Better modalities are needed to further improve patient outcomes. The hope is bringing to the attention of the medical community a fairly well studied, yet paradoxically unknown pathway of global immune modulation.

CAP is a part of a neural reflex termed the inflammatory reflex. It plays a central role in the neural control of inflammation. Inflammatory reflex has an afferent limb that senses systemic inflammation *via* the vagus nerve. This signal is relayed to the NTS, the sensory vagal nucleus in the central nervous system. Interneurons then communicate to the DMV, which is the primary motor nucleus of the vagus nerve. The efferent limb of the inflammatory reflex originates from the DMV *via* motor vagal fibers and trigger various anti-inflammatory mechanisms, reestablishing homeostasis. The systemic anti-inflammatory effects of CAP is thought to be due to suppression of pro-inflammatory cytokines from splenic macrophages. Nicotinic ACh receptors on these splenic macrophages are the point of convergence of this pathway's systemic anti-inflammatory effect. This translates to survival benefits with lower levels of serum TNF-α, and IL-6, along with reduced migration of neutrophils in models of sepsis. The potential of augmenting this pathway to mitigate inflammation has been demonstrated in several animal and human studies.

Nicotine is a commonly used molecule that is a potent activator of α7nAChr, with demonstrated anti-inflammatory effects. Animal models of sepsis show improved survival with nicotine administration. Nicotine patch has been studied in the human model of LPS induced sepsis and demonstrated faster resolution of inflammation compared to controls. Nicotine transdermal patch has been used for decades as a means of nicotine delivery for nicotine replacement therapy in active tobacco users and has demonstrated a favorable safety profile. Thus, nicotine transdermal patch may offer a readily available tool with significant benefit-to-risk ratio in the setting of COVID-19 induced acute hypoxic respiratory failure.

With patients suffering daily across the globe with COVID ARDS, there is little downside to the administration of this relatively inexpensive, widely available medication with a high safety. There is presently a lack of literature regarding the use of nicotine in COVID-19 ARDS patients and it must be further studied first before being applied routinely.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Farrukh Ahmad 0000-0003-0004-441X.

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REFERENCES

1 **Hojyo S**, Uchida M, Tanaka K, Hasebe R, Tanaka Y, Murakami M, Hirano T. How COVID-19 induces cytokine storm with high mortality. *Inflamm Regen* 2020; **40**: 37 [PMID: 33014208 DOI: 10.1186/s41232-020-00146-3]
2 **Delano MJ**, Ward PA. The immune system's role in sepsis progression, resolution, and long-term outcome. *Immunol Rev* 2016; **274**: 330-353 [PMID: 27782333 DOI: 10.1111/imr.12499]
3 **Yang SC**, Tsai YF, Pan YL, Hwang TL. Understanding the role of neutrophils in acute respiratory distress syndrome. *Biomed J* 2021; **44**: 439-446 [PMID: 33087299 DOI: 10.1016/j.bj.2020.09.001]
4 **Chaudhry H**, Zhou J, Zhong Y, Ali MM, McGuire F, Nagarkatti PS, Nagarkatti M. Role of cytokines as a double-edged sword in sepsis. *In Vivo* 2013; **27**: 669-684 [PMID: 24292568]
5 **Schulte W**, Bernhagen J, Bucala R. Cytokines in sepsis: potent immunoregulators and potential therapeutic targets--an updated view. *Mediators Inflamm* 2013; **2013**: 165974 [PMID: 23853427 DOI: 10.1155/2013/165974]
6 **Tisoncik JR**, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. *Microbiol Mol Biol Rev* 2012; **76**: 16-32 [PMID: 22390970 DOI: 10.1128/MMBR.05015-11]

7 **Caricchio R**, Gallucci M, Dass C, Zhang X, Gallucci S, Fleece D, Bromberg M, Criner GJ; Temple University COVID-19 Research Group. Preliminary predictive criteria for COVID-19 cytokine storm. *Ann Rheum Dis* 2021; **80**: 88-95 [PMID: 32978237 DOI: 10.1136/annrheumdis-2020-218323]

8 **Tay MZ**, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020; **20**: 363-374 [PMID: 32346093 DOI: 10.1038/s41577-020-0311-8]

9 **Huang E**, Jordan SC. Tocilizumab for Covid-19 - The Ongoing Search for Effective Therapies. *N Engl J Med* 2020; **383**: 2387-2388 [PMID: 33296566 DOI: 10.1056/NEJMe2032071]

10 **Matthay MA**, Thompson BT. Dexamethasone in hospitalised patients with COVID-19: addressing uncertainties. *Lancet Respir Med* 2020; **8**: 1170-1172 [PMID: 33129421 DOI: 10.1016/S2213-2600(20)30503-8]

11 **Zabrodskiĭ PF**. [Effect of armin on nonspecific resistance factors of the body and on the primary humoral immune response]. *Farmakol Toksikol* 1987; **50**: 57-60 [PMID: 3549354]

12 **Bonaz B**, Picq C, Sinniger V, Mayol JF, Clarençon D. Vagus nerve stimulation: from epilepsy to the cholinergic anti-inflammatory pathway. *Neurogastroenterol Motil* 2013; **25**: 208-221 [PMID: 23360102 DOI: 10.1111/nmo.12076]

13 **Tracey KJ**. The inflammatory reflex. *Nature* 2002; **420**: 853-859 [PMID: 12490958 DOI: 10.1038/nature01321]

14 **Tracey KJ**. Reflex control of immunity. *Nat Rev Immunol* 2009; **9**: 418-428 [PMID: 19461672 DOI: 10.1038/nri2566]

15 **Pavlov VA**, Wang H, Czura CJ, Friedman SG, Tracey KJ. The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation. *Mol Med* 2003; **9**: 125-134 [PMID: 14571320]

16 **Pavlov VA**, Tracey KJ. Neural circuitry and immunity. *Immunol Res* 2015; **63**: 38-57 [PMID: 26512000 DOI: 10.1007/s12026-015-8718-1]

17 **Rosas-Ballina M**, Ochani M, Parrish WR, Ochani K, Harris YT, Huston JM, Chavan S, Tracey KJ. Splenic nerve is required for cholinergic antiinflammatory pathway control of TNF in endotoxemia. *Proc Natl Acad Sci U S A* 2008; **105**: 11008-11013 [PMID: 18669662 DOI: 10.1073/pnas.0803237105]

18 **Satoh T**, Akira S. Toll-Like Receptor Signaling and Its Inducible Proteins. *Microbiol Spectr* 2016; **4** [PMID: 28084212 DOI: 10.1128/microbiolspec.MCHD-0040-2016]

19 **Goehler LE**, Gaykema RP, Hansen MK, Anderson K, Maier SF, Watkins LR. Vagal immune-to-brain communication: a visceral chemosensory pathway. *Auton Neurosci* 2000; **85**: 49-59 [PMID: 11189026 DOI: 10.1016/S1566-0702(00)00219-8]

20 **Simons CT**, Kulchitsky VA, Sugimoto N, Homer LD, Székely M, Romanovsky AA. Signaling the brain in systemic inflammation: which vagal branch is involved in fever genesis? *Am J Physiol* 1998; **275**: R63-R68 [PMID: 9688961 DOI: 10.1152/ajpregu.1998.275.1.R63]

21 **Hosoi T**, Okuma Y, Matsuda T, Nomura Y. Novel pathway for LPS-induced afferent vagus nerve activation: possible role of nodose ganglion. *Auton Neurosci* 2005; **120**: 104-107 [PMID: 15919243 DOI: 10.1016/j.autneu.2004.11.012]

22 **Goehler LE**, Erisir A, Gaykema RP. Neural-immune interface in the rat area postrema. *Neuroscience* 2006; **140**: 1415-1434 [PMID: 16650942 DOI: 10.1016/j.neuroscience.2006.03.048]

23 **Rosas-Ballina M**, Tracey KJ. Cholinergic control of inflammation. *J Intern Med* 2009; **265**: 663-679 [PMID: 19493060 DOI: 10.1111/j.1365-2796.2009.02098.x]

24 **Huston JM**, Ochani M, Rosas-Ballina M, Liao H, Ochani K, Pavlov VA, Gallowitsch-Puerta M, Ashok M, Czura CJ, Foxwell B, Tracey KJ, Ulloa L. Splenectomy inactivates the cholinergic antiinflammatory pathway during lethal endotoxemia and polymicrobial sepsis. *J Exp Med* 2006; **203**: 1623-1628 [PMID: 16785311 DOI: 10.1084/jem.20052362]

25 **Hoover DB**. Cholinergic modulation of the immune system presents new approaches for treating inflammation. *Pharmacol Ther* 2017; **179**: 1-16 [PMID: 28529069 DOI: 10.1016/j.pharmthera.2017.05.002]

26 **Ren C**, Tong YL, Li JC, Lu ZQ, Yao YM. The Protective Effect of Alpha 7 Nicotinic Acetylcholine Receptor Activation on Critical Illness and Its Mechanism. *Int J Biol Sci* 2017; **13**: 46-56 [PMID: 28123345 DOI: 10.7150/ijbs.16404]

27 **Kanashiro A**, Sônego F, Ferreira RG, Castanheira FV, Leite CA, Borges VF, Nascimento DC, Cólon DF, Alves-Filho JC, Ulloa L, Cunha FQ. Therapeutic potential and limitations of cholinergic anti-inflammatory pathway in sepsis. *Pharmacol Res* 2017; **117**: 1-8 [PMID: 27979692 DOI: 10.1016/j.phrs.2016.12.014]

28 **Koopman FA**, Chavan SS, Miljko S, Grazio S, Sokolovic S, Schuurman PR, Mehta AD, Levine YA, Faltys M, Zitnik R, Tracey KJ, Tak PP. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. *Proc Natl Acad Sci U S A* 2016; **113**: 8284-8289 [PMID: 27382171 DOI: 10.1073/pnas.1605635113]

29 **Genovese MC**, Gaylis NB, Sikes D, KivitzA, Horowitz DL, Peterfy C, Glass EV, Levine YA, Chernoff D. Safety and efficacy of neurostimulation with a miniaturised Vagus Nerve stimulation device in patients with multidrug-refractory rheumatoid arthritis: A two-stage multicentre, randomised pilot study. *Lancet Rheumatol* 2020; 2: E527-E538 [DOI: 10.1016/S2665-9913(20)30172-7]

30 **Borovikova LV**, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, Wang H, Abumrad N, Eaton JW, Tracey KJ. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature* 2000; **405**: 458-462 [PMID: 10839541 DOI: 10.1038/35013070]

31 **Kohoutova M**, Horak J, Jarkovska D, Martinkova V, Tegl V, Nalos L, Vistejnova L, Benes J, Sviglerova J, Kuncova J, Matejovic M, Stengl M. Vagus Nerve Stimulation Attenuates Multiple Organ Dysfunction in Resuscitated Porcine Progressive Sepsis. *Crit Care Med* 2019; **47**: e461-e469 [PMID: 30908312 DOI: 10.1097/CCM.0000000000003714]

32 **Hilderman M**, Bruchfeld A. The cholinergic anti-inflammatory pathway in chronic kidney disease-review and vagus nerve stimulation clinical pilot study. *Nephrol Dial Transplant* 2020; **35**: 1840-1852 [PMID: 33151338 DOI: 10.1093/ndt/gfaa200]

33 **Wittebole X**, Hahm S, Coyle SM, Kumar A, Calvano SE, Lowry SF. Nicotine exposure alters *in vivo* human responses to endotoxin. *Clin Exp Immunol* 2007; **147**: 28-34 [PMID: 17177960 DOI: 10.1111/j.1365-2249.2006.03248.x]

34 **Guslandi M**. Nicotine treatment for ulcerative colitis. *Br J Clin Pharmacol* 1999; **48**: 481-484 [PMID: 10583016 DOI: 10.1046/j.1365-2125.1999.00039.x]

35 **Guslandi M**, Tittobello A. Outcome of ulcerative colitis after treatment with transdermal nicotine. *Eur J Gastroenterol Hepatol* 1998; **10**: 513-515 [PMID: 9855069 DOI: 10.1097/00042737-199806000-00014]

36 **Özdemir-Kumral ZN**, Özbeyli D, Özdemir AF, Karaaslan BM, Kaytaz K, Kara MF, Tok OE, Ercan F, Yegen BÇ.

Protective Effect of Nicotine on Sepsis-Induced Oxidative Multiorgan Damage: Role of Neutrophils. *Nicotine Tob Res* 2017; **19**: 859-864 [PMID: 27613897 DOI: 10.1093/ntr/ntw198]

37 **Mabley J**, Gordon S, Pacher P. Nicotine exerts an anti-inflammatory effect in a murine model of acute lung injury. *Inflammation* 2011; **34**: 231-237 [PMID: 20625922 DOI: 10.1007/s10753-010-9228-x]

38 **Kloc M**, Ghobrial RM, Kubiak JZ. How nicotine can inhibit cytokine storm in the lungs and prevent or lessen the severity of COVID-19 infection? *Immunol Lett* 2020; **224**: 28-29 [PMID: 32522666 DOI: 10.1016/j.imlet.2020.06.002]

39 **Gonzalez-Rubio J**, Navarro-Lopez C, Lopez-Najera E, Lopez-Najera A, Jimenez-Diaz L, Navarro-Lopez JD, Najera A. Cytokine Release Syndrome (CRS) and Nicotine in COVID-19 Patients: Trying to Calm the Storm. *Front Immunol* 2020; **11**: 1359 [PMID: 32595653 DOI: 10.3389/fimmu.2020.01359]

40 **Kox M**, Pompe JC, Gordinou de Gouberville MC, van der Hoeven JG, Hoedemaekers CW, Pickkers P. Effects of the α7 nicotinic acetylcholine receptor agonist GTS-21 on the innate immune response in humans. *Shock* 2011; **36**: 5-11 [PMID: 21368716 DOI: 10.1097/SHK.0b013e3182168d56]

41 **Garg BK**, Loring RH. GTS-21 has cell-specific anti-inflammatory effects independent of α7 nicotinic acetylcholine receptors. *PLoS One* 2019; **14**: e0214942 [PMID: 30947238 DOI: 10.1371/journal.pone.0214942]

42 **Ahmad F**. COVID-19 induced ARDS, and the use of galantamine to activate the cholinergic anti-inflammatory pathway. *Med Hypotheses* 2020; **145**: 110331 [PMID: 33038588 DOI: 10.1016/j.mehy.2020.110331]

43 **Pinder N**, Bruckner T, Lehmann M, Motsch J, Brenner T, Larmann J, Knebel P, Hoppe-Tichy T, Swoboda S, Weigand MA, Hofer S, Zimmermann JB. Effect of physostigmine on recovery from septic shock following intra-abdominal infection - Results from a randomized, double-blind, placebo-controlled, monocentric pilot trial (Anticholium® per Se). *J Crit Care* 2019; **52**: 126-135 [PMID: 31035187 DOI: 10.1016/j.jcrc.2019.04.012]

44 **Li G**, Zhou CL, Zhou QS, Zou HD. Galantamine protects against lipopolysaccharide-induced acute lung injury in rats. *Braz J Med Biol Res* 2016; **49**: e5008 [PMID: 26648090 DOI: 10.1590/1414-431X20155008]

45 **Liu ZH**, Ma YF, Wu JS, Gan JX, Xu SW, Jiang GY. Effect of cholinesterase inhibitor galanthamine on circulating tumor necrosis factor alpha in rats with lipopolysaccharide-induced peritonitis. *Chin Med J (Engl)* 2010; **123**: 1727-1730 [PMID: 20819637]

46 **Yoshiyama Y**, Kojima A, Ishikawa C, Arai K. Anti-inflammatory action of donepezil ameliorates tau pathology, synaptic loss, and neurodegeneration in a tauopathy mouse model. *J Alzheimers Dis* 2010; **22**: 295-306 [PMID: 20847440 DOI: 10.3233/JAD-2010-100681]

47 **Consolim-Colombo FM**, Sangaleti CT, Costa FO, Morais TL, Lopes HF, Motta JM, Irigoyen MC, Bortoloto LA, Rochitte CE, Harris YT, Satapathy SK, Olofsson PS, Akerman M, Chavan SS, MacKay M, Barnaby DP, Lesser ML, Roth J, Tracey KJ, Pavlov VA. Galantamine alleviates inflammation and insulin resistance in patients with metabolic syndrome in a randomized trial. *JCI Insight* 2017; **2** [PMID: 28724799 DOI: 10.1172/jci.insight.93340]

48 **Pavlov VA**, Parrish WR, Rosas-Ballina M, Ochani M, Puerta M, Ochani K, Chavan S, Al-Abed Y, Tracey KJ. Brain acetylcholinesterase activity controls systemic cytokine levels through the cholinergic anti-inflammatory pathway. *Brain Behav Immun* 2009; **23**: 41-45 [PMID: 18639629 DOI: 10.1016/j.bbi.2008.06.011]

49 **Musk AW**, de Klerk NH. History of tobacco and health. *Respirology* 2003; **8**: 286-290 [PMID: 14528877 DOI: 10.1046/j.1440-1843.2003.00483.x]

50 **DeVeaugh-Geiss AM**, Chen LH, Kotler ML, Ramsay LR, Durcan MJ. Pharmacokinetic comparison of two nicotine transdermal systems, a 21-mg/24-hour patch and a 25-mg/16-hour patch: a randomized, open-label, single-dose, two-way crossover study in adult smokers. *Clin Ther* 2010; **32**: 1140-1148 [PMID: 20637967 DOI: 10.1016/j.clinthera.2010.06.008]

51 **Moran VE**. Cotinine: Beyond that Expected, More than a Biomarker of Tobacco Consumption. *Front Pharmacol* 2012; **3**: 173 [PMID: 23087643 DOI: 10.3389/fphar.2012.00173]

52 **Hukkanen J**, Jacob P 3rd, Peng M, Dempsey D, Benowitz NL. Effect of nicotine on cytochrome P450 1A2 activity. *Br J Clin Pharmacol* 2011; **72**: 836-838 [PMID: 21599724 DOI: 10.1111/j.1365-2125.2011.04023.x]

53 **Stefan MS**, Pack Q, Shieh MS, Pekow PS, Bernstein SL, Raghunathan K, Nason KS, Lindenauer PK. The Association of Nicotine Replacement Therapy With Outcomes Among Smokers Hospitalized for a Major Surgical Procedure. *Chest* 2020; **157**: 1354-1361 [PMID: 31790653 DOI: 10.1016/j.chest.2019.10.054]

54 **de Jong B**, Schuppers AS, Kruisdijk-Gerritsen A, Arbouw MEL, van den Oever HLA, van Zanten ARH. The safety and efficacy of nicotine replacement therapy in the intensive care unit: a randomised controlled pilot study. *Ann Intensive Care* 2018; **8**: 70 [PMID: 29881956 DOI: 10.1186/s13613-018-0399-1]

55 **Pathak V**, Rendon IS, Lupu R, Tactuk N, Olutade T, Durham C, Stumacher R. Outcome of nicotine replacement therapy in patients admitted to ICU: a randomized controlled double-blind prospective pilot study. *Respir Care* 2013; **58**: 1625-1629 [PMID: 23533293 DOI: 10.4187/respcare.01791]

56 **Cartin-Ceba R**, Warner DO, Hays JT, Afessa B. Nicotine replacement therapy in critically ill patients: a prospective observational cohort study. *Crit Care Med* 2011; **39**: 1635-1640 [PMID: 21494111 DOI: 10.1097/CCM.0b013e31821867b8]

57 **Pack QR**, Priya A, Lagu TC, Pekow PS, Atreya A, Rigotti NA, Lindenauer PK. Short-Term Safety of Nicotine Replacement in Smokers Hospitalized With Coronary Heart Disease. *J Am Heart Assoc* 2018; **7**: e009424 [PMID: 30371184 DOI: 10.1161/JAHA.118.009424]

58 **Ng KT**, Gillies M, Griffith DM. Effect of nicotine replacement therapy on mortality, delirium, and duration of therapy in critically ill smokers: a systematic review and meta-analysis. *Anaesth Intensive Care* 2017; **45**: 556-561 [PMID: 28911284 DOI: 10.1177/0310057X1704500505]

59 **Molander L**, Hansson A, Lunell E, Alainentalo L, Hoffmann M, Larsson R. Pharmacokinetics of nicotine in kidney failure. *Clin Pharmacol Ther* 2000; **68**: 250-260 [PMID: 11014406 DOI: 10.1067/mcp.2000.109006]

60 **Perry RJ**, Griffiths W, Dextraze P, Solomon RJ, Trebbin WM. Elevated nicotine levels in patients undergoing hemodialysis. A role in cardiovascular mortality and morbidity? *Am J Med* 1984; **76**: 241-246 [PMID: 6695947 DOI: 10.1016/0002-9343(84)90780-0]

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MINIREVIEWS

Health-related quality-of-life and health-utility reporting in critical care

Vincent Issac Lau, Jeffrey A Johnson, Sean M Bagshaw, Oleksa G Rewa, John Basmaji, Kimberley A Lewis, M Elizabeth Wilcox, Kali Barrett, Francois Lamontagne, Francois Lauzier, Niall D Ferguson, Simon J W Oczkowski, Kirsten M Fiest, Daniel J Niven, Henry T Stelfox, Waleed Alhazzani, Margaret Herridge, Robert Fowler, Deborah J Cook, Bram Rochwerg, Feng Xie

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Vincent Issac Lau, Sean M Bagshaw, Oleksa G Rewa, Department of Critical Care Medicine, University of Alberta, Edmonton T6G 2B7, AB, Canada

Jeffrey A Johnson, School of Public Health, Inst Hlth Econ, University of Alberta, Edmonton T6G 2B7, AB, Canada

John Basmaji, Department of Medicine, Division of Critical Care, Western University, London N6A 5W9, Canada

Kimberley A Lewis, Division of Critical Care, McMaster University, Hamilton L8N 4A6, Canada

M Elizabeth Wilcox, Kali Barrett, Interdepartmental Division of Critical Care, University of Toronto, Toronto M5T 2S8, Canada

Francois Lamontagne, Department of Medicine, University Sherbrooke, Sherbrooke J1H 5N4, Canada

Francois Lauzier, Departments of Medicine and Anesthesiology, University Laval, Laval G1V 4G2, Canada

Niall D Ferguson, Department Critical Care Medicine, University of Toronto, Toronto M5G 2C4, Canada

Simon J W Oczkowski, Department of Medicine, McMaster Clin, Hamilton Gen Hosp, McMaster University, Hamilton L8N 4A6, Canada

Kirsten M Fiest, Department of Community Health Sciences & Institute for Public Health, University of Calgary, Calgary T2N 2T9, Canada

Daniel J Niven, Department of Critical Care Medicine, University Calgary, Calgary T2N 2T9, Canada

Henry T Stelfox, Department of Community Health Sciences, University of Calgary, Calgary T2N 2T9, Canada

Waleed Alhazzani, Deborah J Cook, Bram Rochwerg, Department of Medicine, McMaster University, Hamilton L8N 4A6, Canada

Margaret Herridge, Indepartmental Division of Critical Care, University Health Network, Toronto M5G 2C4, Canada

Robert Fowler, Departments of Medicine and Critical Care Medicine, Sunnybrook Health Sciences Center, Institute of Health Policy Management and Evaluation, University of Toronto, Toronto M4N 3M5, Canada

Feng Xie, Health Research Methods, Evidence and Impact, McMaster University, Hamilton L8N 3Z5, Canada

Corresponding author: Vincent Issac Lau, FRCP (C), MD, MSc, Assistant Professor, Critical Care Medicine, University of Alberta, 8440 112 Street NW, Edmonton T6G 2B7, AB, Canada. vinceissaclau@gmail.com

Abstract

Mortality is a well-established patient-important outcome in critical care studies. In contrast, morbidity is less uniformly reported (given the myriad of critical care illnesses and complications of each) but may have a common end-impact on a patient's functional capacity and health-related quality-of-life (HRQoL). Survival with a poor quality-of-life may not be acceptable depending on individual patient values and preferences. Hence, as mortality decreases within critical care, it becomes increasingly important to measure intensive care unit (ICU) survivor HRQoL. HRQoL measurements with a preference-based scoring algorithm can be converted into health utilities on a scale anchored at 0 (representing death) and 1 (representing full health). They can be combined with survival to calculate quality-adjusted life-years (QALY), which are one of the most widely used methods of combining morbidity and mortality into a composite outcome. Although QALYs have been use for health-technology assessment decision-making, an emerging and novel role would be to inform clinical decision-making for patients, families and healthcare providers about what expected HRQoL may be during and after ICU care. Critical care randomized control trials (RCTs) have not routinely measured or reported HRQoL (until more recently), likely due to incapacity of some patients to participate in patient-reported outcome measures. Further differences in HRQoL measurement tools can lead to non-comparable values. To this end, we propose the validation of a gold-standard HRQoL tool in critical care, specifically the EQ-5D-5L. Both combined health-utility and mortality (disaggregated) and QALYs (aggregated) can be reported, with disaggregation allowing for determination of which components are the main drivers of the QALY outcome. Increased use of HRQoL, health-utility, and QALYs in critical care RCTs has the potential to: (1) Increase the likelihood of finding important effects if they exist; (2) improve research efficiency; and (3) help inform optimal management of critically ill patients allowing for decision-making about their HRQoL, in additional to traditional health-technology assessments.

Key Words: Critical care; health-related quality of life; Quality-adjusted life-years; Health-utility; Mortality; Morbidity; Kaplan-Meier curves

Core Tip: Health-related quality-of-life and health-utility are patient-important outcome measures that rival even mortality. The purpose of the paper is to outline the steps required for wider adoption of health-related quality-of-life measures in critical care, and what benefits this measurement will yield.

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INTRODUCTION

Mortality is a well-established, patient-important outcome used in critical care trials[1,2], which has many attractive features for use in clinical research. Mortality is a commonly occurring, unambiguous,

dichotomous event, whose adjudication is less susceptible to bias. Unfortunately, most randomized controlled trials (RCTs) in critical care have failed to demonstrate consistent effects or improvements on mortality across a host of intensive care unit (ICU) interventions[3] potentially due to: (1) Underpowering from decreasing mortality over time[4]; (2) heterogeneity of treatment effects[5]; or (3) ineffective treatments. Moreover, mortality is associated with limitations relevant to critical care research. The larger sample sizes required to adequately power studies make clinical trials less feasible and much more expensive to conduct. Mortality is not plausibly affected by certain interventions, and thus is not always the most appropriate endpoint. Finally, mortality is not the only patient-important outcome. Some patients may survive to have a poor health-related quality of life (HRQoL)[1,2,6], which may be unacceptable depending on their individual values and preferences. There is potential to challenge conventional research paradigms, and explore patient-centered outcomes beyond mortality for critical care trials. This may include secondary outcomes of interest, of which morbidity and functional outcomes are important.

Morbidity may be an intuitive alternative to mortality, but has unique challenges for research. Despite certain benefits of measuring morbidity (*e.g.* describes patient's complications and potential suffering from those illnesses), it is less uniformly reported. With large variations in outcomes and complications, this results in a myriad of reported morbidity outcomes[1,2]. There is often a lack of common outcomes and standardization between studies[7], especially for different disease states and illnesses.

With carefully developed, defined, patient-centered outcomes like HRQoL and functional status, morbidity can better represent diverse illnesses and outcomes across critical care populations. Initiatives are being developed for critical care core outcome sets, which could include HRQoL[8]. It is important that we listen to our patients and their health proxies by capturing patient-centered values and self-reported HRQoL, whenever possible[9]. With a growing populace of ICU survivors, HRQoL and morbidity outcomes become increasingly important to measure and optimize in order to characterize the health states in which ICU patients survive[1]. However, we must address specific barriers and challenges to measuring HRQoL in the critical care population.

To this end, we present an overview of HRQoL, health-utility and QALYs, their specific applications, and unique challenges of its use in the critical care population. Furthermore, we present unique opportunities for HRQoL and health-utility research in the critical care population, which may include: (1) end-of-life decision-making and low-utility states, which may only be realized in critically ill patients; and (2) increased use of proxy measurements (*e.g.* substitute decision-makers) given that some patients may lack the capacity to participate in their reported outcomes. We present these issues not merely as responses to the technical challenges of measurement and application in critical care, but as a research imperative to paradigm shift in how we report and measure HRQoL and other patient-important outcomes in critically ill patients.

OVERVIEW: MORBIDITY AS HEALTH-RELATED QUALITY-OF-LIFE, HEALTH-UTILITY, AND QALYS

Health-related quality-of-life (HRQoL) is "an individual's or a group's perceived physical and mental health over time"[10]. Another definition states that HRQoL is a "multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning…[which] goes beyond direct measures of population health, life expectancy, and causes of death, and focuses on the impact health status has on quality-of-life."

A health state can be used to describe HRQoL. Health states can be assigned preference weights and described as a health-utility value. In contrast to HRQoL, which describes one's overall health qualitatively, a health-utility value seeks quantify HRQoL as a number, anchored to zero (representing death) to one (representing perfect health) [11]. However, health states less than zero can also be reported (*e.g.* "states worse than death").

Various tools can be used ascertain HRQoL and health-utility values. These include direct methods (*e.g.* standard gamble, time-trade off) or indirect methods using HRQoL population-derived preference based utility scales (*e.g.* Health Utility Index Mark 3, Short Form-6D, EQ-5D). These health-utility scores can be leveraged to calculate quality-adjusted life-years.

The quality-adjusted life-year (QALY) is measured as a function of length of life (mortality) and time spent in a health-related quality-of-life state (morbidity), and combines the value of these attributes into a single index number[12]. Essentially, the QALY represents "time alive, scaled to reflect health state desirability…and individual values and preferences[9]," where a year in the hypothetical state of "perfect health" is worth one QALY. The QALY can be useful as a standard measure of health states across diverse treatments and settings, as it transforms different illnesses and their severity into a common physical and mental description of their health state. This allows comparisons to be made with a common denominator of QALYs[13]. For these reasons, the QALY is recommended as a measure of health outcomes for economic evaluations[2,12-16].

Despite criticisms (*e.g.* bias against elderly, against those with physical/mental disabilities)[13,17], QALYs remain widely used and are well-validated composite outcome measures for chronic health conditions (*e.g.* chronic obstructive pulmonary disease, congestive heart failure)[1,2]. QALYs can be estimated with an indirect generic preference-based health utility measure, making it patient-centered, with values and preferences for health states incorporated into its calculation[1].

For these reasons, we propose that HRQoL, health-utility and QALYs, rather than mortality alone, should be measured as an important secondary outcome in critical care research. For this incorporation to take place, critical care trialists must first measure HRQoL, which not currently routinely performed.

HISTORY OF EXISTING HEALTH-RELATED QUALITY-OF-LIFE MEASUREMENT TOOLS IN CRITICAL CARE

Critical care studies have not routinely measured HRQoL compared to mortality, likely due to: (1) The incapacitated status of patients; and (2) the time-consuming nature of certain pre-existing measurement tools.

There are two main methods of utility- or preference-based HRQoL measurement. The first are direct HRQoL measurement methods such as the standard gamble, time trade-off, visual analog scale (VAS), and discrete choice experiments[18]. Unfortunately, some of these methods are time-consuming, complex, and thus not always feasible in all studies[18].

The second group of methods are indirect HRQoL measurement tools, which utilize population-based preferences onto a health-utility scale indirectly *via* a generic utility-based HRQoL questionnaire [18]. These tools are derived from the general population, representing that society's values. Commonly used generic instruments include the Short Form [SF]-36 or SF-6D[19], Health Utility Index mark 3 [HUI3][20], and the EQ-5D (Table 1)[21,22], and have been used prior in critical care studies[2].

The Short Form-36 is a proprietary, 36-item, 5-page questionnaire evaluating 10 comprehensive domains: physical functioning, physical role limitations, bodily pain, general health perceptions, energy/vitality, social functioning, emotion role limitations and mental health[19]. The SF-36 is time-consuming to complete, and some patients may have difficulty completing the entire questionnaire[23]. Although Chrispin *et al*[24] observed there was acceptability and reliability of the SF-36 when used in the ICU, they did not assess or formally validate the SF-36 against any other ICU-based HRQoL tools or illness severity scores. The SF-36 was used to derive the SF-6D (a utility-based instrument), using a subset of items/dimensions from the SF-36, which are occasionally used in critical care populations[25-27].

The HUI3, is an 8-item, 3-page questionnaire, which evaluates 8 domains: vision, hearing, speech, ambulation, dexterity, emotion, cognition. The HUI3 has not been widely used given the higher cost and proprietary licensing[20]. Although less cumbersome than the SF-36, both instruments require specific training to administer and complete.

EQ-5D DESCRIPTION, USES, CONVERSION TO HEALTH-UTILITY AND QALYS

The most commonly used indirect method in critical care cost-utility analyses is the EQ-5D[2,18,21]. The instrument is a 5-item, 3 or 5-level Likert scale with a built-in global health VAS for self-reporting health-utility built in its design. The 5 domains evaluated include: Mobility, self-care, usual activities, pain/discomfort, anxiety/depression[14,21,28-31]. Many of these domains are similar to Activities of Daily Living (ADLs)[1,2,28,29] and instrumental activities of daily living (IADLs)[32], which assess function within the patient-important context of how individuals live and work. These ADLs and IADLs are commonly assessed in critically ill patients[33,34], demonstrating the relevance and feasibility of using the EQ-5D in this setting. EQ-5D is shorter and easier to use than the SF-36 and HUI3, with only 5 fundamental patient-important HRQoL outcomes. In response, other HRQoL scales, such as the SF-36 have created shorter versions (*e.g.* SF-6D, *etc.*). The EQ-5D also has advantages over other HRQoL tools, including: (1) Coverage to low health-utilities, including less than zero (1); (2) no licensing fee for non-commercial use; (3) a built-in VAS for self-rating a patient's health status; (4) a large number of versions and language translations; and (5) many country-specific population preference scoring systems to support cost-utility analyses[1,2,18].

Differences between HRQoL tools (*e.g.* EQ-5D *vs* SF) can also lead to scoring of different health-utility values for the same health state in the same patient, with each tool giving a slightly different result. The EQ-5D has been shown to have greater coverage at low health-utility states[1,2,29], which makes it a potentially useful HRQoL tool for use in critical care, as low health-utilities may be expected in this patient population as some are close to end-of-life. Despite being used in the ICU[25,26,35], there is no gold standard HRQoL measurement tool for use in the critical care setting, and none have been rigorously validated in the critically ill population[2]. At present, the EQ-5D is the most promising tool for HRQoL measurement, which merits focused evaluation in critical care.

Table 1 Indirect methods for measuring patient-based preferences mapped on a health-utility scale *via* a generic health-related quality-of-life questionnaire

Utility measurement	Questionnaire description	Levels and health states	Tariff weighting acquisition	Information	Range of health-utility scores
European quality of life five dimensions (EQ-5D)	Five dimensions (mobility; self-care; usual activities; pain/discomfort; anxiety/depression)	5 levels; 3125 health states	Sample of European general population (n = 3395); time trade off valuation; hypothetical scenarios	Mostly used in continental Europe and the United Kingdom	-0.59 to 1.00
Short Form-36 (SF-36)	Ten physical (physical function, physical role limitations, bodily pain, general health perceptions, energy/vitality) and mental health (social functioning, emotional role limitations and mental health) dimensions	4-6 levels; approximately 18000 health states	Sample of United Kingdom general population (n = 611); standard gamble valuation; hypothetical scenarios	Shorter versions available and applicable to SF-12 and SF-6D	0.30 to 1.00
Health utilities index mark 3 (HUI-3)	Eight dimensions (vision; hearing; speech; ambulation; dexterity; emotion; cognition; pain)	5-6 levels; approximately 972000 health states	Representative sample of adults in Ontario, Canada (n = 504); visual analogue scale transformed into standard gamble; hypothetical scenarios	Closely related adaptation of HUI-2, with a more detailed descriptive system; mostly used in Canada	−0.36 to 1.00

EQ-5D: EuroQoL-5 domains; HUI: Health utility index mark; ICU: Intensive care unit; QALY: Quality-adjusted life year; QoL: Quality of life; SF-12: Short form-12; SF-36: Short form-36; SF-6D: Short form-6 domains.

Once measured, EQ-5D HRQoL measurements can be used in variety of ways. First, clinicians and researchers can use the EQ-5D-5L's Likert-scale scores at face value, to determine what a patient's health state is for the five domains[21,29-31]. This may inform the management plan for individual patients, such as referral to consulting services, such as physiotherapy or occupational therapy for physical domains, or psychiatry for mental health domains. Second, the EQ-5D HRQoL measurements can be converted into health-utility index score using a jurisdictional-specific algorithms, such as the validated time-trade off based scoring from the general Canadian population[36]. The Canadian scoring algorithm for the EQ-5D index utilizes population-based health-utility preferences which go from -0.59 to 1.0[18,36], whereby it can describe health states which patients consider to be "states worse than death"[2,18]. The index score can then be used to calculate the QALY, which is an aggregate measure of global health rating (health-utility) multiplied by the duration of time spent in that health state. The EQ-5D has become the most widely used and validated methods of combining morbidity and mortality into QALYs in medicine for a composite outcome[1,2].

HEALTH-UTILITY REPORTING ON SAME GRAPHS AS ESTABLISHED MORTALITY KAPLAN-MEIER CURVES

Like other composite outcomes, it is important to understand the individual component contributions of QALY including both the health-utility (morbidity) and time spent in that state (survival/mortality). For example, a study with 10 patients reported cumulative total of 5 QALYs at 1-year, this could be due to a myriad of combinations of health-utility and life-years. The effects are different if 10 patients survived to 1-year each at a health-utility of 0.5 (Figure 1A) *vs* a scenario where 10 patients survive only until 6-mo, but have full health (health-utility of 1) for the 6-mo prior to their deaths (Figure 1B). Both scenarios would yield a total 5 QALYs; however, each scenario may have different clinical implications to patients involved. Patients and clinical decision-makers may make different treatment choices in each scenario, in accordance with their values and preferences for quality-of-life *vs* duration of life.

Disaggregation of QALYs into component parts of mortality and health-utility using graphical representation (can be shown on the same graph as a Kaplan-Meier curve) may be an important way to describe the specific drivers of QALYs changes (Figure 2). This novel methodology where health-utility and mortality are reported both separately and aggregated as QALYs, may further the acceptance of HRQoL, health-utility and QALYs in critical care. If healthcare providers, patients, and families are aware of what drives a particular QALY outcome difference, this may also help to inform future management plans for critically ill patients, better inform clinicians and families about the trajectory of HRQoL, and potentially impact upfront goals-of-care discussions and clinical decision-making.

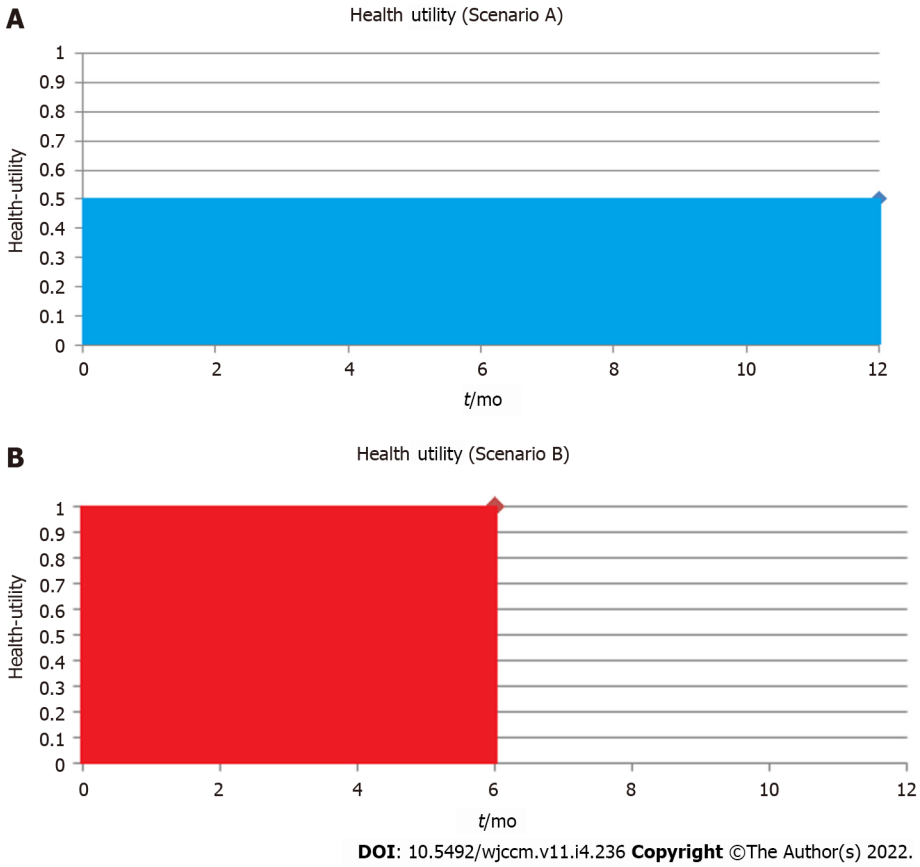

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Figure 1 Health-utility *vs* time. A: 10 patients survive to 1-year, health-utility 0.5; B: 10 patients survive to 6-months, health-utility 1.

HRQOL IMPLEMENTATION AND MEASUREMENT

Healthcare providers, patients, families, and healthcare policy-makers have demonstrated interest in survival and HRQoL before, during, and following discharge from critical care. With advances in ICU technology, our ability to sustain physiologic function of the body may minimize the effects of critical illness and treatment upon ICU survivors' HRQoL[2,37], which could include their suffering alongside their illness. This is a very real concern, as many patients and families may choose to withdraw or defer life-sustaining ICU therapy based upon their individual values and preferences for HRQoL[2,37]. These concerns lend credence to the expression "alive and well" as a desired outcome following critical illness, as patient's wishes and preferences for or against aggressive treatments are usually stable over time, including at end-of-life[38]. HRQoL is key to describe as a patient-important outcome. Furthermore, HRQoL can give a voice to patients as well as their families and friends as proxies.

HRQoL measurement and implementation in critical could mean: (1) An increase in the likelihood of finding important clinical effects for interventions, if they exist; (2) improve research efficiency by powering studies to QALYs rather than mortality; and (3) help inform optimal management of critically ill patients allowing for decision-making about their HRQoL, in additional to traditional health-technology assessments.

There are certain limitations to the measurement of HRQoL in the critical care population. First, there are incapacitated patients that would not be able to report their own HRQoL, emphasizing the need to validate a proxy tool (*e.g.* EQ-5D proxy versions) alongside the patient-reported tool. Second, proxies and patients may differ in rating or HRQoL[39]. Third, subjective *vs* objective HRQoL may differ (*e.g.* EQ-VAS score compared to EQ-5D-5L algorithm score), and could potentially be biased by a patient's own preferences and values[39]. As compared to functional recovery scales, even though health-utility may be more patient-centric, it may also be less generalizable as they are mapped out to general population instead of just critically ill patients. Fourth, different components of HRQoL can move in different directions, making it difficult to assess the composite outcome, as different patients will value mortality and morbidity differently based on their preferences. Finally, most HRQoL measures are usually time-specific when the patient completes the questionnaire. Therefore, baseline measurements may either not be available (due to patient incapacity), or may be subject to recall bias from patients or proxies recalling past HRQoL.

There are also certain challenges associated with QALYs acceptance in general. First, QALYs in the critical care population can be skewed by mortality, presenting difficulties with analytic assumptions (

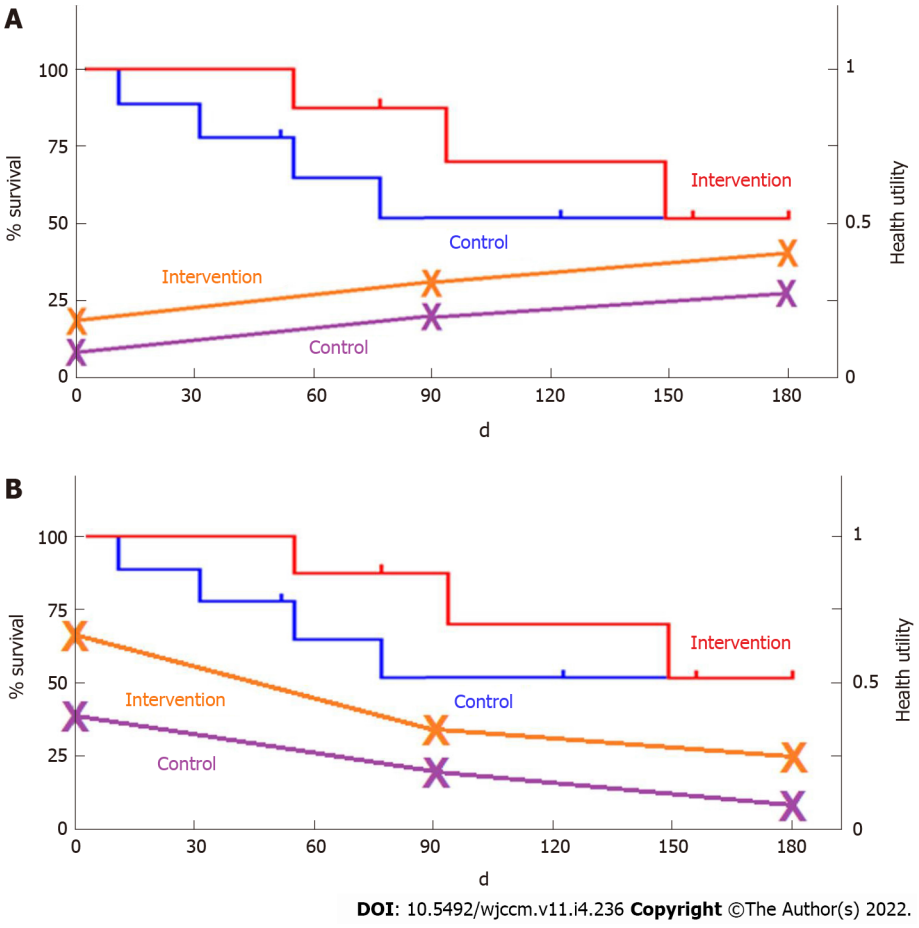

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Figure 2 Combined Kaplan-Meier curves alongside health-utility. A: Improving health-utility trajectory; B: Worsening health-utility.

e.g. parametric testing and reporting, although this can be addressed by non-parametric testing). Second, we are uncertain of the correct time-horizon to extend QALY measurements to for various critically illnesses, with longer time-horizons being affected by further lost-to-follow up and incomplete datasets. More routine HRQoL assessments at any health-related encounter could mitigate this issue (*e.g.* outpatient family practice, at any hospital admission). The relevant time-horizons will vary between illnesses and various patient populations, but perhaps at least a standardized set of time-horizons (*e.g.* in-hospital, 3 mo and 12 mo post-discharge) could be explored in critically ill patient populations. Finally, how should we measure and account for baseline imbalances in health-utility outside of a randomized control trial, and how should changes in responsiveness to treatment be anchored and reported?

Despite these challenges, there are substantial benefits to measuring HRQoL in critically ill patients. Therefore, we encourage researchers and clinicians to consider measuring HRQoL, with input from patients and proxies (*e.g.* surrogate decision-makers or caregivers), as some patients may never regain capacity to participate, but knowing what their values and preferences are is key to providing patient-centered care. We hope to provide the best available information (*e.g.* HRQoL measures, health-utility, QALYs) to decision-makers regarding HRQoL outcomes to aid both clinical decision-making alongside traditional health technology assessments.

CONCLUSION

We propose establishing a rapid, easy-to-use, broad metric, and well-validated HRQoL tool (both patient and proxy versions, which are available from EQ-5D) for use in critical care research as patient-important secondary outcome, which can be standardized across all studies allowing for comparability. We also propose reporting health-utility alongside mortality on Kaplan-Meier curves, to present a disaggregation of morbidity and mortality in addition to the aggregated quality-adjusted life-year.

Future work in this area should include: (1) Pilot validation of HRQoL patient and proxy tools in the critical care population during a cross-sectional study (approximately 50-100 patient recruitment) measuring: Pre-hospital baseline; admission; during ICU stay; and at discharge. We believe the EQ-5D could be validated in critical care (against Short-Form and correlated with other established illness

severity scores), as it is the most promising tool at present; and (2) Future HRQoL validation studies for post-ICU follow-up (*e.g.* 3, 6, 12 mo) are required to determine long-term HRQoL outcomes. These steps will lay the foundation for feasible, reproducible, and interpretable patient-important outcome measures in critical care.

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FOOTNOTES

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Country/Territory of origin: Canada

ORCID number: Vincent Issac Lau 0000-0002-9939-7348; Jeffrey A Johnson 0000-0001-8290-2857; Sean M Bagshaw 0000-0003-3633-6596; Oleksa G Rewa 0000-0002-8718-0547; John Basmaji 0000-0001-9749-1747; Kimberley A Lewis 0000-0002-1621-7664; M Elizabeth Wilcox 0000-0003-0331-5182; Kali Barrett 0000-0001-7147-2222; Francois Lamontagne 0000-0002-0360-3427; Francois Lauzier 0000-0002-6530-5513; Niall D Ferguson 0000-0002-6213-5264; Simon J W Oczkowski 0000-0002-2874-8948; Kirsten M Fiest 0000-0002-7299-6594; Daniel J Niven 0000-0002-9527-0577; Henry T Stelfox 0000-0003-1231-1490; Waleed Alhazzani 0000-0001-8076-9626; Margaret Herridge 0000-0002-2903-1631; Robert Fowler 0000-0003-0328-7150; Deborah J Cook 0000-0002-4087-543X; Bram Rochwerg 0000-0002-8293-7061; Feng Xie 0000-0003-3454-6266.

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REFERENCES

1 **Ferguson ND**, Scales DC, Pinto R, Wilcox ME, Cook DJ, Guyatt GH, Schünemann HJ, Marshall JC, Herridge MS, Meade MO; Canadian Critical Care Trials Group. Integrating mortality and morbidity outcomes: using quality-adjusted life years in critical care trials. *Am J Respir Crit Care Med* 2013; **187**: 256-261 [PMID: 23204250 DOI: 10.1164/rccm.201206-1057OC]

2 **Lau VI**, Xie F, Basmaji J, Cook DJ, Fowler R, Kiflen M, Sirotich E, Iansavichene A, Bagshaw SM, Wilcox ME, Lamontagne F, Ferguson N, Rochwerg B. Health-Related Quality-of-Life and Cost Utility Analyses in Critical Care: A Systematic Review. *Crit Care Med* 2021; **49**: 575-588 [PMID: 33591013 DOI: 10.1097/CCM.0000000000004851]

3 **Santacruz CA**, Pereira AJ, Celis E, Vincent JL. Which Multicenter Randomized Controlled Trials in Critical Care Medicine Have Shown Reduced Mortality? *Crit Care Med* 2019; **47**: 1680-1691 [PMID: 31567349 DOI: 10.1097/CCM.0000000000004000]

4 **Van Cleave J**, Kemper AR, Davis MM. Interpreting negative results from an underpowered clinical trial: warts and all. *Arch Pediatr Adolesc Med* 2006; **160**: 1126-1129 [PMID: 17088515 DOI: 10.1001/archpedi.160.11.1126]

5 **Kent DM**, Rothwell PM, Ioannidis JP, Altman DG, Hayward RA. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. *Trials* 2010; **11**: 85 [PMID: 20704705 DOI: 10.1186/1745-6215-11-85]

6 **Rochwerg B**, Einav S, Chaudhuri D, Mancebo J, Mauri T, Helviz Y, Goligher EC, Jaber S, Ricard JD, Rittayamai N, Roca O, Antonelli M, Maggiore SM, Demoule A, Hodgson CL, Mercat A, Wilcox ME, Granton D, Wang D, Azoulay E, Ouanes-Besbes L, Cinnella G, Rauseo M, Carvalho C, Dessap-Mekontso A, Fraser J, Frat JP, Gomersall C, Grasselli G, Hernandez G, Jog S, Pesenti A, Riviello ED, Slutsky AS, Stapleton RD, Talmor D, Thille AW, Brochard L, Burns KEA. The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline. *Intensive Care Med* 2020; **46**: 2226-2237 [PMID: 33201321 DOI: 10.1007/s00134-020-06312-y]

7 **Gaudry S**, Messika J, Ricard JD, Guillo S, Pasquet B, Dubief E, Boukertouta T, Dreyfuss D, Tubach F. Patient-important outcomes in randomized controlled trials in critically ill patients: a systematic review. *Ann Intensive Care* 2017; **7**: 28 [PMID: 28271450 DOI: 10.1186/s13613-017-0243-z]

8 **Blackwood B**, Marshall J, Rose L. Progress on core outcome sets for critical care research. *Curr Opin Crit Care* 2015; **21**: 439-444 [PMID: 26263299 DOI: 10.1097/MCC.0000000000000232]

9 **Drummond MF**, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Oxford University Press. Available from: https://pure.york.ac.uk/portal/en/publications/methods-for-the-economic-evaluation-of-health-care-programmes(8f69bcee-cdac-44fa-871c-f821470df60a)/export.html

10 Health-Related Quality of Life (HRQOL) | CDC. 2021. Available from: https://www.cdc.gov/hrqol/index.htm

11 **Payakachat N**, Murawski MM, Summers KH. Health utility and economic analysis: theoretical and practical issues. *Expert Rev Pharmacoecon Outcomes Res* 2009; **9**: 289-292 [PMID: 19670986 DOI: 10.1586/erp.09.36]

12 **Prieto L**, Sacristán JA. Problems and solutions in calculating quality-adjusted life years (QALYs). *Health Qual Life Outcomes* 2003; **1**: 80 [PMID: 14687421 DOI: 10.1186/1477-7525-1-80]

13 **Neumann PJ**, Cohen JT. QALYs in 2018-Advantages and Concerns. *JAMA* 2018; **319**: 2473-2474 [PMID: 29800152 DOI: 10.1001/jama.2018.6072]

14 **Garrison LP Jr**, Mansley EC, Abbott TA 3rd, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ISPOR Drug Cost Task Force report--Part II. *Value Health* 2010; **13**: 8-13 [PMID: 19883405 DOI: 10.1111/j.1524-4733.2009.00660.x]

15 Foreword | Guide to the methods of technology appraisal 2013 | Guidance | NICE. Available from: https://www.nice.org.uk/process/PMG9/chapter/Foreword

16 **CADTH**. Guidelines for the Economic Evaluation of Health Technologies: Canada (4th Edition). 76. [DOI: 10.1016/s1098-3015(10)70172-8]

17 **Perfetto EM**. ISPOR's Initiative on US Value Assessment Frameworks: A Missed Opportunity for ISPOR and Patients. *Value Health* 2018; **21**: 169-170 [PMID: 29477396 DOI: 10.1016/j.jval.2017.12.002]

18 **Arnold D**, Girling A, Stevens A, Lilford R. Comparison of direct and indirect methods of estimating health state utilities for resource allocation: review and empirical analysis. *BMJ* 2009; **339**: b2688 [PMID: 22128393 DOI: 10.1136/bmj.b2688]

19 **Ware JE Jr**, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**: 473-483 [PMID: 1593914]

20 **Horsman J**, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI): concepts, measurement properties and applications. *Health Qual Life Outcomes* 2003; **1**: 54 [PMID: 14613568 DOI: 10.1186/1477-7525-1-54]

21 **Wailoo AJ**, Hernandez-Alava M, Manca A, Mejia A, Ray J, Crawford B, Botteman M, Busschbach J. Mapping to Estimate Health-State Utility from Non-Preference-Based Outcome Measures: An ISPOR Good Practices for Outcomes Research Task Force Report. *Value Health* 2017; **20**: 18-27 [PMID: 28212961 DOI: 10.1016/j.jval.2016.11.006]

22 **Brooks R**, Boye KS, Slaap B. EQ-5D: a plea for accurate nomenclature. *J Patient Rep Outcomes* 2020; **4**: 52 [PMID: 32620995 DOI: 10.1186/s41687-020-00222-9]

23 **Andresen EM**, Gravitt GW, Aydelotte ME, Podgorski CA. Limitations of the SF-36 in a sample of nursing home residents. *Age Ageing* 1999; **28**: 562-566 [PMID: 10604509 DOI: 10.1093/ageing/28.6.562]

24 **Chrispin PS**, Scotton H, Rogers J, Lloyd D, Ridley SA. Short Form 36 in the intensive care unit: assessment of acceptability, reliability and validity of the questionnaire. *Anaesthesia* 1997; **52**: 15-23 [PMID: 9014540 DOI: 10.1111/j.1365-2044.1997.015-az014.x]

25 **Herridge MS**, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, Cooper AB, Guest CB, Mazer CD, Mehta S, Stewart TE, Barr A, Cook D, Slutsky AS; Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003; **348**: 683-693 [PMID: 12594312 DOI: 10.1056/NEJMoa022450]

26 **Herridge MS**, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, Guest CB, Mazer CD, Mehta S, Stewart TE, Kudlow P, Cook D, Slutsky AS, Cheung AM; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; **364**: 1293-1304 [PMID: 21470008 DOI: 10.1056/NEJMoa1011802]

27 **Brazier J**, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and SF-6D across seven patient groups. *Health Econ* 2004; **13**: 873-884 [PMID: 15362179 DOI: 10.1002/hec.866]

28 **Stolk E**, Ludwig K, Rand K, van Hout B, Ramos-Goñi JM. Overview, Update, and Lessons Learned From the International EQ-5D-5L Valuation Work: Version 2 of the EQ-5D-5L Valuation Protocol. *Value Health* 2019; **22**: 23-30 [PMID: 30661630 DOI: 10.1016/j.jval.2018.05.010]

29 **McDonough CM**, Grove MR, Tosteson TD, Lurie JD, Hilibrand AS, Tosteson AN. Comparison of EQ-5D, HUI, and SF-36-derived societal health state values among spine patient outcomes research trial (SPORT) participants. *Qual Life Res* 2005; **14**: 1321-1332 [PMID: 16047507 DOI: 10.1007/s11136-004-5743-2]

30 **Dolan P**, Roberts J. Modelling valuations for Eq-5d health states: an alternative model using differences in valuations. *Med Care* 2002; **40**: 442-446 [PMID: 11961478 DOI: 10.1097/00005650-200205000-00009]

31 **Walters SJ**, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005; **14**: 1523-1532 [PMID: 16110932 DOI: 10.1007/s11136-004-7713-0]

32 **Guo HJ**, Sapra A. Instrumental Activity of Daily Living. In: StatPearls. Treasure Island (FL): StatPearls Publishing, 2021 Available from: http://www.ncbi.nlm.nih.gov/books/NBK553126/

33 **Vest MT**, Murphy TE, Araujo KL, Pisani MA. Disability in activities of daily living, depression, and quality of life among

older medical ICU survivors: a prospective cohort study. *Health Qual Life Outcomes* 2011; **9**: 9 [PMID: 21294911 DOI: 10.1186/1477-7525-9-9]

34 **Hopkins RO**, Suchyta MR, Kamdar BB, Darowski E, Jackson JC, Needham DM. Instrumental Activities of Daily Living after Critical Illness: A Systematic Review. *Ann Am Thorac Soc* 2017; **14**: 1332-1343 [PMID: 28463657 DOI: 10.1513/AnnalsATS.201701-059SR]

35 **Dowdy DW**, Eid MP, Dennison CR, Mendez-Tellez PA, Herridge MS, Guallar E, Pronovost PJ, Needham DM. Quality of life after acute respiratory distress syndrome: a meta-analysis. *Intensive Care Med* 2006; **32**: 1115-1124 [PMID: 16783553 DOI: 10.1007/s00134-006-0217-3]

36 **Xie F**, Pullenayegum E, Gaebel K, Bansback N, Bryan S, Ohinmaa A, Poissant L, Johnson JA; Canadian EQ-5D-5L Valuation Study Group. A Time Trade-off-derived Value Set of the EQ-5D-5L for Canada. *Med Care* 2016; **54**: 98-105 [PMID: 26492214 DOI: 10.1097/MLR.0000000000000447]

37 **Kyeremanteng K**, Wan C, D'Egidio G, Neilipovitz D. Approach to economic analysis in critical care. *J Crit Care* 2016; **36**: 92-96 [PMID: 27546754 DOI: 10.1016/j.jcrc.2016.07.004]

38 **Auriemma CL**, Nguyen CA, Bronheim R, Kent S, Nadiger S, Pardo D, Halpern SD. Stability of end-of-life preferences: a systematic review of the evidence. *JAMA Intern Med* 2014; **174**: 1085-1092 [PMID: 24861560 DOI: 10.1001/jamainternmed.2014.1183]

39 **Flokstra-de Blok BM**, Oude Elberink JN, Vlieg-Boerstra BJ, Duiverman EJ, Dubois AE. Measuring health-related quality of life: fundamental methodological issues. *Clin Exp Allergy* 2009; **39**: 1774; author reply 1175 [PMID: 19860820 DOI: 10.1111/j.1365-2222.2009.03376.x]

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ORIGINAL ARTICLE

Observational Study

Septic shock 3.0 criteria application in severe COVID-19 patients: An unattended sepsis population with high mortality risk

José Pedro Cidade, LM Coelho, Vasco Costa, Rui Morais, Patrícia Moniz, Luís Morais, Pedro Fidalgo, António Tralhão, Carolina Paulino, David Nora, Bernardino Valério, Vítor Mendes, Camila Tapadinhas, Pedro Povoa

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José Pedro Cidade, Polyvalent Intensive Care Unit, Hospital São Francisco Xavier, Centro Hospitalar Lisboa Ocidental, Lisboa 1449-005, Portugal

LM Coelho, Polyvalent Intensive Care Unit, Hospital Sao Francisco Xavier, Centro Hospitalar Lisboa Ocidental, Lisbon 1449-005, Portugal

Vasco Costa, Rui Morais, Patrícia Moniz, Luís Morais, Pedro Fidalgo, António Tralhão, Carolina Paulino, David Nora, Bernardino Valério, Camila Tapadinhas, Polyvalent Intensive Care Unit, Hospital São Francisco Xavier, Centro Hospitalar Lisboa Ocidental, Lisbon 1449-005, Portugal

Vítor Mendes, Polyvalent Intesive Care Unit, Hospital São Francisco Xavier, Centro Hospitalar Lisboa Ocidental, Lisbon 1449-005, Portugal

Pedro Povoa, Polyvalent Intens Care Unit; NOVA Medical School, Hospital Sao Francisco Xavier, Centro Hospitalar Lisboa Ocidental, Lisbon 1449-005, Portugal

Corresponding author: José Pedro Cidade, MD, Doctor, Polyvalent Intensive Care Unit, Hospital São Francisco Xavier, Centro Hospitalar Lisboa Ocidental, Estrada forte alto do duque, Lisboa 1449-005, Portugal. zencidade@gmail.com

Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) can be associated with life-threatening organ dysfunction due to septic shock, frequently requiring intensive care unit (ICU) admission, respi-ratory and vasopressor support. There-fore, clear clinical criteria are pivotal for early recognition of patients more likely to need prompt organ support. Although most patients with severe COVID-19 meet the Sepsis-3.0 criteria for septic shock, it has been increasingly recognized that hyperlactatemia is frequently absent, possibly leading to an underestimation of illness severity and mortality risk.

AIM

To identify the proportion of severe COVID-19 patients with vasopressor support requirements, with and without hyperlactatemia, and describe their clinical outcomes and mortality.

METHODS
We performed a single-center prospective cohort study. All adult patients admitted to the ICU with COVID-19 were included in the analysis and were further divided into three groups: Sepsis group, without both criteria; Vasoplegic Shock group, with persistent hypotension and vasopressor support without hyperlactatemia; and Septic Shock 3.0 group, with both criteria. COVID-19 was diagnosed using clinical and radiologic criteria with a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive RT-PCR test.

RESULTS
118 patients (mean age 63 years, 87% males) were included in the analysis (n = 51 Sepsis group, n = 26 Vasoplegic Shock group, and n = 41 Septic Shock 3.0 group). SOFA score at ICU admission and ICU length of stay were different between the groups (P < 0.001). Mortality was significantly higher in the Vasoplegic Shock and Septic Shock 3.0 groups when compared with the Sepsis group (P < 0.001) without a significant difference between the former two groups (P = 0.713). The log rank tests of Kaplan-Meier survival curves were also different (P = 0.007). Ventilator-free days and vasopressor-free days were different between the Sepsis *vs* Vasoplegic Shock and Septic Shock 3.0 groups (both P < 0.001), and similar in the last two groups (P = 0.128 and P = 0.133, respectively). Logistic regression identified the maximum dose of vasopressor therapy used (AOR 1.046; 95%CI: 1.012-1.082, P = 0.008) and serum lactate level (AOR 1.542; 95%CI: 1.055-2.255, P = 0.02) as the major explanatory variables of mortality rates ($R^2$0.79).

CONCLUSION
In severe COVID-19 patients, the Sepsis 3.0 criteria of septic shock may exclude approximately one third of patients with a similarly high risk of a poor outcome and mortality rate, which should be equally addressed.

Key Words: COVID-19; Critical care; SARS-CoV-2; Septic shock; Lactate; Sepsis 3.0 criteria

Core Tip: Coronavirus disease 2019 (COVID-19) can be associated with life-threatening organ dysfunction due to septic shock, frequently requiring intensive care unit admission, respiratory and vasopressor support. Although most patients with severe COVID-19 meet the Sepsis-3.0 criteria for septic shock, it has been increasingly recognized that hyperlactatemia is frequently absent. Our data clearly show that one third of patients with Sepsis by the Sepsis 3.0 criteria present a risk of poor outcomes and a mortality rate similar to those with Septic Shock, which should be equally addressed.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) can be associated with life-threatening organ dysfunction due to septic shock, frequently requiring intensive care unit (ICU) admission, respiratory and vasopressor support[1]. Surviving Sepsis Campaign guidelines for the management of critically ill adults with COVID-19 document a highly variable prevalence of septic shock in these patients ranging from 1 to 35%[2,3].

Clear clinical criteria of septic shock in this population are, therefore, pivotal for early recognition of patients more likely to have poor outcomes and high mortality.

Since its publication in 2016, the Sepsis 3.0 criteria for septic shock have been validated in several studies, as a superior predictor of in-hospital mortality, with an association of a greater than 40% hospital mortality rate[3-5]. Vasopressor requirement in the absence of hypovolemia and serum lactate level greater than 2 mmol/L (> 18 mg/dL) have been recommended for use as a clinical marker combination for risk stratification in patients with infection[3-6].

Although patients with severe COVID-19 frequently meet the Sepsis 3.0 criteria for septic shock, it has been increasingly recognized that, in this population, hyperlactatemia is frequently absent, even in

markedly hypotensive patients requiring high doses of vasopressors. This potentially underrecognized population might still have a high illness severity and mortality risk, indicating the need for similar close clinical surveillance and prompt organ support as COVID-19 septic shock patients defined by Sepsis 3.0 criteria.

This study aimed to identify the proportion of patients with severe COVID-19 and hypotension despite adequate volume resuscitation, requiring vasopressor support to achieve a mean arterial pressure (MAP) > 65 mmHg, with and without hyperlactatemia, in the ICU, and describe their clinical outcomes and mortality rate.

MATERIALS AND METHODS

Study design and population

A single-center prospective observational cohort study was conducted over a 9-month period between March 2020 and January 2021. Data were collected from consecutive adult patients, admitted to the ICU, using the patient's electronic medical records, in Centro Hospitalar Lisboa Ocidental, in Lisbon, Portugal. The study was approved by the National Ethics Committee for Clinical Research (reference REC: 2020_EO_02).

Eligibility criteria included age equal to or above 18 years old and admission to an ICU with multi-organ failure secondary to COVID-19 pneumonia, described as the development of potentially reversible physiological derangement involving two or more organ systems or a change in baseline SOFA score of 2 points or more. COVID-19 respiratory infection was diagnosed using clinical and radiological criteria of pulmonary involvement with a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive RT-PCR test. Subjective complaints of dyspnea, fatigue, loss of taste or smell, fever, chest pain, nausea and diarrhea were considered as clinical criteria and interstitial opacities, alveolar opacities, consolidations and/or pleural effusions were considered as radiological criteria of SARS-CoV-2 pneumonia.

Patients included in the analysis were further divided according to the presence of hyperlactatemia (lactate > 2 mmol/L) and persistent hypotension with vasopressor support, and 3 groups were identified: Sepsis group, without both criteria; Vasoplegic Shock group, with persistent hypotension with vasopressor support without hyperlactatemia; and Septic Shock 3.0 group, with both criteria.

Data collection and end-points

Demographic characteristics were recorded at baseline for all patients including comorbidities, days of symptoms of SARS-CoV-2 infection and SOFA score at admission. Daily measurements of vital signs (including minimum MAP and maximum respiratory rate), ventilation variables (including minimum ratio partial pressure arterial oxygen and the fraction of inspired oxygen, time of ventilation in the prone position and duration of neuromuscular blockade), hemodynamic support (including the use of vasopressor therapy and maximum dosage of vasopressor support), renal function (including rate of replacement therapy and maximum creatinine level registered), laboratory variables (including hemoglobin, troponin I, lactate, C-reactive protein, and procalcitonin), prescribed therapies (remdesivir and dexamethasone) and outcomes (discharged alive or death in the ICU) were also collected for every admitted patient for statistical analysis.

The number of secondary infections per patient was also collected in the three groups. The association of (1) clinical suspicion of new onset infection, (2) with persistent or increased inflammatory serum biomarkers, (3) requiring antibiotic therapy, (4) in a patient with a length of ICU stay of at least 48 h were the criteria used for the definition of secondary infection. Positive microbiological cultures or microbial identification were not used as exclusion criteria for this definition.

Primary outcomes included 28-day mortality rate. As secondary outcomes, in-hospital mortality rate, ventilator-free days and vasopressor-free days at day 28 were determined.

Statistical analysis

All Gaussian distributed variables were expressed as mean and SD, and non-normally distributed variables as median [interquartile range (IQR)]. Categorical variables were expressed as numbers and percentages.

The chi-square test was used for categorical variables, and the *t*-test and Kruskal-Wallis test were used on continuous variables for statistical assessment of outcomes between groups. Kaplan-Meier survival curves and log-rank tests were also obtained to ascertain and compare survival between the groups.

Multiple logistic regression modeling for in-hospital mortality rate was carried out considering minimum blood pressure registered, maximum dose of vasopressor therapy, maximum serum lactate level, maximum troponin level, minimum hemoglobin level, and maximum C-reactive protein and procalcitonin levels as variables to fit the model. The model was further adjusted for patients' gender, age, and SOFA score at admission.

To assess the ability of the "serum lactate level" and "maximum vasopressor therapy used" variables in predicting the primary endpoints, diagnostic performances were calculated and receiver operating characteristic (ROC) curves were constructed in order to ascertain the corresponding area under the ROC curve (AUROC).

In all the hypothesis tests, a P value less than 0.05 was considered statistically significant and the usual confidence intervals of 95% were chosen.

RESULTS

In total, 118 patients were included during the study period, 51 (43.2%) in the Sepsis group, 26 (22%) in the Vasoplegic Shock group, and 41 (34.8%) in the Septic Shock 3.0 group. No patient with hyperlactatemia and normal arterial blood pressure was identified. Patients' baseline characteristics are summarized in Table 1.

The mean age was 63 (± 13.1) years and a statistically significant difference was observed between the three groups with an older subset of patients in the Septic Shock 3.0 group. There was no difference in gender or in patient body mass index distribution.

SOFA score at admission, respiratory support, hemodynamic support, maximum creatinine, C-reactive protein and maximum procalcitonin levels, shown in Table 1, were different between the 3 groups, but without statistical significance between the Vasoplegic Shock and Septic Shock 3.0 groups. In addition, maximum serum lactate level was not different between the Sepsis and Vasoplegic Shock groups (1.64 ± 0.56 mg/dL *vs* 1.39 ± 0.35 mg/dL, respectively, $P = 0.134$). Similarly, secondary infection rates per patient, were different between the three groups ($P < 0.0001$) without statistical significance between the Vasoplegic Shock and Septic Shock 3.0 groups ($P = 0.041$).

The analysis of primary outcomes revealed an overall in-hospital mortality of 23.7%. The mortality rate was significantly higher in the Vasoplegic Shock (26,9%) and Septic Shock 3.0 groups (46%) when compared to the Sepsis group (3.9%) ($P = 0.026$ and $P = 0.0003$, respectively) without statistical significance between the former two groups ($P = 0.713$). 28-day mortality rate was also not statistically different between the Vasoplegic Shock and Septic Shock 3.0 groups ($P = 0.619$) (Figure 1).

Secondary outcomes are presented in Table 2. Ventilator free-days and vasopressor free-days at day 28 were statistically different between the Sepsis group and Vasoplegic Shock ($P < 0.001$, in both tests) and Septic Shock 3.0 groups ($P < 0.001$, in both tests), without statistical differences between the last two groups ($P = 0.128$ and $P = 0.133$, respectively).

Multivariable logistic regression analysis adjusted for gender, age, and SOFA score at admission, identified the maximum dose of vasopressor therapy used (AOR 1.046; 95%CI: 1.012-1.082, $P = 0.008$) and serum lactate level (AOR 1.542; CI 95%: 1.055-2.255, $P = 0.02$) as the major explanatory variables of mortality rates (R^2 0.79).

The AUROC curves for prediction of 28-day mortality rate, by serum lactate level and maximum vasopressor therapy dosage used, were constructed and are presented in Figure 2. The highest AUROC was for the maximum vasopressor therapy dosage used (0.81; 95%CI: 0.696-0.922) when compared to serum lactate level (0.645; 95%CI: 0.491-0.799).

DISCUSSION

Despite the general acceptance of the Sepsis-3 Task Force update of the defining criteria for septic shock, several lines of investigation have questioned its clinical sensitivity to reliably perform clinical decision-making and identification of patients with a high risk of complications and mortality[7-12]. This was further questioned when its criteria were preferably indicated for a coding and epidemiological application, and not intended as a clinical screening tool.

Our study clearly shows that using the Sepsis 3.0 criteria there was a proportion of hypotensive patients with vasopressor support without hyperlactatemia ($n = 26$; 22%), that, despite being classified as "Sepsis", had outcomes that were clearly different to those found in that group and superimposable to those in the Septic Shock 3.0 group. This potential discriminative inaccuracy favors patients to be diagnosed with Sepsis, despite illness severity and mortality similar to Septic Shock 3.0 patients, and they should be treated equally.

Furthermore, COVID-19 patients' mortality rates have been strongly and positively associated with ventilation and hemodynamic support, especially when critically ill and in need of ICU care[13,14], depending on reliable criteria to institute prompt and adequate organ support and improve outcomes.

Our data show that the use of hyperlactatemia as a criterion to clinically classify COVID-19 patients as having septic shock may undermine the sensitivity of our assessment of patients' severity and prognosis in this population. This evidence is in accordance with previously published studies describing the existence of different ICU patients' profiles, within the definition of Sepsis with concomitant different outcome and mortality rates[15,16].

Table 1 Demographic and primary clinical characteristics in the Sepsis, vasoplegic shock and septic shock 3.0 groups

IQR	Sepsis	Vasoplegic shock	Septic shock 3.0	Total	*P*
	(*n* = 51)	(*n* = 26)	(*n* = 41)	(*n* = 118)	
Age, years (mean ± SD)	59.51 ± 13.7	61.9 ± 12.9	68.7 ± 10.6	63.3 ± 13.1	0.005
Gender, males (*n*)	38	19	30	87	0.986
Body mass index (mean ± SD)	27.56 ± 4.44	29.67 ± 6.7	27.9 ± 4.1	28.2 ± 4.9	0.591
SOFA at admission [mean (IQR)]	3.04 (2; 4)	5.88 (3; 8)	7.14 (4; 9)	5.13 (2; 7.8)	< 0.001
Mechanical ventilation (*n*)	5	26	37	68	< 0.001
Length of mechanical ventilation, d [mean (IQR)]	1.06 (0; 2)	12.5 (4.75;17)	19.3 (7.5; 28)	9.9 (0; 17.3)	< 0.001
Minimum paO2/FiO2 registered (mean ± SD)	181.9 ± 82.1	104.9 ± 69.2	92 ± 64.5	133.7 ± 84.4	< 0.001
Ventilation in prone position, h [mean (IQR)]	4.55 (3; 5.1)	70.2 (0; 134.8)	129.1 (0; 187.5)	62.3 (0; 96)	< 0.001
Length of neuromuscular blockade, d [mean (IQR)]	0 (0; 0)	6.5 (2; 9.3)	8.3 (3; 16.5)	4.9 (0; 8.3)	< 0.001
Vasopressor support (*n*)	0	26	41	67	< 0.001
Minimum blood pressure registered, mmHg (mean ± SD)	60.1 ± 11.3	52.8 ± 8.1	48.7 ± 9.5	54.5 ± 11.2	< 0.001
Maximum dose of vasopressor therapy, μg/kg (mean ± SD)	-	22.5 ± 18.8	30.5 ± 16.3	15.6 ± 18.9	< 0.001
Maximum serum lactate level, mg/dL (mean ± SD)	1.64 ± 0.56	1.39 ± 0.35	3.88 ± 2.8	2.36 ± 2	< 0.001
Maximum serum troponin level, ng/mL [mean (IQR)]	22.04 (6; 25)	103.4 (17.75; 124.8)	129.7 (40; 166.5)	77.4 (13; 93)	< 0.001
Minimum serum hemoglobin level, g/dL (mean ± SD)	11.4 ± 2.1	9.3 ± 2	8.1 ± 1.8	9.8 ± 2.5	< 0.001
Maximum serum C-reactive protein, mg/dL (mean ± SD)	18.2 ± 9.45	30.2 ± 9.9	31.9 ± 8.8	25.6 ± 11.3	< 0.001
Maximum serum Procalcitonin, ng/mL [mean (IQR)]	2.29 (0.1; 0.8)	6.65 (0.4; 5.9)	10.4 (1.1; 12.4)	6.23 (0.3; 5.9)	< 0.001
Maximum creatinine level registered, mg/dL [mean (IQR)]	1.68 (0.82; 1.2)	2.66 (0.83; 2.54)	3 (1.3; 3.8)	2.36 (0.9; 2.8)	< 0.001
Renal support therapy (*n*)	4 (8%)	7 (3%)	20 (49%)	31 (26%)	< 0.001
Secondary infections, per patient [mean (IQR)]	0.16 (0; 0)	0.63 (0; 1)	1.1 (0; 1.5)	0.55 (0; 1)	< 0.001
Remdesivir (*n*, %)	22 (43%)	13 (50%)	20 (49%)	55 (47%)	0.8
Corticosteroid therapy (*n*)	14 (27%)	4 (15%)	20 (49%)	38 (32%)	0.01

IQR: Interquartile range; SD: Standard deviation.

Table 2 Primary and secondary outcomes in sepsis, vasoplegic shock and septic shock 3.0 groups

	Sepsis	Vasoplegic shock	Septic shock 3.0	Total	*P*
	(*n* = 51)	(*n* = 26)	(*n* = 41)	(*n* = 118)	
Ventilator free-days at day 28 (mean ± SD)	25.8 ± 6.4	11.4 ± 9.1	5.17 ± 8.9	15.4 ± 12.3	< 0.001
Vasopressor free-days at day 28 (mean ± SD)	26.9 ± 5.5	15.7 ± 10.4	7.76 ± 10.2	17.8 ± 12	< 0.001
ICU length of stay, days (mean ± SD)	6.86 ± 5.1	15.9 ± 8.2	24.3 ± 15.1	14.9 ± 12.8	< 0.001
In-hospital death rate (*n*)	2	7	19	28	< 0.001

SD: Standard deviation.

The overlap in ventilator and vasopressor free-days and in-hospital mortality rate and 28-day mortality rates (Table 2), in the Vasoplegic Shock and Septic Shock 3.0 groups, provides evidence that further supports the premise of a similar illness severity between these two groups. These data might indicate that occult hypoperfusion may still be present in COVID-19 patients[17], even with normal serum lactate levels, accounting for its systemic dysfunction and compromising patients' survivability. This was reinforced by the fact that the maximum dose of vasopressor therapy used was one of the major explanatory variables of mortality rates across the three groups when adjusted to lactate levels.

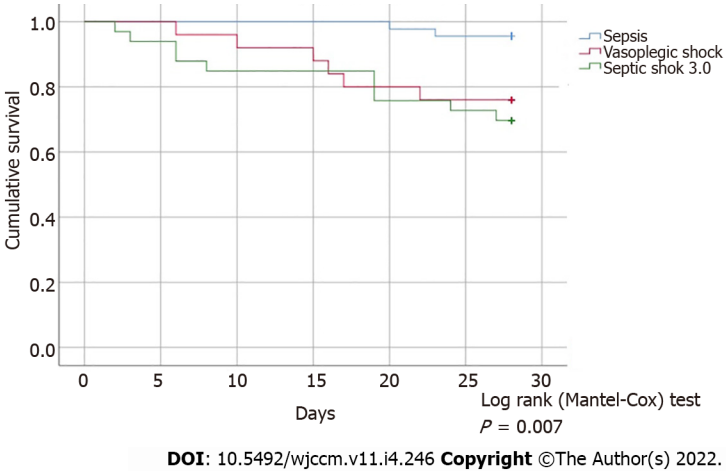

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Figure 1 Kaplan-Meier Survival curves of Sepsis, Vasoplegic shock and Septic shock 3.0 groups.

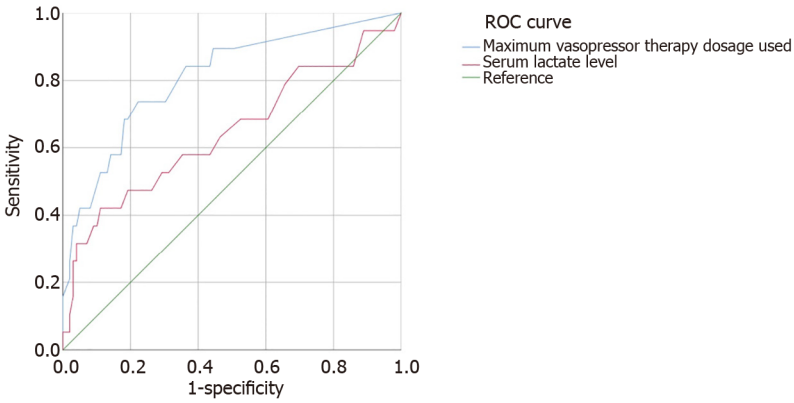

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Figure 2 Receiver operating characteristic curves of maximum vasopressor therapy dosage used and serum lactate level on the cohort's mortality. ROC: Receiver operating characteristic.

Moreover, COVID-19 patients belonging to the Septic shock 3.0 group presented with higher values of SOFA on ICU admission, a higher need for mechanical ventilation, poorer respiratory severity indices, and higher dosages of vasopressor support, when compared to patients in the Vasoplegic Shock group. However, no statistically significant differences were found between these two groups regarding these indices. These results are similar to those previously obtained by Verboom *et al*[18] in 2019, which demonstrated a high percentage of agreement in mortality between patients with and without hyperlactatemia, under septic shock conditions.

Our study provides evidence that the use of Sepsis 3.0 criteria can undervalue severely ill COVID-19 patients. According to their clinical requirements and prognosis, a group of patients, equally severe to Septic Shock 3.0, are being classified as having Sepsis. It is clear that it would be safer for these patients (those with persistent hypotension with vasopressor support without hyperlactatemia) to have a different classification, to account for their increased mortality risk and poor prognosis, in addition to their subsequent need for close clinical monitoring, prompt diagnosis, and adequate resuscitation. This is in concordance with significantly better accuracy of hypotension with vasopressor support when compared to hyperlactatemia, to predict the mortality rate of COVID-19 patients.

These study results are strengthened by the robust structure and data prospectively collected. Furthermore, the homogeneity of supportive care across the compared groups limits some potential biases on the analyzed outcomes. However, it is not without some limitations. Although COVID-19 pneumonia was necessary for statistical analysis eligibility, it lacked information on potential confounders of co-infections or other causes of shock, before ICU admission. On the other hand, the potential complications during ICU stay that could justify hyperlactatemia, not directly related to COVID-19 infection, were also not registered.

CONCLUSION

In severe COVID-19 patients, the Sepsis 3.0 criteria for septic shock may exclude approximately one-third of patients with a similarly high risk of poor outcomes and mortality rate, which should be equally addressed. Considering the importance of early recognition of septic shock in COVID-19 patients to improve their survival, the presence of hypotension with vasopressor support, even without hyperlactatemia, demonstrated strong prognostic accuracy for mortality.

ARTICLE HIGHLIGHTS

Research background

The Sepsis 3.0 criteria for sepsis and septic shock have been extensively used in the definition of severe patients, admitted to hospital care and intensive care, in order to adequately define a subset of patients with poor prognosis and higher mortality rates.

Since its publication in 2016, its use has been presented as a good diagnostic tool to define these patients and to promptly initiate organic support. Coronavirus disease 2019 (COVID-19) patients present a strong association with life-threatening organ dysfunction due to septic shock and frequently require intensive care unit (ICU) admission and organ support.

Research motivation

COVID-19 patients frequently lack hyperlactatemia, a necessary clinical criteria to define septic shock using the Septic Shock 3.0 criteria. Therefore, this could potentially lead to an unrecognized subset of these patients who have a high illness severity and mortality risk, and are inaccurately classified as having sepsis.

Research objectives

This study aimed to identify the proportion of patients with severe COVID-19 with vasopressor requirements without hyperlactatemia and describe their clinical outcomes and mortality rate.

Research methods

A single-center prospective observational cohort study was conducted in a tertiary hospital in Portugal, analyzing adult patients, admitted to the ICU, with COVID-19 pneumonia. Data collection was extensive, providing data on comorbidities, clinical status, severity indices, respiratory, hemodynamic, and renal dysfunction and the outcome of these COVID-19 patients.

Research results

Twenty-two percent of the analyzed COVID-19 patients were found to have persistent hypotension despite adequate volume resuscitation, requiring vasopressor support, and without hyperlactatemia. This "Vasoplegic Shock" group was found to have high 28-day and hospital mortality rates, and few vasopressor-free days and ventilator-free days, without significant differences to those in the "Septic Shock" group, but significantly different to those in the Sepsis group. Multivariable logistic regression identified the maximum dose of vasopressor therapy used and serum lactate level as the major explanatory variables of mortality rates. However, the highest AUROC was for the maximum vasopressor therapy dosage used when compared to serum lactate level.

Research conclusions

The Sepsis 3.0 criteria for septic shock may exclude approximately one-third of patients with similar clinical severity, poor outcomes, and mortality rate, which should be equally addressed.

Research perspectives

Further studies are needed to identify a subset of COVID-19 patients, who were not initially admitted to the ICU, despite persistent hypotension with vasopressor requirements, and describe their clinical course and outcomes, further demonstrating a potential need to redefine the septic shock criteria in COVID-19 patients in order to maximize early recognition and prompt adequate surveillance and support.

FOOTNOTES

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Póvoa P reviewed and edited the original draft and contributed to project supervision.

Institutional review board statement: The study was approved by the Portuguese National Ethics Committee for Clinical Research (reference REC: 2020_EO_02).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare that they have no conflict-of-interest to disclose.

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Country/Territory of origin: Portugal

ORCID number: José Pedro Cidade 0000-0002-8359-5171; LM Coelho 0000-0003-0701-3624; Vasco Costa 0000-0001-8701-7411; Rui Morais 0000-0003-4114-6949; Patrícia Moniz 0000-0003-1415-3545; Luís Morais 0000-0002-3990-2437; Pedro Fidalgo 0000-0001-8835-0969; António Tralhão 0000-0002-0163-6508; Carolina Paulino 0000-0002-5870-9544; David Nora 0000-0002-1133-7368; Bernardino Valério 0000-0002-7560-4891; Vítor Mendes 0000-0002-3074-9392; Camila Tapadinhas 0000-0002-2008-5262; Pedro Povoa 0000-0002-7069-7304.

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REFERENCES

1 **Del Sole F**, Farcomeni A, Loffredo L, Carnevale R, Menichelli D, Vicario T, Pignatelli P, Pastori D. Features of severe COVID-19: A systematic review and meta-analysis. *Eur J Clin Invest* 2020; **50**: e13378 [PMID: 32860457 DOI: 10.1111/eci.13378]

2 **Alhazzani W**, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, Oczkowski S, Levy MM, Derde L, Dzierba A, Du B, Aboodi M, Wunsch H, Cecconi M, Koh Y, Chertow DS, Maitland K, Alshamsi F, Belley-Cote E, Greco M, Laundy M, Morgan JS, Kesecioglu J, McGeer A, Mermel L, Mammen MJ, Alexander PE, Arrington A, Centofanti JE, Citerio G, Baw B, Memish ZA, Hammond N, Hayden FG, Evans L, Rhodes A. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med* 2020; **46**: 854-887 [PMID: 32222812]

3 **Alhazzani W**, Evans L, Alshamsi F, Møller MH, Ostermann M, Prescott HC, Arabi YM, Loeb M, Ng Gong M, Fan E, Oczkowski S, Levy MM, Derde L, Dzierba A, Du B, Machado F, Wunsch H, Crowther M, Cecconi M, Koh Y, Burry L, Chertow DS, Szczeklik W, Belley-Cote E, Greco M, Bala M, Zarychanski R, Kesecioglu J, McGeer A, Mermel L, Mammen MJ, Nainan Myatra S, Arrington A, Kleinpell R, Citerio G, Lewis K, Bridges E, Memish ZA, Hammond N, Hayden FG, Alshahrani M, Al Duhailib Z, Martin GS, Kaplan LJ, Coopersmith CM, Antonelli M, Rhodes A. Surviving Sepsis Campaign Guidelines on the Management of Adults With Coronavirus Disease 2019 (COVID-19) in the ICU: First Update. *Crit Care Med* 2021; **49**: e219-e234 [PMID: 33555780 DOI: 10.1097/CCM.0000000000004899]

4 **Sinha S**, Ray B. Sepsis-3: How useful is the new definition? *J Anaesthesiol Clin Pharmacol* 2018; **34**: 542-543 [PMID: 30774239 DOI: 10.4103/joacp.JOACP_335_16]

5 **Chen QH**, Shao J, Liu WL, Wang HL, Liu L, Gu XH, Zheng RQ. Predictive accuracy of Sepsis-3 definitions for mortality among adult critically ill patients with suspected infection. *Chin Med J (Engl)* 2019; **132**: 1147-1153 [PMID: 30829715 DOI: 10.1097/CM9.0000000000000166]

6 **Freund Y**, Lemachatti N, Krastinova E, Van Laer M, Claessens YE, Avondo A, Occelli C, Feral-Pierssens AL, Truchot J, Ortega M, Carneiro B, Pernet J, Claret PG, Dami F, Bloom B, Riou B, Beaune S; French Society of Emergency Medicine Collaborators Group. Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department. *JAMA* 2017; **317**: 301-308 [PMID: 28114554 DOI: 10.1001/jama.2016.20329]

7 **Giamarellos-Bourboulis EJ**, Tsaganos T, Tsangaris I, Lada M, Routsi C, Sinapidis D, Koupetori M, Bristianou M, Adamis G, Mandragos K, Dalekos GN, Kritselis I, Giannikopoulos G, Koutelidakis I, Pavlaki M, Antoniadou E, Vlachogiannis G, Koulouras V, Prekates A, Dimopoulos G, Koutsoukou A, Pnevmatikos I, Ioakeimidou A, Kotanidou A, Orfanos SE, Armaganidis A, Gogos C; Hellenic Sepsis Study Group. Validation of the new Sepsis-3 definitions: proposal for improvement in early risk identification. *Clin Microbiol Infect* 2017; **23**: 104-109 [PMID: 27856268 DOI:

10.1016/j.cmi.2016.11.003]

8 **Tusgul S**, Carron PN, Yersin B, Calandra T, Dami F. Low sensitivity of qSOFA, SIRS criteria and sepsis definition to identify infected patients at risk of complication in the prehospital setting and at the emergency department triage. *Scand J Trauma Resusc Emerg Med* 2017; **25**: 108 [PMID: 29100549 DOI: 10.1186/s13049-017-0449-y]

9 **Seymour CW**, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 762-774 [PMID: 26903335 DOI: 10.1001/jama.2016.0288]

10 **Ranzani OT**, Prina E, Menéndez R, Ceccato A, Cilloniz C, Méndez R, Gabarrus A, Barbeta E, Bassi GL, Ferrer M, Torres A. New Sepsis Definition (Sepsis-3) and Community-acquired Pneumonia Mortality. A Validation and Clinical Decision-Making Study. *Am J Respir Crit Care Med* 2017; **196**: 1287-1297 [PMID: 28613918 DOI: 10.1164/rccm.201611-2262OC]

11 **Sterling SA**, Puskarich MA, Glass AF, Guirgis F, Jones AE. The Impact of the Sepsis-3 Septic Shock Definition on Previously Defined Septic Shock Patients. *Crit Care Med* 2017; **45**: 1436-1442 [PMID: 28542029 DOI: 10.1097/CCM.0000000000002512]

12 **Carneiro AH**, Póvoa P, Gomes JA. Dear Sepsis-3, we are sorry to say that we don't like you. *Rev Bras Ter Intensiva* 2017; **29**: 4-8 [PMID: 28444066 DOI: 10.5935/0103-507X.20170002]

13 **Izcovich A**, Ragusa MA, Tortosa F, Lavena Marzio MA, Agnoletti C, Bengolea A, Ceirano A, Espinosa F, Saavedra E, Sanguine V, Tassara A, Cid C, Catalano HN, Agarwal A, Foroutan F, Rada G. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. *PLoS One* 2020; **15**: e0241955 [PMID: 33201896 DOI: 10.1371/journal.pone.0241955]

14 **Andrés M**, Leon-Ramirez JM, Moreno-Perez O, Sánchez-Payá J, Gayá I, Esteban V, Ribes I, Torrus-Tendero D, González-de-la-Aleja P, Llorens P, Boix V, Gil J, Merino E; COVID19-ALC research group. Fatality and risk features for prognosis in COVID-19 according to the care approach - a retrospective cohort study. *PLoS One* 2021; **16**: e0248869 [PMID: 33755683 DOI: 10.1371/journal.pone.0248869]

15 **Ranzani OT**, Monteiro MB, Ferreira EM, Santos SR, Machado FR, Noritomi DT; Grupo de Cuidados Críticos Amil. Reclassifying the spectrum of septic patients using lactate: severe sepsis, cryptic shock, vasoplegic shock and dysoxic shock. *Rev Bras Ter Intensiva* 2013; **25**: 270-278 [PMID: 24553507]

16 **Sterling SA**, Puskarich MA, Shapiro NI, Trzeciak S, Kline JA, Summers RL, Jones AE; Emergency Medicine Shock Research Network (EMSHOCKNET). Characteristics and outcomes of patients with vasoplegic versus tissue dysoxic septic shock. *Shock* 2013; **40**: 11-14 [PMID: 23649098 DOI: 10.1097/SHK.0b013e318298836d]

17 **Howell MD**, Donnino M, Clardy P, Talmor D, Shapiro NI. Occult hypoperfusion and mortality in patients with suspected infection. *Intensive Care Med* 2007; **33**: 1892-1899 [PMID: 17618418 DOI: 10.1007/s00134-007-0680-5]

18 **Verboom DM**, Frencken JF, Ong DSY, Horn J, van der Poll T, Bonten MJM, Cremer OL, Klein Klouwenberg PMC. Robustness of sepsis-3 criteria in critically ill patients. *J Intensive Care* 2019; **7**: 46 [PMID: 31489199 DOI: 10.1186/s40560-019-0400-6]

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ORIGINAL ARTICLE

Observational Study

Development and pilot implementation of a patient-oriented discharge summary for critically Ill patients

Anmol Shahid, Bonnie Sept, Shelly Kupsch, Rebecca Brundin-Mather, Danijela Piskulic, Andrea Soo, Christopher Grant, Jeanna Parsons Leigh, Kirsten M Fiest, Henry T Stelfox

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Anmol Shahid, Bonnie Sept, Shelly Kupsch, Rebecca Brundin-Mather, Andrea Soo, Christopher Grant, Jeanna Parsons Leigh, Kirsten M Fiest, Henry T Stelfox, Department of Critical Care Medicine, University of Calgary, Calgary T2N 4Z6, Alberta, Canada

Danijela Piskulic, Department of Psychiatry, Hotchkiss Brain Institute, Calgary T2N 4Z6, Alberta, Canada

Jeanna Parsons Leigh, School of Health Administration, Dalhousie University, Halifax B3H 4R2, Nova Scotia, Canada

Corresponding author: Anmol Shahid, BSc, PhD, Postdoctoral Fellow, Department of Critical Care Medicine, University of Calgary, McCaig Tower, Ground Floor, 3260 Hospital Drive NW, Calgary T2N 4Z6, Alberta, Canada. anmol.shahid1@ucalgary.ca

Abstract

BACKGROUND

Patients leaving the intensive care unit (ICU) often experience gaps in care due to deficiencies in discharge communication, leaving them vulnerable to increased stress, adverse events, readmission to ICU, and death. To facilitate discharge communication, written summaries have been implemented to provide patients and their families with information on medications, activity and diet restrictions, follow-up appointments, symptoms to expect, and who to call if there are questions. While written discharge summaries for patients and their families are utilized frequently in surgical, rehabilitation, and pediatric settings, few have been utilized in ICU settings.

AIM

To develop an ICU specific patient-oriented discharge summary tool (PODS-ICU), and pilot test the tool to determine acceptability and feasibility.

METHODS

Patient-partners (*i.e.*, individuals with lived experience as an ICU patient or family member of an ICU patient), ICU clinicians (*i.e.*, physicians, nurses), and researchers met to discuss ICU patients' specific informational needs and design the PODS-ICU through several cycles of discussion and iterative revisions. Research team nurses piloted the PODS-ICU with patient and family participants in two ICUs in Calgary, Canada. Follow-up surveys on the PODS-ICU and its

impact on discharge were administered to patients, family participants, and ICU nurses.

RESULTS

Most participants felt that their discharge from the ICU was good or better (n = 13; 87.0%), and some (n = 9; 60.0%) participants reported a good understanding of why the patient was in ICU. Most participants (n = 12; 80.0%) reported that they understood ICU events and impacts on the patient's health. While many patients and family participants indicated the PODS-ICU was informative and useful, ICU nurses reported that the PODS-ICU was "not reasonable" in their daily clinical workflow due to "time constraint".

CONCLUSION

The PODS-ICU tool provides patients and their families with essential information as they discharge from the ICU. This tool has the potential to engage and empower patients and their families in ensuring continuity of care beyond ICU discharge. However, the PODS-ICU requires pairing with earlier discharge practices and integration with electronic clinical information systems to fit better into the clinical workflow for ICU nurses. Further refinement and testing of the PODS-ICU tool in diverse critical care settings is needed to better assess its feasibility and its effects on patient health outcomes.

Key Words: Discharge tool; Patient discharge summary; Patient communication; Family communication; Transitions in care; Intensive care unit

Core Tip: Critically ill patients face a difficult transition when moving home from an intensive care unit. In order to ease this transition, we developed and pilot tested a patient-oriented discharge summary tool that included information about medications, activity and diet restrictions, follow-up appointments, symptoms to expect, and who to call if there are questions. We found that critically ill patients and their families found the tool to be very informative. However, nurse practitioners found the discharge tool to be time consuming to complete and a poor fit into their clinical workflow. Further revision and testing of the tool is needed to better assess it's feasibility and determine any impact it may have on patient health outcomes.

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INTRODUCTION

The discharge of patients from the intensive care unit (ICU) is a challenging transition period that leaves patients particularly vulnerable to heightened stress and increases their chances of experiencing adverse events, being readmitted to ICU, and dying[1-4]. Many patients who report experiencing gaps in care during their transition from the ICU are dissatisfied with the quality of care they received[5]. They cite confusion due to poor communication with their healthcare team as a major contributing factor to their dissatisfaction[6,7]. Failures to effectively communicate information such as diagnoses, tests, treatments, and goals of care to patients and their family-caregivers result in poorly executed transitions in care, and impede continuity of care[8-10]. Deficiencies in communication can be further worsened by any combination of patient factors such as lack of understanding of medical terms, limited fluency in English, difficulty retaining verbal instructions, or inability to absorb critical information due to stress [11-16]. While patient-centered summary tools to communicate critical information to patients and family-caregivers (*i.e.*, family members or close friends of the patient) at discharge have been implemented, many of these tools vary in their applicability to diverse care settings and are not standardized across healthcare systems[17].

There have been a number of initiatives to improve patient and family-caregiver communication during transitions in care using written communications that facilitate and support the exchange of information from clinicians to patients and their families[18-20]. Among these are patient- and caregiver-centered discharge summaries that include information on medications, activity and diet restrictions, follow-up appointments, symptoms to expect, and who to call if there are questions[21,22].

Most patient-and caregiver-centered discharge summary tools use evidence-based techniques such as plain language, large fonts, pictograms, and teach-back components to ensure patients are engaged and develop a strong understanding of their health[23-27]. While written patient-centered discharge tools have become commonplace in surgical, rehabilitation, and pediatric settings, few have been employed in critical care settings[28-31].

To address the need for a standardized, written, patient-centered discharge tool suitable for use in the ICU, our team of patient partners (*i.e.*, previous patients and family-caregivers who now represent patients' interest in research), clinicians, and researchers aimed to incorporate ICU-specific elements into the patient-oriented discharge summary tool (PODS) co-developed by patients, the Toronto Central Local Health Integration Network, and OpenLab (Toronto, Canada). Specifically, our objectives were to: (1) Adapt the content of the PODS to the ICU context based on input from key stakeholder groups including patient partners, clinicians, and researchers (PODS-ICU); (2) Pilot test the adapted PODS-ICU in the ICU to determine its acceptability and feasibility; and (3) Gather patient, family-caregiver, and clinician perspectives on the usability of the tool and quality (*e.g.*, comprehensiveness) of information provided to patients and family-caregivers during a discharge from the ICU.

MATERIALS AND METHODS

Setting

We conducted this study in two ICUs in Calgary, Alberta, Canada. ICU A, Foothills Medical Centre, is a 28-bed medical-surgical ICU in a tertiary level academic hospital and ICU B, South Health Campus, is a 10-bed medical-surgical ICU in a community-based hospital (collective catchment population 1.4 million). Both hospitals use the same patient information systems which house ICU patients' demographics along with key clinical, healthcare service, and health outcome data[32].

Design

We designed our study as a collaborative quality improvement research project that adhered to the internationally recognized Revised Standards for Quality Improvement Reporting Excellence (SQUIRE) 2.0 guidelines for reporting new knowledge on improving healthcare[33]. We executed the study in two distinct phases: Development of the PODS-ICU and Pilot testing of the PODS-ICU in two ICUs (ICU A and ICU B).

Development of the PODS-ICU

To create a workable PODS-ICU tool and a standardized implementation process, we formed a working group of stakeholders with diverse backgrounds and extensive critical care experience. The working group included two patient partners (1 patient, 1 family-caregiver), four bedside registered nurses (RNs), two nurse practitioners (NPs), one physician, one clinical nurse specialist, a quality improvement lead, and a researcher. The working group was tasked with producing a printable (*i.e.*, not handwritten) PODS-ICU template for patients who were being discharged from the ICU to a hospital ward or directly into community settings (*i.e.*, their home). The working group met monthly to discuss and reach consensus on the content and the format for the PODS-ICU (*i.e.*, electronic *vs* paper-based templates) and to complete iterative revisions of the tool. After each meeting, minutes were circulated by email to working group members. The researcher incorporated feedback into the tool, circulating documents that mapped out the revised content areas back to the group by email. This process led to agenda building for the next working group meeting and was repeated until a consensus was reached on the PODS-ICU. In order to maximize efficient completion of the PODS-ICU, the working group decided to make the tool easily accessible to clinicians, and to permit editing of its content until it was deemed ready for pilot testing. The group agreed that the PODS-ICU should be paired with effective education methods such as teach-back, which has been shown to optimize communication between clinicians, patients, and family-caregivers[34].

Pilot test of the PODS-ICU tool

Sample and recruitment: Between August 12th and November 5th, 2019, we recruited a sample of patients and family-caregivers transitioning from the ICU to the hospital ward from ICU A. Between January 5th and March 1st, 2020 we recruited a sample of patients and family-caregivers transitioning from ICU to home from ICU B. Trained team members (RNs and NPs) were tasked with piloting the PODS-ICU in the participating sites.

We used eCritical MetaVision Alberta to identify patients who were expected to leave the study ICUs within the next 24-48 h. A patient partner and a research assistant from our study team approached patients if they were: (1) Cleared for discharge; (2) Over 18 years of age; (3) Able to provide written informed consent; and (4) able to communicate in English. Family-caregivers, defined as any individuals providing physical or emotional support to a patient (*e.g.*, a relative, friend or a formal caregiver) who had knowledge of the patient before the ICU admission, were also approached to participate in the

study. Family-caregivers were eligible to participate if they were: (1) Over 18 years of age; (2) Able to provide informed consent; and (3) Able to communicate in English. A recruitment script [Supplementary material] was used to ensure patients and family-caregivers (*i.e.*, collectively referred to as participants) were provided adequate information about the study, and understood the role of study participants. Written informed consent was collected from all participants. Participants were enrolled as dyads (*i.e.*, a patient and a family-caregiver) for this study.

PODS-ICU implementation: Patient partners informed select RNs/NPs (ICU nurses who had agreed to administer the PODS-ICU to participants) when a patient and family-caregiver had been enrolled. RN/NPs then completed the PODS-ICU tool and conducted a teach-back education session with the recruited participant (s) (*i.e.*, patient and/or family-caregiver) prior to the patient's discharge from the ICU. The RN/NP then completed a brief online questionnaire (*via* Qualtrics, Provo, Utah) [Supplementary material] to provide feedback on their experience completing the PODS-ICU (*e.g.*, ease of access, ease of use, time required to review the tool with a patient or family-caregiver) and its perceived impact on their workflow.

Participant questionnaires: The patient partner followed up with study participants, regardless of whether the PODS-ICU was successfully delivered, within one week after patient discharge from ICU to administer questionnaires assessing the quality of the discharge process. Patients and family-caregivers received separate versions of the feedback questionnaire. The follow-up was done in person for patients still present in the hospital, and over the phone for those patients who had left the hospital. Participants were administered questionnaires that inquired about how well they understood their (or the patient's) care trajectory as they were discharged from the ICU [Supplementary material]. Participants who did not respond were contacted by the patient partner up to two additional times.

PODS-ICU acceptability and feasibility: We measured the acceptability of the PODS-ICU by calculating the proportion of eligible patients and family-caregivers who consented to participate in the study. The feasibility was assessed by calculating the proportion of consented participants who received the PODS-ICU prior to discharge.

Statistical analysis

We conducted data analysis as per the standard recommendations for design and analysis of pilot studies[35] in Microsoft Excel v16.0 (Microsoft Corporation, Redmond USA. Given that our study did not involve hypothesis testing, no power analysis was conducted, and no inferential statistics were calculated. We used descriptive statistics (mean, median) to summarize participant characteristics and questionnaire data (from patients, family-caregivers, and clinicians).

RESULTS

Development of PODS-ICU

The working group held 7 meetings between December 2018 and July 2019. After drafting an initial PODS-ICU template, the working group determined that patients discharged from the ICU to another inpatient care unit differed clinically (*i.e.*, were sicker) from patients discharged from the ICU directly to the community. Hence, the two patient groups required different post-discharge information. As such, the working group developed two different versions of the PODS-ICU. Following two rounds of major revisions and multiple rounds of minor revisions, the working group standardized written content where possible to improve efficiencies in completing the PODS-ICU, while still allowing for tailoring of patient-specific information. The working group first developed the PODS-ICU tool as a Microsoft Word (2019, Redmond, USA) template accessible through the hospitals' internal Website. The final template was subsequently developed alongside an in-house collaborator and embedded into a locally developed customized software program that could be run off an encrypted USB or a desktop local drive. A side-by-side comparison of the PODS-ICU Word versions for patients being discharged from the ICU to another care unit, and PODS-ICU for patients being discharged from ICU directly home in the community is shown in Figure 1.

Pilot test of the PODS-ICU tool

Participant enrolment: During the study period, 319 patients were discharged alive from the two study ICUs. Of these, 42 patients were potentially eligible for the study. Participant recruitment and reasons for exclusion are shown in Figure 2. The most common reasons for patient exclusion were ICU stays less than 24 h in duration (n = 181 patients) and discharges on weekends when the study team (*i.e.*, patient partners) was unavailable to approach patients (n = 57). A number (n = 39) of patients were excluded based on recommendations of the clinical team to not approach for clinical or psychosocial reasons (*i.e.*, stress, family not available). Forty-two patients were approached for participation into the study, of which 10 were excluded due to inability to communicate in English and/or provide consent, and 1 for

Patient Oriented Discharge Summary (PODS-ICU) - for discharge to another unit

Alberta Health Services — Department of Critical Care Medicine Calgary

Enter patient's first name. **Intensive Care Unit (ICU) Transfer Summary**

I came to Enter hospital name hospital on **Select a date** and was admitted to the ICU on **Select date**.

I came to the ICU because Describe primary reason.

I am being transferred from the ICU on **Select date** because I have recovered enough to be sent to another inpatient unit. This summary will provide me with information to help my transfer within the hospital and when I am discharged home.

Leaving the ICU to an Inpatient Unit

Hospital Service: Enter info	Unit Number: Enter number	Location: Enter floor & building
Phone: Enter unit phone	Parking: Enter closest visitor parking lot	
Doctor's Name: Enter name or unknown at transfer		

Description of unit: The unit that I am transferring to will be different than the ICU, but the care that I will receive will be the same high standard that I received in the ICU. Nurse to patient ratios may vary; 3-6 patients per nurse is typical. Because the ratio is higher, my nurse may not be able to respond as quickly when I call; the unit may seem busier and louder than the ICU. I may be in a shared room. Hospital visiting hours are usually 9AM to 9PM; exceptions are made at the unit's discretion. I should confirm visiting hours with my new care team.

Doctors generally see patients each day between 9AM and 5PM; times may vary as the doctors also see patients on other units. At least one doctor from my team is available in hospital 24 hours a day for any emergencies that may occur. Like in the ICU, I may see many healthcare providers while on my next care unit. If I wish to see to a healthcare professional who may not immediately be involved in my care, such as a psychologist or social worker, I should talk to my nurse or doctor.

Providers: include other information relevant to transfer (e.g. anticipated time of day; lines and tubes that may travel; transport route through hospital; etc)

What happened to me in the ICU

Briefly summarize the patient's time in the ICU using plain language

How I might feel after ICU

Many patients and families find the transition out of the ICU stressful. During my ICU stay, my family and I have probably become familiar with the unit and my ICU team members (doctors, nurses, physiotherapists, social workers, etc.). Now that my ICU team has carefully evaluated my health condition and determined that I can transition to another patient care unit, all the details of my ICU stay have been handed over to my receiving care team. This includes my current care needs, medications, and ongoing plan to continue my care outside of the ICU.

Once I leave the ICU, I may experience physical, emotional, and psychological issues. My journey to recovery may take a long time. I may find that I am weak or have low energy. It may take a lot of energy to do tasks that I would not normally feel would be difficult. This can be very frustrating, and I may need extra help from a caregiver. My mood may change often. I may worry about getting sick again. My sleep may be affected and there is a chance I could experience nightmares and hallucinations after leaving the ICU. It is very important that I tell my healthcare team about any of these experiences, so they can help provide me with the necessary support. It is common to feel distress over one's ICU stay and recovery. My friends, family, and healthcare team can help me understand my ICU stay, my health condition, and my recovery.

Information about commonly experienced post-ICU issues can be found on the *Alberta Health Services ICU Recovery Website*, http://www.ahs.ca/icurecovery.

Medications I need to take

☐ A list of all my medications is available to my healthcare team on my receiving inpatient unit.

Patient Oriented Discharge Summary (PODS-ICU) - for discharge to community

Alberta Health Services — Department of Critical Care Medicine Calgary

Enter patient's first name. **Intensive Care Unit (ICU) Discharge Summary**

I came to Enter hospital name hospital on **Select a date** and was admitted to the ICU on **Select date**.

I came to the ICU because Describe primary reason..

I am being discharged from the ICU on **Select date** because I have recovered enough to be sent home. However, it is very important that I continue to take care of myself and talk with my family doctor when I get home. This summary will provide me with information to help me do this

"Leaving the ICU to an Inpatient Unit" is not included on Patient ICU Discharge Summary.

What happened to me in the ICU

Briefly summarize the patient's time in the ICU using plain language

How I might feel after ICU

Many patients and families can find the transition out of the ICU stressful. My ICU team has carefully evaluated my health condition and determined that I am now well enough to safely transition directly home. All the details of my ICU stay are available in my electronic medical record which is available to my family doctor. This includes my current care needs, medications, and ongoing care plan to continue my care in the community.

Once I leave the ICU, I may experience physical, emotional, and psychological issues. My journey to recovery may take a long time. I may find that I am weak or have low energy. It may take a lot of energy to do tasks that I would not normally feel would be difficult. This can be very frustrating, and I may need extra help from a caregiver. My mood may change often. I may worry about getting sick again. My sleep may be affected and there is a chance I could experience nightmares and hallucinations after leaving the ICU. It is very important that I address any of these experiences with my healthcare team so they can help provide me with the necessary support. It is common to feel distress over one's ICU stay and recovery. My friends, family, and healthcare team can help me understand my ICU stay, my health condition, and my recovery.

Information about commonly experienced post-ICU issues can be found on the Alberta Health Services ICU Recovery Website, http://www.ahs.ca/icurecovery.

Medications I need to take

☐ Yes	A list of all my medications with instructions has been given to me (**handout**)
☐ Yes	My medications and their purpose has been explained to me.
☐ Yes	Prescriptions for the following medications have been faxed to the pharmacy: Enter pharmacy name/location if needed
☐ Yes	Prescriptions for these medications have been given to me. I need to take these prescriptions to my pharmacy.
	- Enter prescriptions

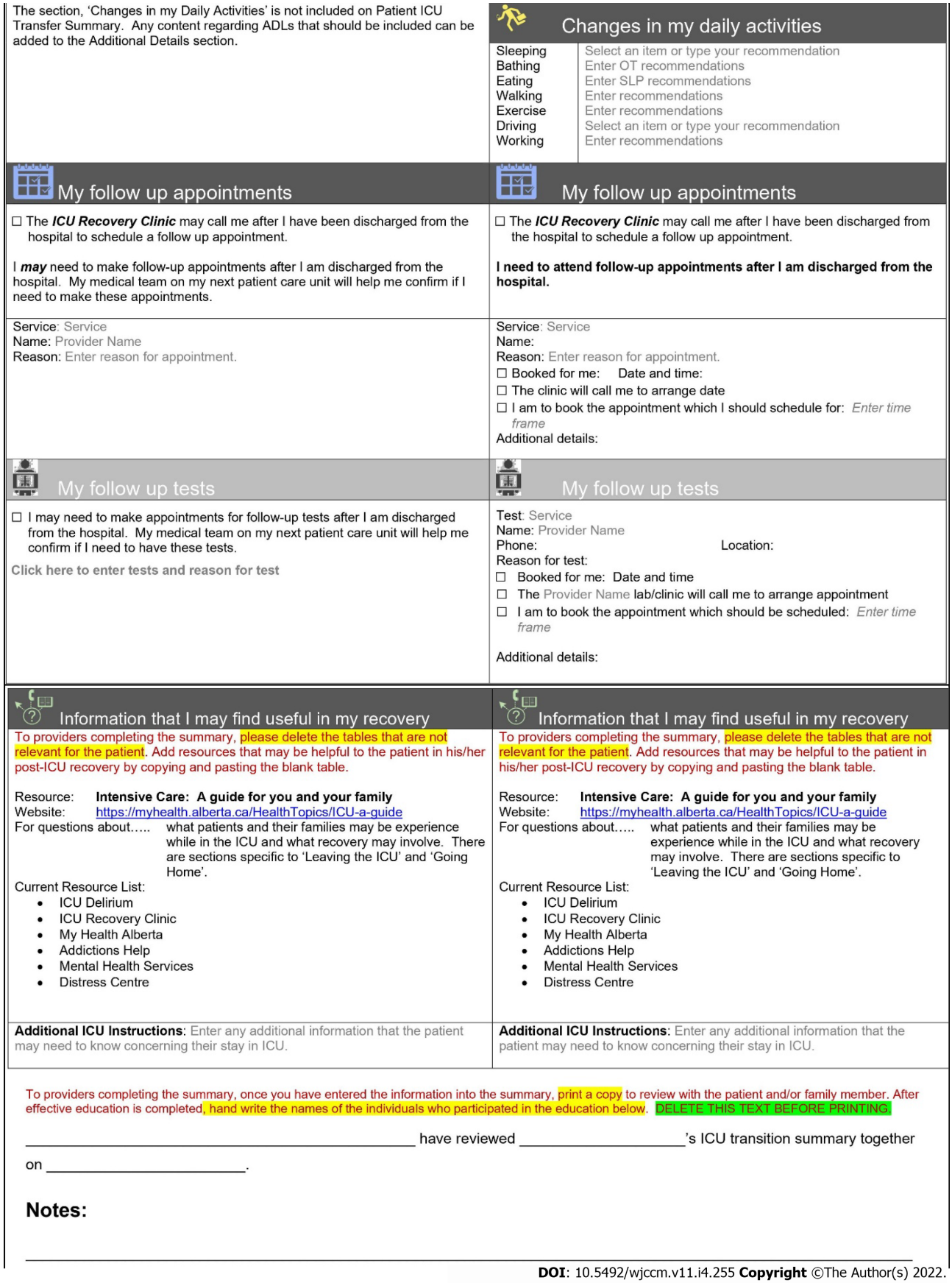

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Figure 1 A side-by-side comparison of the patient-oriented discharge summary intended for patients being discharged from the intensive care unit to another care unit (left) and the patient-oriented discharge summary intended for patients being discharged from intensive care unit to a community care setting, including their home (right).

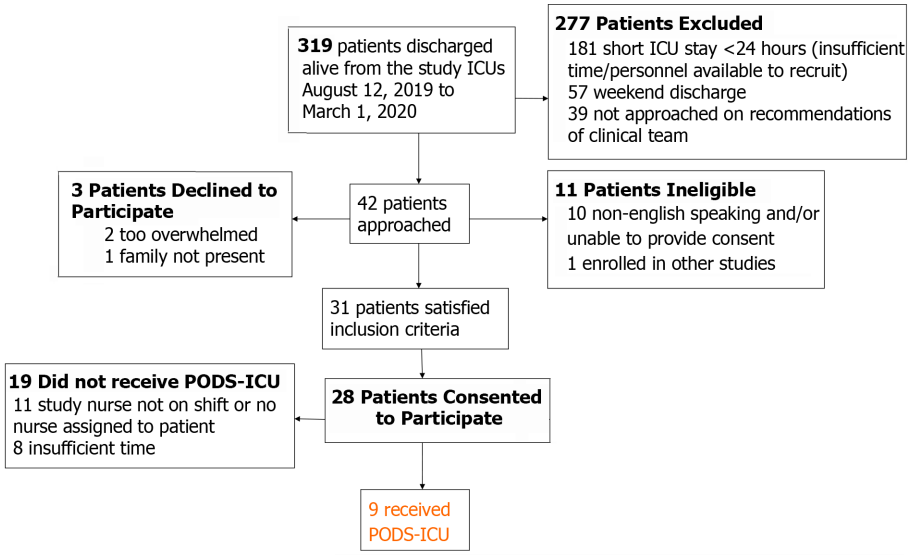

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Figure 2 Patient recruitment and reasons for exclusion of certain patients. ICU: Intensive care unit; PODS-ICU: Patient-oriented discharge summary tool.

being enrolled in another study. Of the 31 eligible patients, 28 (90.3%) consented to be part of the study. Patients who declined to participate in the study indicated that they felt too overwhelmed to participate (n = 2; 9.70%) or that their family was not present at the time they were approached (n = 1; 6.70%). Nine (32.1%) of the consented patients were administered PODS-ICU by the ICU research team nurses, while 19 (68.0%) patients did not receive PODS-ICU because there was either no research team nurse available to administer the tool (n = 11; 40.0%), or there was insufficient time for the research team nurse to complete the PODS-ICU (n = 8; 28.6%) prior to discharge. Twenty-one (75.0%) family-caregivers for the 28 participating patients consented to participate in the study.

The nine patients who received the PODS-ICU were primarily female (n = 6; 66.7%) with a mean age of 63 years with at least some post-secondary education (n = 6; 66.7%). Family-caregivers were primarily women (n = 55.6%) with a mean age of 62 years, and most had some post-secondary education (n = 55.6). Of the 21 family-caregivers that consented to participate in the study, 6 caregivers (66.7%) for the 9 patients who were administered the PODS-ICU received information about the patient's transition from the ICU. Once enrolled, no patients or family-caregivers withdrew from the study. Demographic characteristics of participating patients and family-caregivers are listed in Table 1.

Participants' reported experiences: Of the 15 participants (9 patients and 6 family-caregivers) who received the PODS-ICU, 13 felt that their discharge from the ICU was good (n = 4; 30.1%), very good (n = 5; 38.5%), or excellent (n = 4; 31.0%)) (Figure 3A). Over half of participants (n = 9; 60.0%) felt they were moderately, very, or completely engaged in thinking about the ICU transition process (Figure 3B). Most participants stated they had a good or better understanding of the medical condition that brought the patient to the ICU (n = 11; 73.3%) and that they understood the events that happened in the ICU and the impact of the ICU stay on the patient's health (n = 11; 73.3%) (Figure 3C). When asked about the ICU discharge, most participants (n = 12; 80.0%) said they had a conversation with the ICU team to discuss the transition and next steps (Figure 3D).

Clinician reported experiences: Participating nurses completed the feedback questionnaire for 10 (66.7%) of the 15 patients who had a PODS-ICU completed. It took the study nurses an estimated 45 min on average to complete the PODS-ICU tool (median 25 min) and an additional 30 min on average to review it with the patient and/or family-caregiver (median 15 min). Key data from the survey (which included closed and open-ended questions) are displayed in Table 2.

Participating RNs and NPs reported, that: (1) Patients and family-caregivers appreciated the information the tool provided; (2) Discharge timing often did not allow for an opportunity to complete and teach-back the PODS-ICU, or to do it well; and (3) The process of filling out the PODS-ICU was too time-consuming and did not fit well into the clinical workflow. Select comments received from research team RNs/NPs are shown here: "As I am the provider and tasked with not only putting together the PODS, but contacting community physicians, arranging for outpatient follow up, writing Rx, faxing pharmacies, collaborating with multi-disciplinary teams (like PT/OT/Transitions) reviewing with both patient and family, then returning back to discuss in addition to caring for up to 10 other ICU patients, I have to say a big NO to reasonable in my current work flow. I have come in often on my days off to facilitate patient discharges. Ideas to optimize: once patient is flagged for ICU-Home discharge then

Table 1 Demographic characteristics of participating patients and family-caregivers who received the patient-oriented discharge summary and completed the follow-up survey

		Number of participants (*n*)	
		Patients total *n* = 9	Family caregivers total *n* = 6
Age, mean (range)		63 (54-69)	62 (40-70)
Female		6 (66.7%)	5 (83.3%)
Education	High school or less	3 (33.3%)	1 (16.7%)
	Some post-secondary	2 (22.2.%)	3 (50.0%)
	Post-secondary	4 (44.4%)	2 (33.3%)

Table 2 Clinician semi-structured survey quantitative results (*n* = 10)

		Total responses, *n* = 10
Respondents	Nurse practitioner	3 (30.0%)
	Registered nurse	4 (40.0%)
	Unknown/response missing	3 (30.0%)
Role in PODS-ICU implementation	Completed and delivered[1]	9 (90.0%)
	Completed only	1 (10.0%)
Main PODS-ICU delivery recipient	Patient only	4 (40.0%)
	Friend/family only	2 (20.0%)
	Patient and family/friend	4 (40.0%)
Time taken to complete PODS-ICU	0-15 min	3 (30.0%)
	16-30 min	3 (30.0%)
	31-45 min	1 (10.0%)
	46-60 min	0 (0.00%)
	61+ min	2 (20.0%)
	Unknown/response missing	1 (10.0%)
Time spent discussing PODS-ICU with recipient	0-15 min	6 (60.0%)
	16-30 min	0 (0.00%)
	31-45 min	1 (10.0%)
	46-60 min	1 (10.0%)
	61+ min	0 (0.00%)
	Unknown/response missing	2 (20.0%)

[1]Delivered (in role in patient-oriented discharge summary (PODS-ICU) refers to whether a teach-back session was conducted or whether the ICU nurse only completed the PODS-ICU). PODS: Patient-oriented discharge summary; ICU: Intensive care unit.

start the process at least 24-48 h prior to d/c home"; "Family was very appreciative, the patient's wife seemed to find it more difficult to retain information covered, patient's daughter was taking notes to refer back to and was able to follow along better. Wife expressed she was overwhelmed with everything and was glad to be getting a written summary"; "Time constraint was the most problematic on my part, felt like teach back was rushed".

DISCUSSION

We designed and pilot tested the PODS-ICU, a patient- and family-caregiver- focused written discharge summary tool to provide critically ill patients and their family-caregivers with key information on the

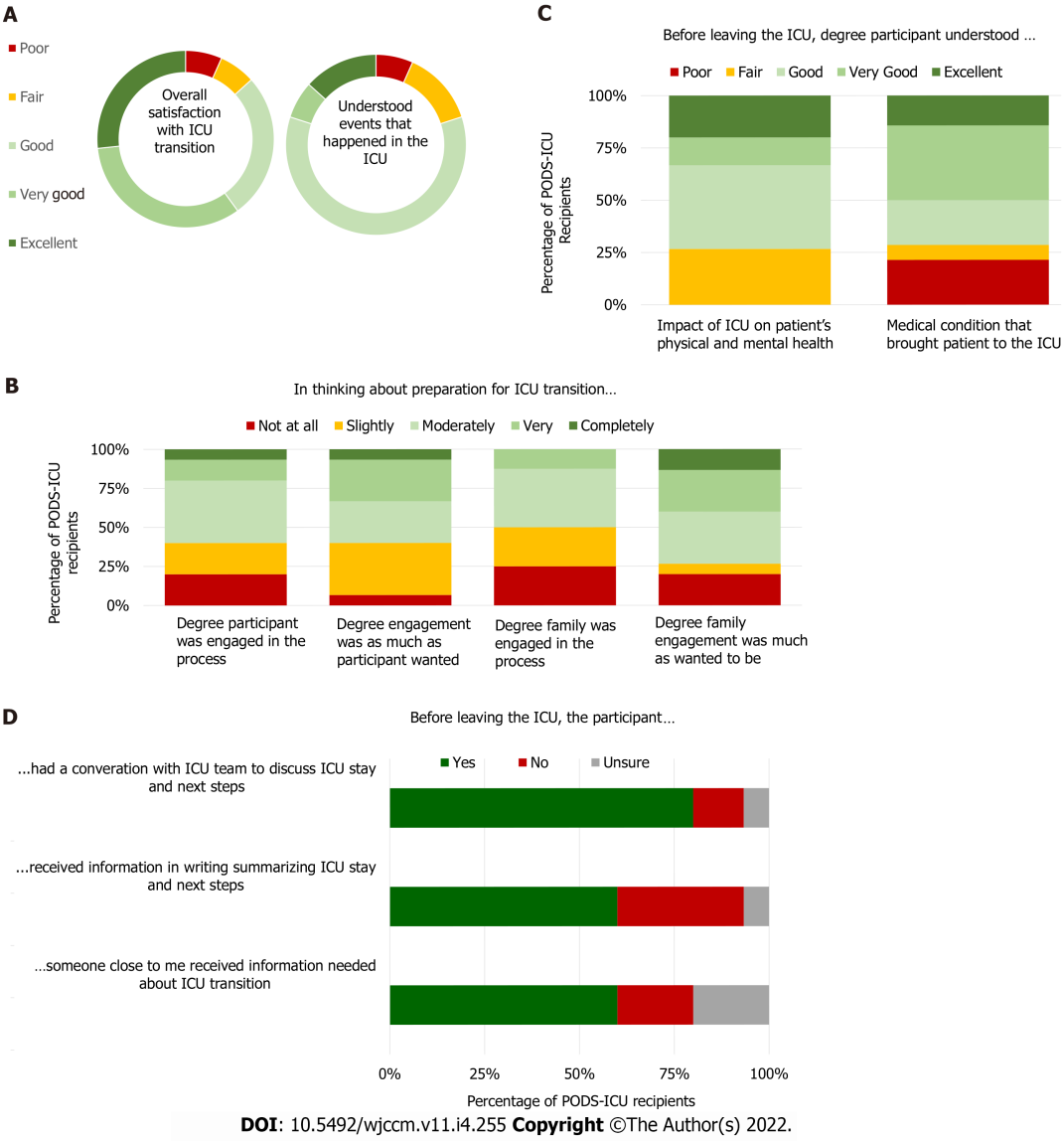

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Figure 3 Data display of key questions from the follow-up surveys administered to patients and family-caregivers to collect their feedback on transitioning from the intensive care unit. Data is displayed in percentages. ICU: Intensive care unit; PODS: Patient-oriented discharge summary.

patient's stay in ICU, transition (*i.e.*, discharge) from the ICU, and what to expect post-ICU. Our pilot study showed that the PODS-ICU was well accepted and participants viewed their discharge from the ICU positively when it was used. However, the pilot study also showed that while the tool had high acceptability, it was not feasible to administer in the ICU settings as: (1) The time to discharge varies for each patient and current clinical practices did not allow for the tool to be consistently delivered; and (2) Clinicians found the PODS-ICU to be time consuming and fit poorly within their clinical workflow.

The practice of providing written information to patients and/or their family-caregivers at the point of discharge from the ICU remains uncommon, with very few existing tools to aid in that process[31,36]. Previous evaluations of written discharge communications for patients and family-caregivers in ICU have shown that these tools can improve family-caregiver satisfaction with care in the ICU, decrease family-caregiver 'transfer' anxiety around transitions from the ICU, help patients and families understand and accept ICU events, help 'fill in the gaps' for patients with memory lapses, and improve longer term patient outcomes[37-44]. In developing the PODS-ICU tool, we relied on the pre-existing OpenLab PODS tool and input from patient-partners to ensure the tool addressed specific informational needs of patients in the ICU (*e.g.*, summary of ICU events, medications, upcoming tests and appointments, what to expect during recovery, resources for help)[21,27,45]. This allowed the PODS-ICU to support reliable delivery of essential information from clinicians to patients and family-caregivers at discharge from the ICU, whether the patient was being transferred to a ward in the hospital or directly home. In our study, clinicians reported the PODS-ICU tool to generate comprehensive and beneficial summaries. Interestingly, previous evaluations of summary tools have reported similar challenges to those we observed in implementing the PODS-ICU, such as varying clinician motivation to complete the

tool due to lack of time, competing priorities, and/or negative perceptions of the tool's utility[40]. Due to these limitations, clinicians in our study struggled with the feasibility of incorporating this tool into their workflow.

Outside of ICU settings, patient-centered discharge communications (both written and oral) have shown benefit in cardiovascular, maternity and neonatal, and surgical settings. Like the PODS-ICU, discharge communications in other settings have aimed to convey information on next steps (*e.g.*, what to expect), identification and management of risk factors and complications (*e.g.*, when to seek care, pain management), and medications from healthcare providers to patients and their families[46-57]. Similarly to the PODS-ICU, many discharge communications from various acute care settings have been reported as time consuming and adding to healthcare provider workload[40,45,57,58]. However, they have also been reported to reduce hospital readmissions, improve treatment adherence, and enhance patient satisfaction and can be considered important to successful transitions in care[40,57,58]. This suggests a high value to improving upon ICU discharge tools (like the PODS-ICU), which could be expected to have cost-savings comparable to discharge communications between hospital and community-based healthcare providers[59].

Pilot implementation of the PODS-ICU highlights important opportunities to improve clinician-patient communication during a discharge from the ICU. These include: 1) earlier discharge planning (*i.e.*, preparation for discharge begins as soon as a patient is admitted), 2) integration of discharge communication with electronic clinical information systems, and 3) regular incorporation of teach-back into clinician-patient communications. At a practical level, earlier discharge planning could prompt clinicians to begin completing parts of the discharge summary as soon as a patient is admitted, perhaps fitting better into their workflow. Electronic clinical information systems provide the potential to partially automate the population of patient data into discharge summaries, a time-consuming aspect of the PODS-ICU. Pre-population of discharge summaries with patient data can increase efficiency and potentially reduce the risk of human transcription error[60,61]. Finally, incorporating the teach-back method into clinician-patient and clinician-family-caregiver communications, an important aspect of the PODS-ICU and recommended by the Agency for Healthcare Research and Quality (AHRQ), has been shown to improve patients' understanding of their health information[62,63]. This could foster better connections between patients and clinicians[34], further benefitting communication efforts. Apart from the above discussed methods to increase time efficiency of completing the PODS-ICU (*i.e.*, earlier discharge planning, integration with electronic clinical information systems), further engaging patients and families to modify the PODS-ICU to only include information important to patients may be a valuable refinement to the tool.

There are a number of limitations to consider when interpreting the results of our pilot study. First, only a small number of participants (n = 9 patients and n = 6 family-caregivers) received the PODS-ICU tool. Although we were able to ascertain some reasons for the low delivery of PODS-ICU (*i.e.*, availability of research team nurses and time required to complete the tool), an assessment by more patients, family-caregivers and clinicians could provide more insights into the usability of the tool. Second, we pilot tested the PODS-ICU in two study ICUs in a single city (Calgary) in Canada. We recognize that ICU populations differ in type and severity of illness and some ICU staff may have more capacity to implement the PODS-ICU. As the OpenLab's PODS has shown the potential to improve patient outcomes in various care settings[21,45], the PODS-ICU may be more successful in settings where it is better integrated into clinician work flow[45].

CONCLUSION

We developed a written discharge summary tool (PODS-ICU) that provides patients and their family-caregivers with the essential information they need as they transition out of the ICU. While the PODS-ICU may require pairing with earlier discharge practices and integration with electronic clinical information systems to fit better into the clinical workflow, the tool has the potential to engage and empower patients and family-caregivers in ensuring continuity of care. Further refinement and testing of the PODS-ICU tool in diverse ICUs is needed to determine its broader feasibility and the effects on patient health outcomes as well as patient-centered care.

ARTICLE HIGHLIGHTS

Research background

Gaps in discharge communication can leave critically ill patients vulnerable to stress, poor health outcomes, and death. There are no standard written discharge summaries available for critically ill patients and their families.

Research motivation

Written discharge summaries can provide patients and their families with important information (*e.g.*, medications, activity and diet restrictions, follow-up appointments, symptoms to expect, who to call if there are questions).

Research objectives

To develop and pilot test a patient-oriented discharge summary tool for critically ill patients and their families.

Research methods

We worked alongside former critically ill patients and their families, clinicians, and researchers to discuss patient needs and develop a written discharge summary tool. Intensive care unit nurses piloted the tool in two intensive care units in Calgary, Canada. Research team members administered follow-up surveys to patients, family participants, and ICU nurses on the impact of the summary tool on discharge.

Research results

Most participants felt the discharge summary tool was useful and informative. Most participants reported that they understood intensive care unit events and impacts on the patient's health. Participating intensive care unit nurses reported time constraint in completing the discharge summary tool and encouraged refinement of the tool.

Research conclusions

The patient-oriented discharge summary tool could benefit from further refinement and testing in diverse critical care settings to better assess its feasibility and its effects on patient health outcomes.

Research perspectives

Written discharge communication provides patients and their families with essential information as they discharge from the intensive care unit. Future directions for a written patient-oriented discharge summary tool for critically ill patients include pairing the tool with earlier discharge practices and integrating the tool with electronic clinical information systems to fit better into the clinical workflow for ICU nurses.

ACKNOWLEDGEMENTS

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FOOTNOTES

Author contributions: Shahid A drafted the manuscript; all authors have contributed to the conception, design of this study, critically revised the manuscript and approved of the final submitted version.

Institutional review board statement: The study was conducted in accordance with the Declaration of Helsinki (1983). All methods were performed in accordance with the relevant guidelines and regulations by the University of Calgary Health Research Ethics Board, which granted institutional ethics approval for this study (18-1770). We also established a research agreement with the primary health custodian, Alberta Health Services (AHS) to permit us to conduct this study in the two identified ICUs and to access participant data *via* AHS health information systems.

Informed consent statement: Written informed consent was collected from all participants prior to the study enrollment.

Conflict-of-interest statement: There are no conflicts-of-interest to declare.

Data sharing statement: The dataset is available from the corresponding author at tstelfox@ucalgary.ca.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Canada

ORCID number: Anmol Shahid 0000-0001-5638-4988; Danijela Piskulic 0000-0002-4954-8929; Kirsten M Fiest 0000-0002-7299-6594; Henry T Stelfox 0000-0003-1231-1490.

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REFERENCES

1 **Whittaker J**, Ball C. Discharge from intensive care: a view from the ward. *Intensive Crit Care Nurs* 2000; **16**: 135-143 [PMID: 10859622 DOI: 10.1054/iccn.2000.1488]
2 **Forster AJ**, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. *Ann Intern Med* 2003; **138**: 161-167 [PMID: 12558354 DOI: 10.7326/0003-4819-138-3-200302040-00007]
3 **Niven DJ**, Bastos JF, Stelfox HT. Critical care transition programs and the risk of readmission or death after discharge from an ICU: a systematic review and meta-analysis. *Crit Care Med* 2014; **42**: 179-187 [PMID: 23989177 DOI: 10.1097/CCM.0b013e3182a272c0]
4 **Kramer AA**, Higgins TL, Zimmerman JE. The association between ICU readmission rate and patient outcomes. *Crit Care Med* 2013; **41**: 24-33 [PMID: 23128381 DOI: 10.1097/CCM.0b013e3182657b8a]
5 **Naylor M**, Brooten D, Jones R, Lavizzo-Mourey R, Mezey M, Pauly M. Comprehensive discharge planning for the hospitalized elderly. A randomized clinical trial. *Ann Intern Med* 1994; **120**: 999-1006 [PMID: 8185149 DOI: 10.7326/0003-4819-120-12-199406150-00005]
6 **Hunziker S**, McHugh W, Sarnoff-Lee B, Cannistraro S, Ngo L, Marcantonio E, Howell MD. Predictors and correlates of dissatisfaction with intensive care. *Crit Care Med* 2012; **40**: 1554-1561 [PMID: 22511136 DOI: 10.1097/CCM.0b013e3182451c70]
7 **de Grood C**, Leigh JP, Bagshaw SM, Dodek PM, Fowler RA, Forster AJ, Boyd JM, Stelfox HT. Patient, family and provider experiences with transfers from intensive care unit to hospital ward: a multicentre qualitative study. *CMAJ* 2018; **190**: E669-E676 [PMID: 29866892 DOI: 10.1503/cmaj.170588]
8 **Coleman EA**, Berenson RA. Lost in transition: challenges and opportunities for improving the quality of transitional care. *Ann Intern Med* 2004; **141**: 533-536 [PMID: 15466770 DOI: 10.7326/0003-4819-141-7-200410050-00009]
9 **Arora V**, Johnson J, Lovinger D, Humphrey HJ, Meltzer DO. Communication failures in patient sign-out and suggestions for improvement: a critical incident analysis. *Qual Saf Health Care* 2005; **14**: 401-407 [PMID: 16326783 DOI: 10.1136/qshc.2005.015107]
10 **Kattel S**, Manning DM, Erwin PJ, Wood H, Kashiwagi DT, Murad MH. Information Transfer at Hospital Discharge: A Systematic Review. *J Pat Safety* 2020; **16** [DOI: 10.1097/pts.0000000000000248]
11 **Engel KG**, Buckley BA, Forth VE, McCarthy DM, Ellison EP, Schmidt MJ, Adams JG. Patient understanding of emergency department discharge instructions: where are knowledge deficits greatest? *Acad Emerg Med* 2012; **19**: E1035-E1044 [PMID: 22978730 DOI: 10.1111/j.1553-2712.2012.01425.x]
12 **Samuels-Kalow ME**, Stack AM, Porter SC. Effective discharge communication in the emergency department. *Ann Emerg Med* 2012; **60**: 152-159 [PMID: 22221840 DOI: 10.1016/j.annemergmed.2011.10.023]
13 **Miquel-Verges F**, Donohue PK, Boss RD. Discharge of infants from NICU to Latino families with limited English proficiency. *J Immigr Minor Health* 2011; **13**: 309-314 [PMID: 20490681 DOI: 10.1007/s10903-010-9355-3]
14 **Marcus C**. Strategies for improving the quality of verbal patient and family education: a review of the literature and creation of the EDUCATE model. *Health Psychol Behav Med* 2014; **2**: 482-495 [PMID: 25750796 DOI: 10.1080/21642850.2014.900450]
15 **Mistraletti G**, Mezzetti A, Anania S, Ionescu Maddalena A, Del Negro S, Giusti GD, Gili A, Iacobone E, Pulitanò SM, Conti G, Bocci MG. Improving communication toward ICU families to facilitate understanding and reduce stress. Protocol for a multicenter randomized and controlled Italian study. *Contemp Clin Trials* 2019; **86**: 105847 [PMID: 31525488 DOI: 10.1016/j.cct.2019.105847]
16 **Makaryus AN**, Friedman EA. Patients' understanding of their treatment plans and diagnosis at discharge. *Mayo Clin Proc* 2005; **80**: 991-994 [PMID: 16092576 DOI: 10.4065/80.8.991]
17 **Harel Z**, Wald R, Perl J, Schwartz D, Bell CM. Evaluation of deficiencies in current discharge summaries for dialysis patients in Canada. *J Multidiscip Healthc* 2012; **5**: 77-84 [DOI: 10.2147/jmdh.s27572]
18 **D VN**, Rajavelu P, Rajagopalan A. Pre-formatted written discharge summary-a step towards quality assurance in the emergency department. *Int J Emerg Med* 2008; **1**: 321-325 [DOI: 10.1007/s12245-008-0077-4]
19 **Reid DB**, Parsons SR, Gill SD, Hughes AJ. Discharge communication from inpatient care: an audit of written medical discharge summary procedure against the new National Health Service Standard for clinical handover. *Aust Health Rev* 2015; **39**: 197-201 [PMID: 25494034 DOI: 10.1071/AH14095]
20 **Bench SD**, Day TL, Griffiths P. Developing user centred critical care discharge information to support early critical illness rehabilitation using the Medical Research Council's complex interventions framework. *Intensive Crit Care Nurs* 2012; **28**:

123-131 [PMID: 22386848 DOI: 10.1016/j.iccn.2012.02.002]
21 **Hahn-Goldberg S**, Okrainec K, Damba C, Huynh T, Lau D, Maxwell J, McGuire R, Yang L, Abrams HB. Implementing Patient-Oriented Discharge Summaries (PODS): A Multisite Pilot Across Early Adopter Hospitals. *Healthc Q* 2016; **19**: 42-48 [PMID: 27133607 DOI: 10.12927/hcq.2016.24610]
22 **Wimsett J**, Harper A, Jones P. Review article: Components of a good quality discharge summary: a systematic review. *Emerg Med Australas* 2014; **26**: 430-438 [PMID: 25186466 DOI: 10.1111/1742-6723.12285]
23 **Nomura M**, Tronbacke B. Guidelines for easy-to-read materials: revision. Hague: International Federation of Library Associations and Institutions, 2010 [DOI: 10.1515/9783111356662-002]
24 **van Beusekom MM**, Grootens-Wiegers P, Bos MJ, Guchelaar HJ, van den Broek JM. Low literacy and written drug information: information-seeking, leaflet evaluation and preferences, and roles for images. *Int J Clin Pharm* 2016; **38**: 1372-1379 [PMID: 27655308 DOI: 10.1007/s11096-016-0376-4]
25 **Hong YR**, Huo J, Jo A, Cardel M, Mainous AG, 3rd. Association of Patient-Provider Teach-Back Communication with Diabetic Outcomes: A Cohort Study. *J Am Board Fam Med* 2020; **33**: 903-912 [DOI: 10.3122/jabfm.2020.06.200217]
26 **Ha Dinh TT**, Bonner A, Clark R, Ramsbotham J, Hines S. The effectiveness of the teach-back method on adherence and self-management in health education for people with chronic disease: a systematic review. *JBI Database System Rev Implement Rep* 2016; **14**: 210-247 [PMID: 26878928 DOI: 10.11124/jbisrir-2016-2296]
27 **Hahn-Goldberg S**, Okrainec K, Huynh T, Zahr N, Abrams H. Co-creating patient-oriented discharge instructions with patients, caregivers, and healthcare providers. *J Hosp Med* 2015; **10**: 804-807 [PMID: 26406116 DOI: 10.1002/jhm.2444]
28 **Lumpkin S**, Kratzke I, Duke M, Chaumont N. Twelve Tips for Preparing a Surgical Discharge Summary: Enabling a Safe Discharge. *MedEdPublish* 2019; **8** [DOI: 10.15694/mep.2019.000039.1]
29 **Gandara E**, Moniz TT, Ungar J, Lee J, Chan-Macrae M, O'Malley T, Schnipper JL. Deficits in discharge documentation in patients transferred to rehabilitation facilities on anticoagulation: results of a systemwide evaluation. *Jt Comm J Qual Patient Saf* 2008; **34**: 460-463 [PMID: 18714747 DOI: 10.1016/s1553-7250]
30 **Lakhaney D**, Banker SL. An Evaluation of the Content of Pediatric Discharge Summaries. *Hosp Pediatr* 2020; **10**: 949-954 [PMID: 33097565 DOI: 10.1542/hpeds.2020-0148]
31 **Stelfox HT**, Lane D, Boyd JM, Taylor S, Perrier L, Straus S, Zygun D, Zuege DJ. A scoping review of patient discharge from intensive care: opportunities and tools to improve care. *Chest* 2015; **147**: 317-327 [PMID: 25210942 DOI: 10.1378/chest.13-2965]
32 **Brundin-Mather R**, Soo A, Zuege DJ, Niven DJ, Fiest K, Doig CJ, Zygun D, Boyd JM, Parsons Leigh J, Bagshaw SM, Stelfox HT. Secondary EMR data for quality improvement and research: A comparison of manual and electronic data collection from an integrated critical care electronic medical record system. *J Crit Care* 2018; **47**: 295-301 [PMID: 30099330 DOI: 10.1016/j.jcrc.2018.07.021]
33 **Ogrinc G MS**, Estrada C. Revised Standards for Quality Improvement Reporting Excellence SQUIRE 2.0. [cited 20 January 2022]. Available from: http://squire-statement.org/index.cfm? *n* = PageID=471
34 **Yen PH**, Leasure AR. Use and Effectiveness of the Teach-Back Method in Patient Education and Health Outcomes. *Fed Pract* 2019; **36**: 284-289 [PMID: 31258322]
35 **Lancaster GA**, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract* 2004; **10**: 307-312 [PMID: 15189396 DOI: 10.1111/j..2002.384.doc.x]
36 **Wong D**, Wickham A. A survey of intensive care unit discharge communication practices in the UK. *J Intensive C Society* 2013; **14**: 330-333 [DOI: 10.1177/175114371301400411]
37 **Mitchell ML**, Courtney M. An intervention study to improve the transfer of ICU patients to the ward- evaluation by family members. *Australian Critical Care* 2005; **18**: 61-69 [DOI: 10.1016/s1036-7314]
38 **Bouve LR**, Rozmus CL, Giordano P. Preparing parents for their child's transfer from the PICU to the pediatric floor. *Appl Nurs Res* 1999; **12**: 114-120 [DOI: 10.1016/s0897-1897]
39 **Linton S**, Grant C, Pellegrini J. Supporting families through discharge from PICU to the ward: the development and evaluation of a discharge information brochure for families. *Intensive Crit Care Nurs* 2008; **24**: 329-337 [DOI: 10.1016/j.iccn.2008.06.002]
40 **Bench SD**, Heelas K, White C, Griffiths P. Providing critical care patients with a personalised discharge summary: a questionnaire survey and retrospective analysis exploring feasibility and effectiveness. *Intensive Crit Care Nurs* 2014; **30**: 69-76 [PMID: 24211048 DOI: 10.1016/j.iccn.2013.08.007]
41 **Van Waning NR**, Kleiber C, Freyenberger B. Development and implementation of a protocol for transfers out of the pediatric intensive care unit. *Crit Care Nurse* 2005; **25**: 50-55 [PMID: 15946928]
42 **Löf L**, Berggren L, Ahlström G. ICU patients' recall of emotional reactions in the trajectory from falling critically ill to hospital discharge: follow-ups after 3 and 12 mo. *Intensive Crit Care Nurs* 2008; **24**: 108-121 [PMID: 17897829 DOI: 10.1016/j.iccn.2007.08.001]
43 **Gourley GR**. Shwachman Award remarks for Emeritus Professor Gerard B. Odell, M.D., annual meeting of NASPGN/ESPGAN, Westin Galleria Hotel, Houston, Texas, October 10, 1994. *J Pediatr Gastroenterol Nutr* 1995; **20**: 245-247 [PMID: 7608820 DOI: 10.1097/00005176-199504000-00001]
44 **Bench S**, Day T, Griffiths P. Effectiveness of critical care discharge information in supporting early recovery from critical illness. *Crit Care Nurse* 2013; **33**: 41-52 [PMID: 23727851 DOI: 10.4037/ccn2013134]
45 **Hahn-Goldberg S**, Huynh T, Chaput A, Krahn M, Rac V, Tomlinson G, Matelski J, Abrams H, Bell C, Madho C, Ferguson C, Turcotte A, Free C, Hogan S, Nicholas B, Oldershaw B, Okrainec K. Implementation, spread and impact of the Patient Oriented Discharge Summary (PODS) across Ontario hospitals: a mixed methods evaluation. *BMC Health Serv Res* 2021; **21**: 361 [PMID: 33865385 DOI: 10.1186/s12913-021-06374-8]
46 **Gwadry-Sridhar FH**, Arnold JM, Zhang Y, Brown JE, Marchiori G, Guyatt G. Pilot study to determine the impact of a multidisciplinary educational intervention in patients hospitalized with heart failure. *Am Heart J* 2005; **150**: 982 [PMID: 16290975 DOI: 10.1016/j.ahj.2005.08.016]
47 **Haerem JW**, Rønning EJ, Leidal R. Home access to hospital discharge information on audiotape reduces sick leave and

readmissions in patients with first-time myocardial infarction. *Scand Cardiovasc J* 2000; **34**: 219-222 [PMID: 10872714 DOI: 10.1080/14017430050142297]

48 **Eshah NF**. Predischarge education improves adherence to a healthy lifestyle among Jordanian patients with acute coronary syndrome. *Nurs Health Sci* 2013; **15**: 273-279 [PMID: 23302042 DOI: 10.1111/nhs.12018]

49 **Ho SM**, Heh SS, Jevitt CM, Huang LH, Fu YY, Wang LL. Effectiveness of a discharge education program in reducing the severity of postpartum depression: a randomized controlled evaluation study. *Patient Educ Couns* 2009; **77**: 68-71 [PMID: 19376677 DOI: 10.1016/j.pec.2009.01.009]

50 **Shieh SJ**, Chen HL, Liu FC, Liou CC, Lin YI, Tseng HI, Wang RH. The effectiveness of structured discharge education on maternal confidence, caring knowledge and growth of premature newborns. *J Clin Nurs* 2010; **19**: 3307-3313 [PMID: 20946444 DOI: 10.1111/j.1365-2702.2010.03382.x]

51 **Whitby M**, McLaws ML, Doidge S, Collopy B. Post-discharge surgical site surveillance: does patient education improve reliability of diagnosis? *J Hosp Infect* 2007; **66**: 237-242 [PMID: 17582652 DOI: 10.1016/j.jhin.2007.04.014]

52 **Moore SM**. The effects of a discharge information intervention on recovery outcomes following coronary artery bypass surgery. *Int J Nurs Stud* 1996; **33**: 181-189 [PMID: 8675378 DOI: 10.1016/0020-7489]

53 **Reynolds MA**. Postoperative pain management discharge teaching in a rural population. *Pain Manag Nurs* 2009; **10**: 76-84 [DOI: 10.1016/j.pmn.2008.07.003]

54 **Morice AH**, Wrench C. The role of the asthma nurse in treatment compliance and self-management following hospital admission. *Respir Med* 2001; **95**: 851-856 [PMID: 11716197 DOI: 10.1053/rmed.2001.1166]

55 **Marušić S**, Meliš P, Lucijanić M, Grgurević I, Turčić P, Neto PRO, Bilić-Ćurčić I. Impact of pharmacotherapeutic education on medication adherence and adverse outcomes in patients with type 2 diabetes mellitus: a prospective, randomized study. *Croat Med J* 2018; **59**: 290-297 [PMID: 30610771]

56 **Marusic S**, Gojo-Tomic N, Erdeljic V, Bacic-Vrca V, Franic M, Kirin M, Bozikov V. The effect of pharmacotherapeutic counseling on readmissions and emergency department visits. *Int J Clin Pharm* 2013; **35**: 37-44 [PMID: 23007693 DOI: 10.1007/s11096-012-9700-9]

57 **Christoph Becker SZ**, Katharina Beck, Alessia Vincent, Nina Loretz, Jonas Müller, , Simon Amacher RS, Sabina Hunziker. Interventions to Improve Communication at Hospital Discharge and Rates of Readmission. *Jama Net Open* 2021; **4** [DOI: 10.1001/jamanetworkopen.2021.19346]

58 **Okrainec K**, Lau D, Abrams HB, Hahn-Goldberg S, Brahmbhatt R, Huynh T, Lam K, Bell CM. Impact of patient-centered discharge tools: A systematic review. *J Hosp Med* 2017; **12**: 110-117 [PMID: 28182809 DOI: 10.12788/jhm.2692]

59 **Sevick LK**, Esmail R, Tang K, Lorenzetti DL, Ronksley P, James M, Santana M, Ghali WA, Clement F. A systematic review of the cost and cost-effectiveness of electronic discharge communications. *BMJ Open* 2017; **7**: e014722 [PMID: 28674136 DOI: 10.1136/bmjopen-2016-014722]

60 **Motamedi SM**, Posadas-Calleja J, Straus S, Bates DW, Lorenzetti DL, Baylis B, Gilmour J, Kimpton S, Ghali WA. The efficacy of computer-enabled discharge communication interventions: a systematic review. *BMJ Qual Saf* 2011; **20**: 403-415 [PMID: 21262793 DOI: 10.1136/bmjqs.2009.034587]

61 **Parsons Leigh J**, Brundin-Mather R, Zjadewicz K, Soo A, Stelfox HT. Improving transitions in care from intensive care units: Development and pilot testing of an electronic communication tool for healthcare providers. *J Crit Care* 2020; **56**: 265-272 [PMID: 31986370 DOI: 10.1016/j.jcrc.2020.01.019]

62 **Quality AfHRa**. Use the Teach-Back Method: Tool #5. In: Second edition, 2020: 18-20 [DOI: 10.17918/00000016]

63 **Griffey RT**, Shin N, Jones S, Aginam N, Gross M, Kinsella Y, Williams JA, Carpenter CR, Goodman M, Kaphingst KA. The impact of teach-back on comprehension of discharge instructions and satisfaction among emergency patients with limited health literacy: A randomized, controlled study. *J Commun Healthc* 2015; **8**: 10-21 [PMID: 26617669 DOI: 10.1179/1753807615Y.0000000001]

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SYSTEMATIC REVIEWS

Immunomodulatory therapy for the management of critically ill patients with COVID-19: A narrative review

David Andaluz-Ojeda, Pablo Vidal-Cortes, Álvaro Aparisi Sanz, Borja Suberviola, Lorena Del Río Carbajo, Leonor Nogales Martín, Estefanía Prol Silva, Jorge Nieto del Olmo, José Barberán, Ivan Cusacovich

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David Andaluz-Ojeda, Department of Critical Care, Hospital Universitario HM Sanchinarro, Hospitales Madrid, Madrid 28050, Spain

Pablo Vidal-Cortes, Lorena Del Río Carbajo, Estefanía Prol Silva, Jorge Nieto del Olmo, Department of Intensive Care, Complejo Hospitalario Universitario de Ourense, Ourense 32005, Spain

Álvaro Aparisi Sanz, Department of Cardiology, Hospital del Mar, Barcelona 08003, Spain

Borja Suberviola, Department of Intensive Care, Hospital Universitario Marqués de Valdecilla, Santander 39008, Spain

Leonor Nogales Martín, Department of Intensive Care, Hospital Clínico Universitario de Valladolid, Valladolid 47005, Spain

José Barberán, Department of Internal Medicine, Hospital Universitario HM Montepríncipe, Hospitales Madrid, Boadilla del Monte 28860, Madrid, Spain

Ivan Cusacovich, Department of Internal Medicine, Hospital Clínico Universitario de Valladolid, Valladolid 47005, Spain

Corresponding author: David Andaluz-Ojeda, MD, PhD, Assistant Professor, Consultant Physician-Scientist, Department of Critical Care, Hospital Universitario HM Sanchinarro, Hospitales Madrid, Oña, 10, Madrid 28050, Spain. davidandaluz78@yahoo.es

Abstract

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the ongoing coronavirus disease 2019 (COVID-19) pandemic. Understanding the physiological and immunological processes underlying the clinical manifestations of COVID-19 is vital for the identification and rational design of effective therapies.

AIM

To describe the interaction of SARS-CoV-2 with the immune system and the subsequent contribution of hyperinflammation and abnormal immune responses to disease progression together with a complete narrative review of the different immunoadjuvant treatments used so far in COVID-19 and their indication in

severe and life-threatening subsets.

METHODS
A comprehensive literature search was developed. Authors reviewed the selected manuscripts following the PRISMA recommendations for systematic review and meta-analysis documents and selected the most appropriate. Finally, a recommendation of the use of each treatment was established based on the level of evidence of the articles and documents reviewed. This recommendation was made based on the consensus of all the authors.

RESULTS
A brief rationale on the SARS-CoV-2 pathogenesis, immune response, and inflammation was developed. The usefulness of 10 different families of treatments related to inflammation and immunopathogenesis of COVID-19 was reviewed and discussed. Finally, based on the level of scientific evidence, a recommendation was established for each of them.

CONCLUSION
Although several promising therapies exist, only the use of corticosteroids and tocilizumab (or sarilumab in absence of this) have demonstrated evidence enough to recommend its use in critically ill patients with COVID-19. Endotypes including both, clinical and biological characteristics can constitute specific targets for better select certain therapies based on an individualized approach to treatment.

Key Words: COVID-19; Critically ill patients; Treatment; Immunomodulary drugs; Phenotype; Immunosupression

Core Tip: Two years after the onset of the pandemic the search for the most appropriate treatment of coronavirus disease 2019 (COVID-19) continues. Few treatments have been evaluated in the context of critically ill patients with COVID-19 considering it in most clinical trials as a negative "end point" of the disease rather than a study subject. This fact makes it extremely difficult to establish degrees of recommendation regarding the different therapeutic options currently available. This review aims to summarize the immunopathogenesis and the current evidence regarding the different immunomodulatory strategies tested in critically ill patients with COVID-19. In addition, the presence of different immunophenotypes that in the future will serve as a basis for individualized treatments is demonstrated.

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INTRODUCTION

In late 2019, a virus, currently named coronavirus disease 2019 (COVID-19), caused an outbreak of 27 acute respiratory distress syndrome cases related to a seafood market in Wuhan, China. From that moment, the virus has spread rapidly worldwide until, on March 11th, the World Health Organization (WHO) classified it as a pandemic[1]. As of July 24th, 2021, more than 190 million people have been infected, and it has caused more than 4 million deaths[2].

Although most people with COVID-19 have only mild or uncomplicated symptoms, 10%-15% requires hospitalization and oxygen therapy[3,4]. From the beginning, a large number of patients presented severe respiratory failure, needing mechanical ventilation (MV) and intensive care unit (ICU) admission, exceeding the capacity of many of them and turning COVID-19 into a challenge for health systems all over the world[5-9]. Furthermore, we observed a relationship between ICU caseload and mortality[10,11].

The lack of an available, effective treatment has led to a spate of treatment recommendations[12-15], which are not always backed by sufficient scientific evidence[16,17]. We paid particular attention to a presumed specific cytokine storm secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection[18-20], with a special effort to modulate the inflammatory response of these patients. One year after the onset of the disease, many questions remain unanswered, and we continue to search

for the most appropriate treatment. This review aims to summarize the current evidence regarding the different immunomodulatory strategies tested in critically ill patients with COVID-19.

MATERIALS AND METHODS

A comprehensive literature search was developed by using the keywords: "immunotherapy", "immunosuppressives", "haemophagocytic syndrome", "inflammation", "antimalarials", "hydroxychloroquine", "chloroquine", "anakinra", "canakinumab", "tocilizumab", "sarilumab", "corticosteroids", "dexamethasone", "methylprednisolone", "immunoglobulins or convalescent" "JAK inhibitors", "cyclosporine", "colchicine", "statins", "interleukin 7", "thymosin", "PD1 and PD1-L blockers". We restricted the search to: "SARS-CoV-2", "COVID-19", "severe COVID-19" and "treatment" to identify articles published in English from MEDLINE, PubMed, and The Cochrane Library (until January 2021). The meta-analysis, clinical trials, case-control or cohort studies, brief reports, reviews, and systematic reviews were included. *Reference Citation Analysis*, an artificial intelligence technology-based open citation analysis database was employed. Current international guidelines on the management of COVID-19 were also retrieved and included (Centers for Disease Control and Prevention, European Centre for Disease Prevention and Control, Infectious Diseases Society of America, WHO, National Health Service, Spanish Society of Intensive Care Medicine). Articles in preprint format were also evaluated if they were considered relevants and well designed. The authors reviewed the selected manuscripts and selected the most appropriate. Finally, we established a recommendation of the use of each treatment based on the level of evidence of the articles and documents reviewed. This recommendation was made based on the consensus of all the authors. We carried out the rest of the work methodology following the PRISMA recommendations for systematic review and meta-analysis documents (http://prisma-statement.org/PRISMAStatement/Checklist).

RESULTS

Viral infection and the inflammatory response

SARS-CoV-2 infects cells that express surface receptors for angiotensin-converting enzyme 2 (ACE-2) like airway epithelial cells, type II pneumocytes, vascular endothelial cells, and macrophages in the lung, and transmembrane protease, serine 2[21-23]. Active replication and release of the virus cause the host cell to undergo pyroptosis and release of damage-associated molecular patterns, including nucleic acids, adenosine triphosphate (ATP), and atypical squamous cell oligomers. These molecules are recognized by neighboring epithelial cells, endothelial cells, and alveolar macrophages, triggering the liberation of proinflammatory cytokines and chemokines [including interleukin (IL)-2γ, IL-6, IL-8, granulate-macrophage colony-stimulating factor, macrophage inflammatory protein 1α (MIP1α), MIP1β, and monocyte chemoattractant protein 1]. These mediators attract macrophages, monocytes, and T lymphocytes to the site of infection, promoting increased inflammation and establishing a pro-inflammatory feedback loop[24]. This inflammatory response is much more exaggerated in the subgroup of patients who require ICU admission and those with fatal outcomes and affects different organs and systems, including the endothelium[25-28].

Dysregulated immune response and COVID-19 immunophenotypes

In severe COVID-19, many patients express a dysregulated immune response characterized by a defective adaptive response and an exacerbated innate immune response. This situation leads to poor control of the virus, and overproduction of proinflammatory cytokines that initially damage lung infrastructure[29-31]. A cytokine storm similar to that in hemophagocytic syndrome has been described in a subgroup of COVID-19 patients with elevated levels of proinflammatory cytokines, particularly soluble receptor for IL-2γ, IL-6, and tumor necrosis factor-α (TNF-α)[32]. The resulting hypercytokinemia extends to other tissues and can cause considerable organic damage[28]. This finding would justify the use of immunosuppressive therapies such as corticosteroids or cytokine-targeted therapy.

Inflammation is not always the dominant phenomenon in COVID-19[33-35]. Different authors have revealed that in many severe cases of COVID-19 the presence of immune downregulation with profound immunosuppression as primary phenomenon precedes hyperinflammation. These immunological alterations are varied and can be classified into different subsets or phenotypes[30,36,37]. One of these immunophenotypes would be characterized by the presence in most patients with severe COVID-19 of coexisting alterations in numbers, subset composition, cycling, activation, and gene expression of T cells. Numerous studies show a relationship between profound lymphopenia with a worse prognosis and higher mortality in COVID-19[38-40]. This lymphopenia affects the different subsets of T cells, and the cause is not well established. We postulate several causes: T cell exhaustion, migration and sequestration of T cells to affected tissues (especially the lungs), a deficit of lymphopoiesis induced by the

presence of hypercytokinemia, or an increase in apoptosis mediated by a virus-induced overexpression of type 1 programmed death receptors (PD-1) and its ligand (PD-L1).

Another immunophenotype is characterized by decreased antigen presentation capacity, demonstrated by a deficit in human leukocyte antigen-DR expression in mononuclear-phagocytic system cells, particularly in intermediate monocytes. We observed this phenotype in more than 50% of severe and critical forms of COVID-19, and it is inversely related to the inflammatory activity mediated by cytokines such as IL-6[37,41]. In this regard, hypercitokinemia (both: Pro and anti-inflammatory cytokines) is another typical phenotype in severe forms of COVID-19. IL-6, IL-8, IL-1β, and IL-10 levels were higher in COVID-19, and the increases were severity-related. Induced protein 10 (IP-10) CXCL10, a chemokine rapidly and transiently induced following vaccination and other virus infections, almost invariably increased in COVID-19 and was severity-related[42]. Thus, many patients with COVID-19 were described by a severity-related triad of IP-10, IL-6, and IL-10[20,32,36,43]. Finally, emerging data indicate that complement and neutrophils contribute to an inadequate immune response that fuels hyperinflammation and thrombotic microangiopathy, increasing COVID-19 mortality. High plasma levels of neutrophil extracellular traps, tissue factor activity, and sC5b-9 were detected in critical patients[44,45]. All these conditions constitute immune signatures associated with a worse prognosis of COVID-19 that, on the other hand, could also suppose therapeutic targets.

Antimalarials: Hydroxychloroquine and chloroquine

Hydroxychloroquine (HCQ) is an antimalarial 4-aminoquinoline that showed *in vitro* activity against various RNA viruses, including SARS-CoV-2[46]. Some authors believe that HCQ acts against SARS-CoV-2 through multiple mechanisms[47]: Inhibition of viral entry; inhibition of viral release in the host cell; reduction of viral infectivity and immune modulation.

The absence of efficacious treatment tools at the beginning of the pandemic led to the wide use of chloroquine and HCQ. Thus, in several controlled studies carried out in Chinese hospitals, chloroquine treatment was able, compared to controls, to prevent the development of pneumonia, improve the radiological lung image, accelerate the elimination of the virus and shorten the duration of the disease [48-50]. Similarly, a French study with a small sample size found that treatment with HCQ accelerated conversion to a state of seronegativity for the virus[51]. However, these studies had significant methodological limitations that made their results questionable.

Nowadays, the body of evidence on HCQ e showed no benefit in terms of mortality reduction, invasive MV requirements, or time to clinical improvement. Until now, 31 randomized controlled trials (RCTs), including 16536 patients, have compared HCQ or chloroquine against standard of care or other treatments. The Recovery trial was the biggest, with over 11800 patients randomized to different treatment arms. 1561 patients were randomized to receive HCQ and 3155 to receive usual care after an interim analysis determined a lack of efficacy. Death within 28 d occurred in 421 patients (27.0%) in the HCQ group and in 790 (25.0%) in the usual-care group [rate ratio (RR) = 1.09; 95% confidence interval (CI): 0.97-1.23; P = 0.15]. The results suggested that patients in the HCQ group were less likely to be discharged from the hospital alive within 28 d than those in the usual-care group (59.6% *vs* 62.9%; RR = 0.90; 95%CI: 0.83-0.98). Moreover, among the patients who were not undergoing MV at baseline, those in the HCQ group had a higher frequency of invasive MV or death (30.7% *vs* 26.9%; RR = 1.14; 95%CI: 1.03-1.27)[52]. More recently, in the Solidarity trial, 947 patients were assigned to receive HCQ. Death occurred in 104 of 947 patients receiving HCQ and in 84 of 906 receiving its control (RR = 1.19; 95%CI: 0.89-1.59; P = 0.23)[53].

The main RCTs that have compared the effect of HCQ or chloroquine on mortality have been included in two metanalyses. The one made by the WHO combined the Recovery and Solidarity trials with other six smaller studies involving hospitalized patients with suspected or confirmed COVID-19. The results of this metanalysis showed that HCQ or chloroquine probably increase mortality, RR = 1.08 (95%CI: 0.99-1.19); does not reduce invasive MV requirement; RR = 1.05 (95%CI: 0.9-1.22) and may not improve time to symptom resolution, RR = 1.05 (95%CI: 0.94-1.18)[54]. These results are consistent with other published metanalysis that included 28 published or unpublished RCTs, with 10319 patients, obtaining a combined odds ratio (OR) on all-cause mortality for HCQ of 1.11 (95%CI: 1.02-1.20; I^2 = 0%; 26 trials; 10012 patients) and a combined OR for chloroquine of 1.77 (95%CI: 0.15-21.13, I^2 = 0%; 4 trials; 307 patients)[55]. In contrast, in a recent retrospective observational study conducted by Schlesinger *et al* [56] in 3451 unselected patients hospitalized in 33 clinical centers in Italy, HCQ use was associated with a 30% lower risk of in-hospital death COVID-19 hospitalized patients. In conclusion, awaiting new randomized clinical trials focused on critically ill patients, the treatment with HCQ is associated with increased risk of mortality in COVID-19 patients, and there was no benefit of chloroquine. For these reasons, its use is discouraged in patients with severe COVID-19 infection.

Colchicine

Colchicine has been in the spotlight as a treatment for SARS-CoV-2 infected patients given its anti-inflammatory and antiviral properties, which lead to the hypothesis that it might be beneficial with the systemic inflammation observed in the most severe cases. Many are the mechanism of action involved in colchicine's properties, but they are underpinned mainly by inhibiting neutrophil chemotaxis by interfering with microtubule formation, modulation of proinflammatory cytokines, and attenuation of

Table 1 Summary of studies addressing interleukin-1 blockers on coronavirus disease 2019

Ref.	Patients	Intervention	Comparison	Outcome
CORIMUNO-19 Collaborative group[74], RCT	Hospitalized patient with mild-to-moderate pneumonia, non-ICU admitted	Anakinra (200 mg twice a day on days 1-3, 100 mg twice on day 4, 100 mg once on day 5) (n = 59)	Standard care (n = 55)	No difference in NIV/MV/death at day 4. Stopped early following the recommendation of the data and safety monitoring board
Cavalli *et al*[75], observational	Pneumonia with moderate-to-severe ARDS and hyperinflammation (non-MV, non-ICU admitted)	Anakinra (high dose: 5 mg/kg twice a day intravenously, n = 29; or low dose: 100 mg twice a day subcutaneously, n = 7)	Standard care (retrospective cohort) (n = 16)	Survival. High-dose anakinra: 72%, SC: 56%, P = 0.009
Huet *et al*[76], observational	Bilateral pneumonia (non-ICU admitted)	Anakinra (100 mg twice daily for 72 h, followed by 100 mg daily for 7 d) (n = 52)	Standard care (historical group) (n = 44)	Death/MV. Anakinra: HR = 0.22 (95%CI: 0.11-0.41), P < 0.0001. Death. Anakinra: HR = 0.30 (95%CI: 0.12-0.71), P = 0.0063. MV: Anakinra: HR = 0.22 (95%CI: 0.09-0.56), P = 0.0015
Kooistra *et al*[77], observational	ICU admitted pneumonia (MV: 100%)	Anakinra (300 mg iv, followed by 100 mg iv/6 h) (n = 21)	Standard care (n = 39)	No differences in duration of MV, ICU length of stay, or mortality

RCT: Randomized clinical trial; ICU: Intensive care unit, NIV: Non-invasive ventilation; MV: Mechanical ventilation; ARDS: Acute respiratory distress syndrome; HR: Hazard ratio; SC: Standard of care; CI: Confidence interval.

NOD-like receptor family pyrin domain containing 3 inflammasome formation, among others[56].

Several studies have explored the potential risk-benefit ratio of colchicine in ambulatory and inpatient based on its properties. A meta-analysis reported a survival benefit (OR = 0.62; 95%CI: 0.48-0.81) of patients with Colchicine treatment with a tendency towards a decreased need of MV [0.75 (95%CI: 0.45-1.25)][57]. However, most studies focus on the out-hospital or mild cases of COVID-19 patients. Not much has been reported about colchicine in the most severe cases. In this sense, Scarsi *et al* [58] observed that colchicine was independently associated with survival [hazards ratio (HR) = 0.151; 95%CI: 0.062-0.368] despite it was given to patients with worse PaO_2/FiO_2. Similarly, Brunetti *et al*[59] also observed a significant decreased mortality in patients with severe COVID-19 among those who received colchicine (OR = 0.20; 95%CI: 0.05-0.80; P = 0.023).

To date, only one prospective, open-label, randomized trial has explored the potential benefits of colchicine among severe COVID-19 patients. In this trial, patients who received colchicine did show an improved time to clinical deterioration compared to those without colchicine[60]. However, recently, the RECOVERY trial closed the recruitment of colchicine for hospitalized COVID-19 patients after a review did not observe any clinical benefit[61].

In conclusion, given the disparity, we cannot recommend colchicine despite initial data being promising until further evidence. Among more than 30 clinical randomized trials ongoing analyzing the effect of Colchicine in COVID-19, only 3 focus specifically on severe cases or patients admitted to the ICU: In particular ECLA PHRI COLCOVID Trial (NCT04328480), COMBATCOVID trial (NCT04363437), and COLHEART-19 (NCT04762771). These trials will explore the requirement for MV, severe complications, or death among moderate-to-severe hospitalized COVID-19 patients.

Calcineurin inhibitors: Cyclosporine A and tacrolimus

Cyclosporine A and tacrolimus (also called FK-506) are immunosuppressive drugs known to prevent rejection after organ transplantation and for autoimmune diseases. These drugs bind to different cellular cyclophilins and FK506-binding proteins, respectively. This binding inhibits calcineurin (calcium-calmodulin-activated serine/threonine-specific phosphatase) blocking the translocation of the nuclear factor of the activated T cells from the cytosol to the nucleus, preventing the transcription of several genes that encode key cytokines involved in different immunological mechanisms[62-64].

Cyclosporin A binds cyclophilin A, which is essential for the replication of, among other viruses, SARS-CoV-2[65]. Therefore, the binding of cyclosporin A with the corresponding cyclophilin can block the replication of SARS-CoV-2[66]. Tacrolimus binds to FK506-binding proteins and inhibits calcineurin, in addition to suppressing the early phase of T-cell activation and the expression of numerous cytokines (IL-2, IL-4, TNF-α, INF-γ), which are necessary for the activation of the T cell in the immune response, perhaps preventing the cytokine storm seen in severe COVID-19 pneumonia[67].

In vitro evidence of inhibition of cyclosporine-mediated replication of various coronaviruses (including SARS) has been found. The cyclosporin analog, alisporivir, has been reported to inhibit SARS-CoV-2 *in vitro* but has never been tested in a clinical setting[68]. Given the antiviral and anti-inflammatory properties of calcineurin inhibitors, they could have the potential to prevent the uncontrolled inflammatory response and replication of SARS-CoV-2, in addition to acute lung injury. However, there is not enough evidence to recommend its use in severe COVID-19. Currently, several clinical trials are studying the possible benefit of the administration of cyclosporine (NCT04492891,

NCT04540926, and NCT04341038) or tacrolimus (NCT04341038) in the treatment of hospitalized patients with pneumonia due to COVID-19. Unfortunately, to date, there are no studies with these drugs focused on critically ill patients.

IL-1 blocker: Anakinra, canakinumab

Anakinra is a recombinant human IL-1 receptor antagonist that blocks the activity of the proinflammatory cytokines IL-1α and IL-1β, and it is approved to treat patients with rheumatoid arthritis, Still's disease, and some rare auto-inflammatory syndrome. Reanalysis of data from a phase III randomized controlled trial showed anakinra is related to a significant improvement in survival in the subset of septic patients with features of macrophage activation syndrome (MAS)[69,70].

MAS is a subgroup of secondary hemophagocytic lymphohistiocytosis mainly appearing in rheumatologic disorders. It is an acute syndrome with a hyperinflammatory immune state characterized by the activation and expansion of macrophages and T-lymphocytes. This persistent activation leads to a cytokine storm with high IL-1, IL-6, IL-18, soluble IL-2 receptor (CD 25), IFN-γ, and TNF-α, and is thought to be responsible for the multiorgan failure and the high mortality of this syndrome[71,72].

A subgroup of severe COVID-19 patients shows hyperinflammatory symptoms similar to MAS, with the release of IL-1, IL-6, IL 18, and IFN-γ, and the evidence shows a direct correlation between the severity of systemic inflammation, progression to respiratory failure, and fatal outcome[73,74]. For this reason, it has been proposed to treat this patient subgroup with anakinra. At the date, only the RCT CORIMUNO-ANA-1 investigating the role of anakinra in COVID-19 patients has been published[75]. In this trial, patients were randomized to intravenous anakinra or usual care in mild-to-moderate COVID-19 pneumonia (not requiring ICU admission) with serum C-reactive protein (CRP) levels higher than 25 mg/L. They could not demonstrate that the use of anakinra effectively reduced the need for non-invasive ventilation (NIV), MV, or mortality. The study was stopped due to futility. Another trial within the CORINOMUNO platform (CORINOMUNO-ANA-2) aimed to assess the effect of anakinra in patients with more severe COVID-19 patients (ICU admitted) has now been completed, and it is being analyzed.

Few observational studies analyze the treatment with anakinra in COVID-19 patients, and they have methodological limitations (Table 1). Cavalli *et al*[75] have analyzed high-dose (5 mg/kg twice daily) of intravenous anakinra compared to standard care: Higher survival rate and progressive improvements in PaO_2/FiO_2 ratio have been observed, without significant differences in days free of MV. Huet *et al*[76] have studied subcutaneous anakinra *vs* standard treatment, and they observed that anakinra significantly reduced the need for MV or mortality. The control group was a historical cohort with high mortality (about 50%).

Kooistra *et al*[77] have analyzed mechanically ventilated COVID-19 patients treated with intravenous anakinra *vs* standard care in critically ill patients. Anakinra has been linked to a significant reduction in clinical signs of hyperinflammation, without significant differences in clinical outcomes. Dimopoulos *et al*[78] have studied rescue treatment with intravenous anakinra in seven MV-ICU patients and one non-ICU patient, all of them with a hemophagocytosis score positive. They concluded that anakinra could improve respiratory function and reduce mortality compared with the historical series of patients with MAS in sepsis. Canakinumab is a monoclonal antibody against IL-1β approved to treat familial Mediterranean fever and other chronic autoinflammatory syndromes[79].

In the setting of COVID-19 pneumonia, a small retrospective study has analyzed 10 patients with respiratory failure (not requiring MV) and hyperinflammation treated with canakinumab. A rapid improvement of the inflammatory response and oxygenation was observed[80]. An ongoing clinical phase 3, randomized, double-blind trial studies the efficacy and safety of canakinumab on Cytokine Release Syndrome in patients with COVID-19 pneumonia (NCT04362813). In conclusion, there is not enough data supporting the efficacy or safety of anakinra or canakinumab in treating critically ill patients with COVID-19, and therefore, we can't establish a recommendation on their use or the optimal timing to start the treatment.

IL-6 blockers: Tocilizumab and sarilumab

COVID-19 patients who develop severe respiratory failure use to show a hyperinflammatory response, either MAS (driven by IL-1β) or, primarily, immune dysregulation (driven by IL-6). IL-6 is an inflammatory cytokine that exerts its effects inducing acute phase reactants (as CRP, fibrinogen, and hepcidin) in the liver and promotes antibody production and CD4 T helper and CD8 cytotoxic T cell differentiation[81,82]. A direct relationship between IL-6 levels and viral load, duration of SARS-CoV-2 viral positivity, the severity of COVID-19, and the need for MV has been observed[83-88].

Tocilizumab (TCZ) and sarilumab are two monoclonal antibodies that work by blocking the IL-6 soluble and membrane receptor. TCZ is approved to treat inflammatory diseases such as rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, and cytokine release syndrome associated with chimeric antigen receptor T-cell therapy and sarilumab is approved for the treatment of rheumatoid arthritis[89]. Its use has been proposed to reduce the inflammatory response in COVID-19 patients. The first available data obtained from case series showed clinical, analytical, and radiological improvement after TCZ administration, even in patients needing MV[90-94].

Table 2 Summary of studies addressing interleukin-6 blockers on coronavirus disease 2019 (randomized clinical trials and observational studies including critically ill patients)

Ref.	Patients	Intervention	Comparison	Outcomes	Overinfection rate
Salama *et al*[110], RCT	377	TCZ (8 mg/kg, 1-2 doses)	Placebo	MV/ECMO/mortality 28 d; 19.3% TCZ *vs* 12% placebo, $P = 0.004$	TCZ 10% *vs* placebo 12.6%
Rosas *et al*[113], RCT	438	TCZ (8 mg/kg, 1-2 doses)	Placebo	Mortality: NS. Hospital LOS: TCZ: 20, placebo: 28 d ($P = 0.037$). ICU admission: TCZ: 23.6%, SC: 40.6% ($P = 0.01$). ICU, LOS: TCZ: 9.8, SC: 15.5 d ($P = 0.045$)	TCZ 21% *vs* placebo 25.9%
Stone *et al*[90], RCT	242	TCZ (8 mg/kg, max 800 mg, 1 dose)	Placebo	MV or death. TCZ: 10.6%, SC: 12.5% (NS). Clinical worsening. TCZ: 19.3%, SC: 17.4% (NS)	TCZ 8.15% *vs* placebo 17.1%
Salvarani *et al* [111], RCT	123	TCZ (8 mg/kg, max 800 mg, 1-2 doses)	Standard of care	NS	TCZ 1.7% *vs* TE 6.3%
Mariette *et al* [112], RCT	131	TCZ (8 mg/kg, max 800 mg, 1-2 doses)	Standard of care	NIV/MV/death at day 4. TCZ: 19%, SC: 28% (NS). Survival without HFNO/NIV/MV at day 14. TCZ: 24%, SC: 36% (probability: 95%). 28 d mortality. TCZ: 10.9%, SC: 11.9% (NS)	TCZ 3.2% *vs* TE 16.4%
RECOVERY Collaborative Group[115], RCT	4166	TCZ (different regimes)	Standard of care	28 d mortality: TCZ: RR = 0.86 (95%CI: 0.77-0.96, $P = 0.006$)	Not available
REMAP-CAP Investigators *et al* [116], RCT	826	TCZ (8 mg/kg, max 800 mg, 1-2 doses) ($n = 366$). Sarilumab (400 mg) ($n = 48$)	Standard of care	Days free of respiratory/hemodynamic support at day 21. TCZ: 10 d, sarilumab: 11 d, SC: 0 d. Hospital mortality. TCZ: 28%, sarilumab: 22.2% SC: 35.8% (probability TCZ better: 99.6%, probability sarilumab better: 99.5%)	TCZ 0.2% *vs* TE 0%
Veiga *et al*[114], RCT	129	TCZ (8 mg/kg, max 800 mg)	Standard of care	Stopped early due to higher mortality in TCZ patients	PB 15% *vs* SC 16%
Tleyjeh *et al*[121], MA	9850	TCZ (variable regimen)	Standard of care	Mortality: TCZ: OR = 0.58 (0.51-0.66)	TCZ: RR = 0.63 (0.38-1.06)
Gupta *et al*[106], OS	3491	TCZ (regimen not specified)	Standard of care	Hospital mortality. TCZ: HR = 0.71 (95%CI: 0.56-0.92)	TCZ 32.3% *vs* SC 31.1%
Somers *et al*[108], OS	154	TCZ (8 mg/kg, max 800 mg)	Standard of care	Mortality. TCZ: HR = 0.54 (95%CI: 0.35-0.84)	TCZ 54% *vs* SC 26%. Pneumonia 45% *vs* 20%. Bacteremia 14% *vs* 9%
Fisher *et al*[109], OS	115	TCZ (400 mg)	Standard of care	30 d mortality. TCZ: OR = 1.04 (95%CI: 0.27-3.75)	TCZ 28.9% *vs* SC 25.7%
Biran *et al*[102], OS	764	TCZ (400 mg, 1-2 doses)	Standard of care	Hospital mortality. TCZ: HR = 0.64 (95%CI: 0.47-0.87, $P = 0.004$)	TCZ 17% *vs* SC 13%
Guaraldi *et al* [101], OS	544	TCZ (8 mg/kg, max 800 mg, 2 doses) ($n = 179$)	Standard of care	Death/MV. TCZ: HR = 0.61 (95%CI: 0.4-0.92), $P = 0.020$	TCZ 13% *vs* SC 4%
Rossotti *et al* [105], OS	222	TCZ (8 mg/kg, max 800 mg, 1-2 doses) ($n = 74$)	Standard of care	Survival rate TCZ: HR = 2.004 (95%CI: 1.050-3.817), $P = 0.035$. Survival rate in critically ill patient. HR = 30.055 (95%CI: 1.420-636.284), $P = 0.029$	TCZ 24.4%; SC: NA
Rojas-Marte *et al* [107], OS	193	TCZ (regimen not specified)	Standard of care	Mortality TCZ: 52%, SC: 62%, $P = 0.09$. Mortality in non-ventilated patients: TCZ: 6.1%, SC: 26.5%, $P = 0.024$	Bacteremia: TCZ 12.5% *vs* SC 23.7%. Fungemia: TCZ 4.2% *vs* SC 3.1%

TCZ: Tocilizumab; RCT: Randomized clinical trial; MA: Metha-analysis; OS: Observational study; MV: Mechanical ventilation; ICU: Intensive care unit; NIV: Non-invasive ventilation; LOS: Long of stay; HNFO: High nasal flow oxygen therapy; ECMO: Extracorporeal extracorporeal membrane oxygenation; SC: Standard of care; NS: Non-significative; RR: Relative risk; OR: Odds ratio; CI: Confidence interval; HR: Hazard ratio; NA: Not applicable.

The results obtained from comparative observational studies (cohorts or case-controls) were also promising[95-98]. Although some studies failed to show relevant differences between TCZ-treated and untreated patients[99,100], most of them showed a beneficial effect of the administration of TCZ: Oxygenation improvement, more days free of MV, less need for ICU admission or MV, and higher survival[101-105].

There are scarce studies that analyze the effect of TCZ in critically ill patients with COVID-19. In one of them, Biran *et al*[102] in 630 propensity score-matched ICU patients (> 90% of them receiving MV) found a lower in-hospital mortality risk (HR = 0.64; 95%CI: 0.47-0.87; $P = 0.004$) in patients treated with TCZ (400 mg). Rossotti *et al*[105] described similar results showing a lower risk of mortality in the

general analysis and patients receiving MV, but not in less severe cases; Gupta *et al*[106] found an in-hospital reduction in mortality in those critically ill patients who received TCZ in the first 2 d of ICU admission. On the other hand, Rojas-Marte *et al*[107] analyzed 193 patients (62.7% with MV) and found that TCZ was related to lower mortality in non-ventilated patients (6.1% *vs* 26.5%, $P = 0.024$), but not in MV patients.

In addition, we have contradictory data from two studies focused on patients on MV. One of them shows a reduction in mortality risk (HR = 0.55; 95%CI: 0.33-0.90)[108], and the other failed to detect significant differences between those treated with TCZ and untreated patients[109,110]. More recently, we began to know the results of RCT investigating the effects of TCZ in COVID patients[85,111-113]. Among these, once again, there is no unanimity regarding the results. Salama *et al*[110] and Mariette *et al*[112], in hospitalized patients with SARS-CoV-2 pneumonia (not needing respiratory support), demonstrated a reduction in the risk of death or need of MV in patients treated with one or two doses of TCZ (8 mg/kg, maximum 800 mg). However, Stone *et al*[90] and Salvarani *et al*[111] failed to demonstrate a beneficial effect in patients treated with TCZ in similar patients (respiratory failure needing conventional oxygen therapy).

In a mixed population, including 38% of patients on MV, the COVACTA trial shows no evidence of improvement in the clinical situation on day 28 (primary outcome) but it shows a shorter hospital stay, less ICU admission, and less clinical failure rate in patients randomized to treatment with TCZ (8 mg/kg, max 800 mg, one or two doses)[113]. TOCIBRAS trial was prematurely interrupted because an excess of deaths at 15 d after randomization was detected in the TCZ group; this study included severe and critically ill COVID patients (23% receiving HFNO/NIV and 16% receiving MV)[114].

Recently, results of the RECOVERY platform trial were released[115]. In patients with clinical evidence of progressive COVID-19 (CRP ≥ 75 mg/L and need for supplemental oxygen to achieve oxygen saturation > 92%), treatment with TCZ improved survival and decreased the need for MV. The reduction in mortality with TCZ was higher in patients who also receive corticosteroids. REMAP-CAP trial addressed the impact of TCZ focused on critically ill patients. In this RCT, patients were randomized to be treated with TCZ ($n = 366$), sarilumab ($n = 48$), or usual care ($n = 412$). The authors reported that patients treated with IL-6 blockers (TCZ 8 mg/kg, max 800 mg, one or two doses; or sarilumab, 400 mg), within 24 h after the start of organ support, had more days free of hemodynamic or respiratory support and lower in-hospital mortality. Furthermore, it appears that the treatment effect is more significant when TCZ was combined with corticosteroids[116]. A summary of studies addressing IL-6 blockers on COVID-19 is available in Table 2.

One of the main concerns when using TCZ is the risk of superinfections. However, a higher incidence of superinfections in patients treated with TCZ has not been confirmed in critically ill COVID-19 patients (see Table 2). In the same way as TCZ, sarilumab administration has been related to series, clinical, analytical, and radiological improvement but the available data are scarce[117-120]. It has not shown benefit in comparative observational studies[121], but it has been shown in the aforementioned REMAP-CAP trial[116]. In most positive studies, TCZ is associated with corticosteroids (see Table 3), thus given the positive results described and the absence of significant side effects of this combination, it should be considered early in COVID-19 patients admitted to the ICU.

Janus kinase pathway inhibition: Ruloxitinib, bariticinib

Most viruses, SARS-CoV-2 included, enter cells through receptor-mediated endocytosis after binding its spike protein to the human ACE-2 receptor[122]. This endocytosis is mediated by clatrine and other mechanisms. AP2-associated protein kinase 1 (AAK1) and cycling G-associated kinase (GAK) regulates this process[123]. Disabling AAK1 might stop the virus's entry into cells and the intracellular assembly of virus particles[124]. Janus kinase (JAK) inhibitors are biological agents that mainly inhibit type I/II cytokine receptors[125]. There are several JAK inhibitors such as fedratinib, tofacitinib, sunitinib, or erlotinib. Still, they have many secondary effects, which turns their use in COVID-19 patients controversial, but ruxolitinib and baricitinib may play a role in this setting. However, Food and Drug Administration recently raised a warning regarding treatment with JAK-inhibitors that we have to bear in mind before starting treatment: Increased thromboembolism risk or increased frequency of herpes zoster virus reactivation; pan-JAK inhibitors may repress some cytokines required for antiviral defense (IFN-α/β) or immune restoration (IL-2, IL-7)[126-128].

Baricitinib is an oral anti-JAK inhibitor, acting against JAK1 and JAK2, with less potency for JAK3, with an exceptionally high affinity for AAK1. It inhibits the JAK signal transducer and activator of the transcription (STAT) pathway[129]. Moreover, it can also inhibit the cyclin GAK, another regulator of endocytosis, so it has been suggested as a potential drug against SARS-CoV-2 due to its double effect: Decreasing both the immune response (inhibiting the proinflammatory signal of several cytokines, such as IL-6, IL-12, IL-23, and IFN-α) and interrupting the virus entry and assembly in the cells[130]. It is currently approved for rheumatoid arthritis[131]. Its advantages include once-a-day oral administration (either 2 mg or 4 mg), acceptable safety profile (can be used in combination with other treatments because of low plasma protein binding and minimum cytochrome P450 interactions), and the double mechanism of action[132]. There is certain reluctance about baricitinib due to the simultaneous inhibition of AAK1 and JAK, which can reduce IFN-α levels, leading to a worse immune response, as mentioned above[133]. A pilot study from Italy showed significantly improved clinical and laboratory

Table 3 Coronavirus disease 2019 patients treated with tocilizumab and corticosteroids

Ref.	Tocilizumab group	Control
Salama *et al*[110], RCT	80.3%	87.5%
Rosas *et al*[113], RCT	36.1%	54.9%
Stone *et al*[90], RCT	11%	6%
Salvarani *et al*[111], RCT	10%	7.6%
Mariette *et al*[112], RCT	33%	61%
RECOVERY Collaborative Group[115], RCT	82%	82%
REMAP-CAP Investigators *et al*[116], RCT	> 80%	
Veiga *et al*[114], RCT	69%	73%
Gupta *et al*[189], observational	18.7%	12.6%
Somers *et al*[108], observational	29%	20%
Fisher *et al*[109], observational	73.3%	78.6%
Biran *et al*[102], observational	46%	42%
Guaraldi *et al*[101], observational	30%	17%
Rossotti *et al*[105], observational	Not reported	
Rojas-Marte *et al*[107], observational	43%	33%

RCT: Randomized clinical trial.

parameters in 12 patients with mild to moderate COVID-19 pneumonia. None of them required admission to the ICU nor MV[134].

An RCT evaluated baricitinib plus remdesivir in hospitalized COVID-19 patients. The treatment group needed fewer days to recovery (7 *vs* 8 d, $P = 0.03$) and 30% higher odds of improvement in clinical status at day 15. Precisely, patients on NIV or HFNO needed significantly less time to recovery (10 *vs* 18 d) and had fewer serious adverse events (16% *vs* 21%, $P = 0.03$)[135]. In conclusion, baricitinib combines anti-inflammatory characteristics and antiviral activity, making it a strong candidate for future evaluation in RCT.

Ruxolitinib is another oral JAK-kinase inhibitor currently indicated for intermediate or high-risk myelofibrosis, polycythemia vera, hemophagocytic lymphohistiocytosis, or steroid-refractory graft-*versus*-host disease. Ruxolitinib reduces the high level of cytokine release associated with these diseases [136,137]. It blocks JAK kinase activity and impedes STAT activation, decreasing levels of inflammatory cytokines (such as IL-1β, IL-2, IL-5, IL-6, IL-7, IL-13, IL-15, and IFN-γ)[138]. Pharmacokinetically, ruxolitinib has rapid oral absorption and a half-life of approximately 3 h and reaches peak plasma concentrations[139].

A non-randomized clinical study conducted in 93 severe COVID-19 patients not requiring MV at baseline showed a significant improvement in survival rate (89.1% *vs* 57.1%, $P = 0.0034$), a reduction of the inflammatory response (absence of fever and a decrease of at least 30% in CRP levels; 87% *vs* 23%, $P = 0.0001$) and no significant adverse event in patients treated with half the approved dose of ruxolitinib for hematologic diseases plus corticosteroids[140]. Similar results were communicated by La Rosée *et al* [140], in his retrospective study performed in 14 patients receiving ruxolitinib (10 receiving NIV, 1 HFNO, and 1 MV); they used a COVID inflammation score to evaluate the systemic inflammation, watching a reduction by 42% and 58% achieved on day 5 and 7 of treatment.

Only one Chinese RCT studied the efficacy of ruxolitinib. No death (14.3% *vs* 0%, $P = 0.232$) or deterioration [need for NIV/MV: (29% *vs* 10%, $P = 0.663$)/(14.3% *vs* 0%, $P = 0.232$)] occurred in ruxolitinib group, but no statistically difference was found. Both groups received a similar proportion of corticosteroids and antivirals[141]. To summarize, ruxolitinib may play a role in those patients with hypoxemic COVID-19 pneumonia but not yet needing MV, attenuating the immune response and therefore may prevent the progression of lung damage, bearing in mind that an early administration could favor viral replication. There is no data in critically ill patients regarding JAK inhibitors to establish a strong recommendation but, maybe, baricitinib could be used in patients on NIV or HFNO who are also receiving remdesivir, in order to shorten the time to recovery.

Corticosteroids

Corticosteroids have been widely used for years in autoimmune diseases with great success. A cytokine

storm[32], similar to the hemophagocytic syndrome, may develop in some severe COVID-19 patients. In this setting, immunosuppressive treatments may decrease this hyper-inflammatory state, and this is the rationale for use corticosteroids in SARS-CoV-2 infection. Corticosteroids are hormones that may change the transcription pattern of 20% of the human genome[142], and they act in virtually all immune cells [143]. They inhibit the migration of leukocytes to inflamed tissues, increasing migration from bone marrow to blood and decreasing programmed leukocyte death[144,145]. They also inhibit leukocyte reactive oxygen species secretion, increase anti-inflammatory cytokines like IL-10[146,147], and alter the maturation and differentiation of dendritic cells[148-150]. Corticosteroids modify natural killer (NK) cytolytic activity and monocyte activation[150].

The use of up 100 mg of prednisone or an equivalent dose, acts over cytosolic corticosteroids receptors (cGCR), and we call this the genomic pathway[151,152]. The complex glucocorticoid-cGCR has two actions: Transactivation, which means that the complex promotes anti-inflammatory transcription factors as IL-10 or annexin 1. The other action is transrepression that produces an inhibition of inflammatory transcription factors (IL-1, IL-2, IL-6, IL-8, prostaglandins, TNF-α, and IFN-γ). That modifications happen in hours and may take up to a few days[151].

If we use corticosteroid pulses (doses higher than 100 mg of prednisone), we reach the highest effect of the genomic pathway, but we also obtain additional effects by the "non-genomic pathway"[150]. The non-genomic pathway induces membrane dysfunction in all immune cells and delays the calcium and sodium channel flow through the membrane. This process decreases ATP production. Non-genomic effects induce the bounding to the membrane of glucocorticoid receptors in the T lymphocytes[151]. They also release the Src protein from the complex cGCR-multiprotein, generating anti-inflammatory effects. These mechanisms take effect in hours and are very useful in autoimmune diseases with high disease activity[151].

The effect of corticosteroids depends not only on the dose (as seen before) but also on the timing used. We can preferably use corticosteroids in three moments: The onset of acute lung injury, the initial phase of acute respiratory distress syndrome (ARDS), and when ARDS is refractory to conventional treatment[153-155]. Historically, many studies used corticosteroids for viral pneumonia (including influenza and SARS-CoV-1)[156-161], and ARDS[162-167], with different results. We found no benefit in viral infection, and only a few of these studies demonstrated good results of corticosteroids on mortality [162,166]. Based on these, some authors analyzed the effect of corticosteroids in COVID-19 (see Table 4). Early in the pandemic, initial recommendations were not to use or limit corticosteroids to concrete situations[168-171]. WHO even recommended not to use corticosteroids routinely in COVID-19 pneumonia[172,173]. They base these recommendations on previous bad results in the SARS and Middle East respiratory syndrome (MERS) infections with corticosteroids. Some months later, some observational studies based on the Chinese hospitals' experience recommended using corticosteroids under certain conditions[174-176].

The Recovery trial[177] could demonstrate a mortality improvement with dexamethasone treatment in COVID-19 patients requiring oxygen supplementation, especially in those admitted to ICUs. This improvement does not remain in patients who do not need oxygen supplementation, worsening mortality in this subgroup.

From July to December 2020, several clinical trials demonstrated the benefits of corticosteroids on mortality in COVID-19 associated pneumonia[178-181]. Hydrocortisone, methylprednisolone, and dexamethasone are corticosteroids that demonstrated survival improvement used at a median dose for five to ten days. These corticosteroids at this dose demonstrated moderate mortality reductions. All studies showed that the mortality improvement was more significant in critical patients than in-hospital patients (see Table 4). Corticosteroids can also be used at a higher dose with methylprednisolone pulses for three days (250 mg for three days). One small clinical trial and some observational studies showed essential improvements in mortality using corticosteroid pulses[182-185]. Again using corticosteroid pulses, mortality improvement was more significant in the critical patient subgroup. This regimen (by the non-genomic pathway) showed better results than the median doses of corticosteroids for more extended periods in the few published results. If this regimen is significantly better than lower doses and more prolonged periods must be demonstrated in ongoing head-to-head clinical trials[186].

Progression to MV was lower in the corticosteroid arm in clinical trials and meta-analyses[187,188]. There was a non-significant trend to hyperglycemia and infections in the corticosteroid arm treatment (see Table 4). Results about viral shedding are controversial and different between studies, so we can't extract conclusions. As a final recommendation, corticosteroids should be used in COVID-19 pneumonia requiring oxygen supplementation, including critically ill patients, as proven in the Recovery trial and data obtained with the corticosteroid pulses studies. The 6 mg daily dexamethasone for ten days is the most accepted regimen because it is proven in clinical trials. The 250 mg daily methylprednisolone regimen for three days may be considered as an alternative too.

Intravenous immunoglobulin and hyperimmune immunoglobulin

Intravenous immunoglobulin (IVIG) is a product derived from the plasma of thousands of donors. It contains primarily polyclonal immunoglobulin G [with two functional fragments, the F(ab)2 fragment, for antigen recognition, and the crystallizable fragment (Fc), for the activation of innate immune responses], with small amounts of immunoglobulin (Ig)A and IgM. IVIG provides temporary protection

Table 4 Summary of studies using corticosteroids in coronavirus disease 2019

Ref.	Patients	Treatment regimen	Population	Mortality[2]	ICU administration	In-hospital stay	Secondary infections
RECOVERY Collaborative Group *et al* [177], RCT	11303	DXM 6 mg daily × 10 d	In-hospital	Decrease 2.8% RR 0.83	NS	Increase discharged 28 d (3.7%)	NA
RECOVERY Collaborative Group *et al* [177], RCT	1007	DXM 6 mg daily × 10 d	MV	Decrease 12.1% RR 0.64	NA	Increased discharged 28 d (9.7% RR 1.48)	NA
Tomazini *et al*[176], RCT	299	DXM 20 mg × 5d + DXM 10 mg × 5d	ICU patients	Decrease 2.4% (alive or ventilator-free)		NA	DXM 21.9% *vs* 29.1% standard. (7.9% *vs* 9.5% bacteremia)
Jeronimo *et al*[178], RCT	416	MPD (0.5 mg/kg twice daily) × 5d	In-hospital	NS	NS (MV)	NS	No significant differences
Dequin *et al*[179], RCT	149	HCT 200 mg daily × 7d then decrease dose × 7d (14 d)	ICU patients	NS		NS	NA
Angus *et al*[180], RCT	384	HCT 50 or 100 mg/6 h × 7 d	ICU patients	93% and 80% of superiority in organ support free		NS	NA
Edalatifard *et al*[181], RCT	68	MPD 250 mg × 3 d	In-hospital	Decrease 37%	No patients on MV	Decrease 4.6 d	2.9% (1 pt) in MPD *vs* 0% (0 pt) standard
Corral-Gudino *et al* [188], RCT[1]	85	MPD 40 mg/12 h × 3 d, then MPD 20 mg/12 h × 3 d	In-hospital	Decrease 24% composite death, ICU Adm or NIV		NS	NA
Kim *et al*[186], MA	49569	Variable regimens	ICU patients	OR 0.54 (0.40-0.73)	NA	NS	NA
Van Paassen *et al* [187], MA	20197	Variable regimens	In- hospital	OR 0.72 (0.57-0.87)	RR 0.71 (0.54-0.97)	NS	NA

[1]Preprint, not peer-reviewed.

[2]Absolute risk of mortality reduction in randomized clinical trial or odds ratio in meta-analysis.

ICU: Intensive care unit; RCT: Randomized clinical trial; MA: Meta-analysis; DXM: Dexamethasone; MPD: Methylprednisolone; HCT: Hydrocortisone; NS: Non-significant; NA: Not applicable; Adm: Admission; MV: Mechanical ventilation; NIV: Non-invasive ventilation; RR: Relative risk; OR: Odds ratio.

before being metabolized, requiring several doses over the disease course[189]. IVIG has been used to treat several immunodeficiencies, neurologic disorders, inflammatory and infectious conditions, such as pneumonia by influenza, SARS, and MERS[190].

The rationale for using IVIG in SARS-CoV-2 infection is a modulation of inflammation. The central mechanism of action of IVIG is the inactivation of phagocytes (neutrophils, monocytes, and macrophages) through FCyR. Moreover, it has a neutralizing effect by creating an antibodies-virus complex that prevents the binding of the virus to alveolar epithelial cells. Furthermore, it can also influence the process of lymphocyte differentiation and maturation[191,192].

Xie *et al*[193] conducted a retrospective study among 58 cases of severe or critically ill COVID-19 patients with lymphopenic immunophenotype (absolute lymphocyte count fell under 0.5 × 10^9/L), receiving IVIG (20 g/d), differentiating two groups: Those receiving IVIG early (< 48 h after admission) and after 48 h. There was a significant reduction in 28-d mortality (23% *vs* 57%, $P = 0.009$), need for MV (6.67% *vs* 32.14%, $P = 0.0016$) and length of stay (11 ± 1 d *vs* 1696 ± 16 d, $P = 0.005$) in the < 48 h group. However, a more recent RCT including 84 patients with severe COVID-19 (52 of which received IVIG at a dose of 400 mg/kg/d for three days plus standard care) showed no difference in terms of mortality nor need for MV or admission to the ICU[194]. Finally, an Iranian RCT including 59 patients who did not respond to initial treatments, showed a significantly lower in-hospital mortality (20% *vs* 48.3%, $P = 0.025$) in those patients ($n = 30$) receiving IVIG (20 g daily for three days)[195].

Taken together, the results of the studies show some limitations to attribute clinical improvement only to IVIG use (variations in previous/concomitants treatments, a small number of patients, or variations in dosage). So, in conclusion, we can't make a statement recommending its use. Considering its overall safety profile, it may be a promising option at the early stage of severe COVID-19 disease. On the other hand, hyperimmune immunoglobulin (H-IG) is an IVIG obtained from patients with high antibody titers to specific pathogens. Its pharmacokinetic properties are similar to IVIG, suggesting that a single dose may be enough in an acute setting[196,197]. It has been used in previous coronavirus epidemics such as SARS1 in 2003, MERS in 2012, and influenza A[198]. H-IG was used at a dosage of 5 mL/kg with an antibodies neutralizing titer of 1:160, with an optimal administration within the first 7 d. One of its limitations is the generation of neutralizing antibodies in specific individuals who have

passed an infection. Another limitation is that donor availability is limited. A recent Cochrane revision was conducted regarding convalescent plasma and H-IG including 98 ongoing studies[199].

Recently an Indian RCT included 464 moderate COVID-19 patients (PaO_2/FiO_2 between 200-300 mmHg or a respiratory rate higher than 24 rpm with SaO_2 < 93% on room air), 235 of which received convalescent plasma (two doses of 200 mL separated 24 h): No difference was observed with the control group regarding the progression of disease or mortality[200]. Another RCT conducted in Wuhan involved 103 severe COVID-19 patients (44 on NIV or high-flow nasal cannula, 25 on MV or extra-corporeal membrane oxygenation), where 52 received convalescent plasma plus standard therapy, observed an improvement of the negative conversion rate of viral polymerase chain reaction (87.2% *vs* 37.5%, P < 0.001) but did not result in a statistically significant improvement in time to clinical improvement within 28 d or in 28-d mortality[201].

We have limited data regarding critically ill patients. A small case series involving 5 critically ill patients on MV treated with convalescent plasma between day 10 to 22 from admission observed an improvement in their clinical status [increased PaO_2/FiO_2, decreased Sequential Organ Failure Assessment (SOFA) score, and body temperature normalized][202]. Another case report involving 4 critically ill patients (who received 200-2400 mL of convalescent plasma ranging from day 11 to day 18 post-admission) observed lung lesions resolution and decreased SARS-CoV-2 viral load clinical improvement[203]. A summary of RCTs and observational studies, including critically ill patients addressing IVIG and H-IG on COVID-19, is available in Table 5. Therefore, there are not enough data to support the use of H-IG and controversial results on convalescent plasma, so we can't establish a recommendation.

Other potential therapies: Statins and T-lymphocyte restorative therapies

Statins: Statins are potent 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors that prevent the activation of Rho-kinase, and thus, gain cardiovascular protective effects that are low-density lipoprotein-cholesterol independent[204]. The existing published evidence suggests a potential benefit of statins[205,206], despite the higher risk profile of statin-users as opposed to non-users, with some discordant results[207,208].

Statins improve endothelial dysfunction through upregulation of ACE-2 and endothelial nitric oxide synthase, decrease endothelin-1 and reactive oxygen species, and decrease nuclear factor-kB activation as well as proinflammatory cytokine expression[204,209]. Statins might also lessen myocardium injury by increasing nitric oxide, improving coronary perfusion, and decreasing IL-6 synthesis[210-212]. Finally, we can obtain a potential reduction of acute coronary syndromes and cerebrovascular events (both increased in COVID-19 patients)[213,214].

If statins might benefit ARDS due to their pleiotropic properties, it has been evaluated before the current global pandemic. Two RCTs with rosuvastatin and simvastatin did not improve clinical outcomes in ARDS[215,216]. Similar findings were reported in a meta-analysis where stains did not have a clear net benefit among patients with acute lung injury or ARDS[217]. However, a sub-analysis of the HARP-2 trial (HMG-CoA reductase inhibition with simvastatin in acute lung injury to reduce pulmonary dysfunction) observed in the subgroup of patients with hyperinflammatory phenotype a survival benefit of simvastatin that was not observed with rosuvastatin[218]. The presence in most cases of severe COVID-19 both, of hyperinflammation and endothelial dysfunction might theoretically justify why statin treatment showed a protective effect against the need for MV and ICU admission in COVID-19 patients[25,28,30,219]. Unfortunately, no studies seem to have explicitly focused on lipid-lowering agents in critically ill patients with COVID-19. The lack of prospective data on this subset of patients does not allow us to provide a recommendation. However, several ongoing clinical trials will give us evidence-based insights about statin efficacy in severe COVID-19 (NCT04486508; NCT04390074). Until then, the decision about continuation should be individualized.

T-lymphocyte restorative therapies: As mentioned before, the presence of hypercytokinemia with lymphopenia represents a biological signature of a pathogen uncontrolled damage in critically ill patients with COVID-19. NK cells and cytotoxic T cells can kill the virally infected cells, whereas the helper T lymphocytes adjust the total adaptive immune response. In this regard, the lymphopenic immunophenotype is considered a bad prognosis factor and targets novel therapies. Several T-lymphocyte restorative treatments as IL-7 or thymosin alpha are under evaluation. IL-7 is a pleiotropic cytokine essential for lymphocyte survival and expansion. Administration of IL-7 invariably increases circulating and tissue lymphocytes and has an excellent safety profile[220,221]. Several trials are evaluating its use among patients with severe COVID-19 (NCT04442178, NCT04379076, NCT04407689). A recent clinical series by Laterre *et al*[222] evaluated the compassionate use of IL-7 in 12 critically ill patients with COVID-19 and severe lymphopenia (defined as two consecutive absolute lymphocyte counts of less than 700/μL). An initial safety dose of 3 μg/kg was followed by a dose of 10 μg/kg by intramuscular injection twice a week for 2 wk. 13 patients with COVID-19 received standard-of-care treatment matched as a comparator control cohort. On day 30, secondary infections occurred in 7 patients (58%) in the IL-7 group compared with 11 (85%) in the control group; 30-d mortality was 42% *vs* 46%, respectively. IL-7 was associated with a restored lymphocyte count, with the IL-7 group having levels more than 2-fold higher than the control group without associated adverse effects noted in the

Table 5 Summary of randomized clinical trials and observational studies including critically ill patients addressing intravenous immunoglobulin and hyperimmune immunoglobulin on coronavirus disease 2019

Ref.	Patients	Intervention	Comparison	Outcome
Xie *et al*[193], observational	Severe/critical pneumonia and. Lymphocyte count < 0.5×10^9/L (18.9% on MV, 13.8% on NIV/HFNC)	IVIG (20 g/d)	> 48 h after admission (n = 28) *vs* < 48 h after admission (n = 30)	Reduction in 28-d mortality (23% *vs* 57%, P = 0.009), need for MV (6.67% *vs* 32.14%, P = 0.001) and LOS (11.5 ± 1.0 *vs* 16.9 ± 1.6 d, P = 0.005) in the < 48 h group
Tabarsi *et al* [194], RCT	Severe pneumonia (36.9% on MV, 78.6% ICU-admitted)	IVIG (400 mg/kg/24 h for 3 d) (n = 52)	Standard care (n = 32)	No difference in mortality (46.1% *vs* 43.7%, P = 0.83), need for MV (40.4% *vs* 31.2%, P = 0.39) or ICU admission (75% *vs* 84.4 %, P = 0.3)
Gharebaghi *et al* [195], RCT	Severe pneumonia with persisting symptoms or need for supplementary oxygen to maintain SaO_2 > 90% after 48 h of treatment	IVIG (20 g daily for three days) (n = 30)	Standard care (n = 29)	Lower in-hospital mortality (20% *vs* 48.3%, P = 0.022). Mortality. IVIG: OR = 0.003 (95%CI: 0.001-0.815, P = 0.042)
Agarwal *et al* [200], RCT	Moderate pneumonia	Convalescent plasma (200 mL, 2 doses) (n = 235)	Standard care (n = 229)	Disease progression or mortality: No difference
Li *et al*[201], RCT	Severe/critical pneumonia (NIV/HFNO: 42.7%, MV/ECMO: 24.3%)	Convalescent plasma (4-13 mL/kg) (n = 52)	Standard care (n = 51)	No improvement in time to clinical improvement within 28 d

RCT: Randomized clinical trial; MV: Mechanical ventilation; NIV: Non-invasive ventilation; LOS: Length of stay; HNFO: High nasal flow oxygen therapy; ICU: Intensive care unit; OR: Odds ratio; IVIG: Intravenous immunoglobulin; ECMO: Extracorporeal membrane oxygenation; CI: Confidence interval.

intervention arm.

In a recent Chinese study, thymosin alpha-1 (Tα1), another lymphopoiesis-stimulating drug, was employed in two cohorts of critically ill patients with COVID-19[223]. Compared with the untreated group, Tα1 treatment significantly reduced the mortality of severe COVID-19 patients (11.1% *vs* 30%, P = 0.044). Interestingly, patients with counts of CD8+ T cells or CD4+ T cells in circulation less than 400/μL or 650/μL, respectively, gained more benefits from Tα1. Other drugs targeting lymphocyte apoptosis by suppressing PD1/PD-L1, like nivolumab, are also being studied as potential candidates for treatment COVID-19. Currently, several trials are analyzing the role of these novel drugs. Unfortunately, they only focus on mild and moderate forms of COVID-19.

DISCUSSION

Few treatments proposed in COVID-19 have been evaluated in patients critically ill with COVID-19, despite a high mortality rate (20%-40%)[224,225]. This fact makes it extremely difficult to establish degrees of recommendation regarding the different therapeutic options currently available. Therefore, new studies are needed to analyse the role of these and other novel treatments in this subset of patients. In this sense, future trials must employ a better design and careful selection criteria. It is critical not to consider all patients with severe forms of COVID-19 the same. Some of these patients (but not all) show specific hallmarks characterized by profound immunity alterations, hyperinflammatory states, and even severe endothelial dysfunction that favors progression to different degrees of organ failure. This triad (hyperinflammation, immune dysregulation, and endothelial dysfunction) in presence of organ failure is not restricted to COVID-19, and we can find it in sepsis, which would support the theory that severe COVID-19 is a form of viral sepsis. These alterations allow the classification of critically ill COVID-19 patients into different phenotypes[226-228]. Recently Chen *et al*[229], in a single-center study of critically ill patients with COVID-19, identified by a machine learning approach two phenotypes: One hyperinflammatory, characterized by elevated pro-inflammatory cytokines, higher SOFA score, and higher rates of complications and another hypo-inflammatory. Interestingly, corticosteroid therapy was associated with reduced 28-d mortality (HR = 0.45; 95%CI: 0.25-0.80; P = 0.0062) only in patients with the hyperinflammatory phenotype. These endotypes include clinical and biological characteristics and can constitute specific targets for better select specific therapies based on an individualized approach to treatment.

CONCLUSION

Likely many of the treatments above reviewed in this work might be helpful in specific subgroups of patients with certain clinical, analytical and biological characteristics, as occurs in other pathologies such as cancer, certain autoimmune diseases, or even sepsis. This approach, based on a personalized and precision medicine model, could help to better randomization of new clinical trials targeting the specific treatment of severe and critical forms of COVID-19.

ARTICLE HIGHLIGHTS

Research background

Although most people with coronavirus disease 2019 (COVID-19) have only mild or uncomplicated symptoms, 10%-15% requires hospitalization and oxygen therapy and, from the beginning, a large number of patients presented severe respiratory failure, needing mechanical ventilation (MV) and intensive care unit (ICU) admission. The lack of an available, effective treatment in this setting has led to a spate of treatment recommendations, which are not always backed by sufficient scientific evidence. Particular attention were paid to a presumed specific cytokine storm secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with a special effort to modulate the inflammatory response of these patients.

Research motivation

Two years after the onset of the pandemic, many questions remain unanswered, and we continue to search for the most appropriate treatment. This review aims to summarize the current evidence regarding the different immunomodulatory strategies tested in critically ill patients with COVID-19. Most of the main trials that have shown benefit of any immunomodulatory therapeutic agent against COVID-19 focus on hospitalized patients but not on critically ill patients. Furthermore, many of these studies consider ICU admission as a primary negative endpoint. Very few studies consider treatment in this setting (ICU) as a starting point, sometimes unavoidable, given that many patients with COVID-19 required admission to the ICU already in the first hours of their hospital admission. Therefore, there is a lack of information on the therapeutic approach in these patients.

Research objectives

To summarize the pathophysiology of SARS-CoV-2, including the normal and pathological inflammatory and immune responses that would justify the use of different immunomodulatory therapies in critically ill patients. To analyze the mechanism of action of the different immunomodulatory agents used against COVID-19. Review the scientific evidence collected so far and issue a recommendation for or against the use of each specific agent in this scenario.

Research methods

A comprehensive literature search was developed by using the keywords: "immunotherapy", "immunosuppressives", "haemophagocytic syndrome", "inflammation", "antimalarials", "hydroxychloroquine", "chloroquine", "anakinra", "canakinumab", "tocilizumab", "sarilumab", "corticosteroids", "dexamethasone", "methylprednisolone", "immunoglobulins or convalescent" "JAK inhibitors", "cyclosporine", "colchicine", "statins", "interleukin 7", "tymosin", "PD1 and PD-L1 blockers". We restricted the search to: "SARS-CoV-2", "COVID-19", "severe COVID-19" and "treatment" to identify articles published in English from MEDLINE, PubMed, and The Cochrane Library (until January 2021). The authors reviewed the selected manuscripts and selected the most appropriate. Finally, we established a recommendation of the use of each treatment based on the level of evidence of the articles and documents reviewed. This recommendation was made based on the consensus of all the authors. We carried out the rest of the work methodology following the PRISMA recommendations.

Research results

Different recommendations regarding the use of these immunomodulatory agents ("antimalarials", "hydroxychloroquine" "chloroquine", "anakinra", "canakinumab", "tocilizumab", "sarilumab", "corticosteroids", "dexamethasone", "methylprednisolone", "immunoglobulins or convalescent", "JAK inhibitors", "cyclosporine", "colchicine", "statins", "interleukin 7", "tymosin", "PD1 and PD-L1 blockers") were performed.

Research conclusions

Until then, although several promising therapies exist, only the use of corticosteroids and tocilizumab (or sarilumab in absence of this) has demonstrated evidence enough to recommend its use in critically ill patients with COVID-19. Probably other treatments of those analyzed could be beneficial in certain

critical patients with COVID-19 if they were administered in a selective and personalized way.

Research perspectives

From this work, two simple and clear messages can be extracted that could guide the future therapeutic approach of severe forms of COVID-19: (1) The critically ill patient constitutes a special subgroup of patients that should be studied differently from other patients, considering the ICU as an initial and not a final stage in the course of the disease; and (2) It is a mistake to administer the same treatments to all patients. It is key to individualize these treatments based on the immunological and clinical phenotypes of each patient.

FOOTNOTES

Author contributions: Andaluz-Ojeda D, Vidal-Cortes P, and Cusacovich I designed the study, developed the material and methods section, the introduction and a global discussion; Aparisi Sanz Á, Suberviola B, Del Río Carbajo L, Nogales Martín L, Prol Silva E, Nieto del Olmo J, and Barberán J carried out a selective bibliographic search in relation to each of the study points and developed a partial discussion; and all authors participated in the final recommendations for each class.

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Country/Territory of origin: Spain

ORCID number: David Andaluz-Ojeda 0000-0001-8167-0871; Pablo Vidal-Cortes 0000-0003-0225-9975; Álvaro Aparisi Sanz 0000-0002-3230-6368; Borja Suberviola 0000-0001-7681-3890; Lorena Del Río Carbajo 0000-0002-1606-8785; Leonor Nogales Martín 0000-0003-2736-3760; Estefanía Prol Silva 0000-0002-4893-3075; Jorge Nieto del Olmo 0000-0002-4304-7795; José Barberán 0000-0002-8364-5765; Ivan Cusacovich 0000-0002-4984-0639.

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REFERENCES

1 **World Health Organization**. WHO Director-General's opening remarks at the media briefing on COVID-19 - 18 March 2020. [cited 13 April 2020]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---18-march-2020
2 **World Health Organization**. WHO Coronavirus (COVID-19) Dashboard. [cited 28 January 2021]. Available from: https://covid19.who.int/
3 **Rodríguez A**, Moreno G, Gómez J, Carbonell R, Picó-Plana E, Benavent Bofill C, Sánchez Parrilla R, Trefler S, Esteve Pitarch E, Canadell L, Teixido X, Claverias L, Bodí M; por el HJ23-COVID-19 working group; Listado de Investigadores del HJ23-COVID-19 Working Group. Laboratorio clínico; Epidemiología y prevención de la infección nosocomial; Departamento de enfermería UCI; Farmacia clínica; Médicos UCI; UCI Data-Analitics. Severe infection due to the SARS-CoV-2 coronavirus: Experience of a tertiary hospital with COVID-19 patients during the 2020 pandemic. *Med Intensiva (Engl Ed)* 2020; **44**: 525-533 [PMID: 32654921 DOI: 10.1016/j.medin.2020.05.018]
4 **Vidal-Cortés P**, Del Río-Carbajo L, Nieto-Del Olmo J, Prol-Silva E, Tizón-Varela AI, Rodríguez-Vázquez A, Rodríguez-Rodríguez P, Díaz-López MD, Fernández-Ugidos P, Pérez-Veloso MA. COVID-19 and Acute Respiratory Distress Syndrome. Impact of corticosteroid treatment and predictors of poor outcome. *Rev Esp Quimioter* 2021; **34**: 33-43 [PMID: 33317261 DOI: 10.37201/req/091.2020]
5 **Grasselli G**, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A; COVID-19 Lombardy ICU Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020; **323**: 1574-1581 [PMID: 32250385 DOI: 10.1001/jama.2020.5394]
6 **Bhatraju PK**, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, Greninger AL, Pipavath S, Wurfel MM, Evans L, Kritek PA, West TE, Luks A, Gerbino A, Dale CR, Goldman JD, O'Mahony S, Mikacenic C. Covid-19 in Critically Ill

Patients in the Seattle Region - Case Series. *N Engl J Med* 2020; **382**: 2012-2022 [PMID: 32227758 DOI: 10.1056/NEJMoa2004500]

7 **Arentz M**, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, Lee M. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA* 2020; **323**: 1612-1614 [PMID: 32191259 DOI: 10.1001/jama.2020.4326]

8 **Xie J**, Wu W, Li S, Hu Y, Hu M, Li J, Yang Y, Huang T, Zheng K, Wang Y, Kang H, Huang Y, Jiang L, Zhang W, Zhong M, Sang L, Zheng X, Pan C, Zheng R, Li X, Tong Z, Qiu H, Du B. Clinical characteristics and outcomes of critically ill patients with novel coronavirus infectious disease (COVID-19) in China: a retrospective multicenter study. *Intensive Care Med* 2020; **46**: 1863-1872 [PMID: 32816098 DOI: 10.1007/s00134-020-06211-2]

9 **Barrasa H**, Rello J, Tejada S, Martín A, Balziskueta G, Vinuesa C, Fernández-Miret B, Villagra A, Vallejo A, San Sebastián A, Cabañes S, Iribarren S, Fonseca F, Maynar J; Alava COVID-19 Study Investigators. SARS-CoV-2 in Spanish Intensive Care Units: Early experience with 15-day survival in Vitoria. *Anaesth Crit Care Pain Med* 2020; **39**: 553-561 [PMID: 32278670 DOI: 10.1016/j.accpm.2020.04.001]

10 **Ramírez P**, Gordón M, Martín-Cerezuela M, Villarreal E, Sancho E, Padrós M, Frasquet J, Leyva G, Molina I, Barrios M, Gimeno S, Castellanos Á. Acute respiratory distress syndrome due to COVID-19. Clinical and prognostic features from a medical Critical Care Unit in Valencia, Spain. *Med Intensiva (Engl Ed)* 2021; **45**: 27-34 [PMID: 32919796 DOI: 10.1016/j.medin.2020.06.015]

11 **Bravata DM**, Perkins AJ, Myers LJ, Arling G, Zhang Y, Zillich AJ, Reese L, Dysangco A, Agarwal R, Myers J, Austin C, Sexson A, Leonard SJ, Dev S, Keyhani S. Association of Intensive Care Unit Patient Load and Demand With Mortality Rates in US Department of Veterans Affairs Hospitals During the COVID-19 Pandemic. *JAMA Netw Open* 2021; **4**: e2034266 [PMID: 33464319 DOI: 10.1001/jamanetworkopen.2020.34266]

12 **Bhimraj A**, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, Edwards KM, Gandhi R, Muller WJ, O'Horo JC, Shoham S, Murad MH, Mustafa RA, Sultan S, Falck-Ytter Y. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin Infect Dis* 2020 [PMID: 32338708 DOI: 10.1093/cid/ciaa478]

13 **Alhazzani W**, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, Oczkowski S, Levy MM, Derde L, Dzierba A, Du B, Aboodi M, Wunsch H, Cecconi M, Koh Y, Chertow DS, Maitland K, Alshamsi F, Belley-Cote E, Greco M, Laundy M, Morgan JS, Kesecioglu J, McGeer A, Mermel L, Mammen MJ, Alexander PE, Arrington A, Centofanti JE, Citerio G, Baw B, Memish ZA, Hammond N, Hayden FG, Evans L, Rhodes A. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med* 2020; **46**: 854-887 [PMID: 32222812 DOI: 10.1007/s00134-020-06022-5]

14 **Bai C**, Chotirmall SH, Rello J, Alba GA, Ginns LC, Krishnan JA, Rogers R, Bendstrup E, Burgel PR, Chalmers JD, Chua A, Crothers KA, Duggal A, Kim YW, Laffey JG, Luna CM, Niederman MS, Raghu G, Ramirez JA, Riera J, Roca O, Tamae-Kakazu M, Torres A, Watkins RR, Barrecheguren M, Belliato M, Chami HA, Chen R, Cortes-Puentes GA, Delacruz C, Hayes MM, Heunks LMA, Holets SR, Hough CL, Jagpal S, Jeon K, Johkoh T, Lee MM, Liebler J, McElvaney GN, Moskowitz A, Oeckler RA, Ojanguren I, O'Regan A, Pletz MW, Rhee CK, Schultz MJ, Storti E, Strange C, Thomson CC, Torriani FJ, Wang X, Wuyts W, Xu T, Yang D, Zhang Z, Wilson KC. Updated guidance on the management of COVID-19: from an American Thoracic Society/European Respiratory Society coordinated International Task Force (29 July 2020). *Eur Respir Rev* 2020; **29** [PMID: 33020069 DOI: 10.1183/16000617.0287-2020]

15 **Díaz E**, Amézaga Menéndez R, Vidal Cortés P, Escapa MG, Suberviola B, Serrano Lázaro A, Marcos Neira P, Quintana Díaz M, Catalán González M. [Pharmacological treatment of COVID-19: Narrative review of the Working Group in Infectious Diseases and Sepsis (GTEIS) and the Working Groups in Transfusions and Blood Products (GTTH)]. *Med Intensiva (Engl Ed)* 2021; **45**: 104-121 [PMID: 32854988 DOI: 10.1016/j.medin.2020.06.017]

16 **Kalil AC**. Treating COVID-19-Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics. *JAMA* 2020; **323**: 1897-1898 [PMID: 32208486 DOI: 10.1001/jama.2020.4742]

17 **Estella Á**, Garnacho-Montero J. [From empiricism to scientific evidence in antiviral treatment in severe cases of coronavirus infection in times of epidemic]. *Med Intensiva (Engl Ed)* 2020; **44**: 509-512 [PMID: 32423569 DOI: 10.1016/j.medin.2020.04.009]

18 **Siddiqi HK**, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. *J Heart Lung Transplant* 2020; **39**: 405-407 [PMID: 32362390 DOI: 10.1016/j.healun.2020.03.012]

19 **Sinha P**, Matthay MA, Calfee CS. Is a "Cytokine Storm" Relevant to COVID-19? *JAMA Intern Med* 2020; **180**: 1152-1154 [PMID: 32602883 DOI: 10.1001/jamainternmed.2020.3313]

20 **de la Rica R**, Borges M, Gonzalez-Freire M. COVID-19: In the Eye of the Cytokine Storm. *Front Immunol* 2020; **11**: 558898 [PMID: 33072097 DOI: 10.3389/fimmu.2020.558898]

21 **Zou X**, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front Med* 2020; **14**: 185-192 [PMID: 32170560 DOI: 10.1007/s11684-020-0754-0]

22 **Letko M**, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol* 2020; **5**: 562-569 [PMID: 32094589 DOI: 10.1038/s41564-020-0688-y]

23 **Walls AC**, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell* 2020; **181**: 281-292.e6 [PMID: 32155444 DOI: 10.1016/j.cell.2020.02.058]

24 **Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X]

25 **Zeng Z**, Yu H, Chen H, Qi W, Chen L, Chen G, Yan W, Chen T, Ning Q, Han M, Wu D. Longitudinal changes of inflammatory parameters and their correlation with disease severity and outcomes in patients with COVID-19 from Wuhan, China. *Crit Care* 2020; **24**: 525 [PMID: 32854750 DOI: 10.1186/s13054-020-03255-0]

26 **Qin C**, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W, Tian DS. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis* 2020; **71**: 762-768 [PMID:

32161940 DOI: 10.1093/cid/ciaa248]

27 **Janssen NAF**, Grondman I, de Nooijer AH, Boahen CK, Koeken VACM, Matzaraki V, Kumar V, He X, Kox M, Koenen HJPM, Smeets RL, Joosten I, Brüggemann RJM, Kouijzer IJE, van der Hoeven HG, Schouten JA, Frenzel T, Reijers MHE, Hoefsloot W, Dofferhoff ASM, van Apeldoorn MJ, Blaauw MJT, Veerman K, Maas C, Schoneveld AH, Hoefer IE, Derde LPG, van Deuren M, van der Meer JWM, van Crevel R, Giamarellos-Bourboulis EJ, Joosten LAB, van den Heuvel MM, Hoogerwerf J, de Mast Q, Pickkers P, Netea MG, van de Veerdonk FL. Dysregulated Innate and Adaptive Immune Responses Discriminate Disease Severity in COVID-19. *J Infect Dis* 2021; **223**: 1322-1333 [PMID: 33524124 DOI: 10.1093/infdis/jiab065]

28 **García de Guadiana-Romualdo L**, Calvo Nieves MD, Rodríguez Mulero MD, Calcerrada Alises I, Hernández Olivo M, Trapiello Fernández W, González Morales M, Bolado Jiménez C, Albaladejo-Otón MD, Fernández Ovalle H, Conesa Hernández A, Azpeleta Manrique E, Consuegra-Sánchez L, Nogales Martín L, Conesa Zamora P, Andaluz-Ojeda D. MR-proADM as marker of endotheliitis predicts COVID-19 severity. *Eur J Clin Invest* 2021; **51**: e13511 [PMID: 33569769 DOI: 10.1111/eci.13511]

29 **Tay MZ**, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020; **20**: 363-374 [PMID: 32346093 DOI: 10.1038/s41577-020-0311-8]

30 **García LF**. Immune Response, Inflammation, and the Clinical Spectrum of COVID-19. *Front Immunol* 2020; **11**: 1441 [PMID: 32612615 DOI: 10.3389/fimmu.2020.01441]

31 **Boechat JL**, Chora I, Morais A, Delgado L. The immune response to SARS-CoV-2 and COVID-19 immunopathology - Current perspectives. *Pulmonology* 2021; **27**: 423-437 [PMID: 33867315 DOI: 10.1016/j.pulmoe.2021.03.008]

32 **Mehta P**, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033-1034 [PMID: 32192578 DOI: 10.1016/S0140-6736(20)30628-0]

33 **Remy KE**, Mazer M, Striker DA, Ellebedy AH, Walton AH, Unsinger J, Blood TM, Mudd PA, Yi DJ, Mannion DA, Osborne DF, Martin RS, Anand NJ, Bosanquet JP, Blood J, Drewry AM, Caldwell CC, Turnbull IR, Brakenridge SC, Moldwawer LL, Hotchkiss RS. Severe immunosuppression and not a cytokine storm characterizes COVID-19 infections. *JCI Insight* 2020; **5** [PMID: 32687484 DOI: 10.1172/jci.insight.140329]

34 **Henry BM**, Benoit SW, Vikse J, Berger BA, Pulvino C, Hoehn J, Rose J, Santos de Oliveira MH, Lippi G, Benoit JL. The anti-inflammatory cytokine response characterized by elevated interleukin-10 is a stronger predictor of severe disease and poor outcomes than the pro-inflammatory cytokine response in coronavirus disease 2019 (COVID-19). *Clin Chem Lab Med* 2021; **59**: 599-607 [PMID: 33554561 DOI: 10.1515/cclm-2020-1284]

35 **Monneret G**, Benlyamani I, Gossez M, Bermejo-Martin JF, Martín-Fernandez M, Sesques P, Wallet F, Venet F. COVID-19: What type of cytokine storm are we dealing with? *J Med Virol* 2021; **93**: 197-198 [PMID: 32681651 DOI: 10.1002/jmv.26317]

36 **Laing AG**, Lorenc A, Del Molino Del Barrio I, Das A, Fish M, Monin L, Muñoz-Ruiz M, McKenzie DR, Hayday TS, Francos-Quijorna I, Kamdar S, Joseph M, Davies D, Davis R, Jennings A, Zlatareva I, Vantourout P, Wu Y, Sofra V, Cano F, Greco M, Theodoridis E, Freedman JD, Gee S, Chan JNE, Ryan S, Bugallo-Blanco E, Peterson P, Kisand K, Haljasmägi L, Chadli L, Moingeon P, Martinez L, Merrick B, Bisnauthsing K, Brooks K, Ibrahim MAA, Mason J, Lopez Gomez F, Babalola K, Abdul-Jawad S, Cason J, Mant C, Seow J, Graham C, Doores KJ, Di Rosa F, Edgeworth J, Shankar-Hari M, Hayday AC. A dynamic COVID-19 immune signature includes associations with poor prognosis. *Nat Med* 2020; **26**: 1623-1635 [PMID: 32807934 DOI: 10.1038/s41591-020-1038-6]

37 **Giamarellos-Bourboulis EJ**, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, Damoraki G, Gkavogianni T, Adami ME, Katsaounou P, Ntaganou M, Kyriakopoulou M, Dimopoulos G, Koutsodimitropoulos I, Velissaris D, Koufargyris P, Karageorgos A, Katrini K, Lekakis V, Lupse M, Kotsaki A, Renieris G, Theodoulou D, Panou V, Koukaki E, Koulouris N, Gogos C, Koutsoukou A. Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure. *Cell Host Microbe* 2020; **27**: 992-1000.e3 [PMID: 32320677 DOI: 10.1016/j.chom.2020.04.009]

38 **Huang I**, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. *J Intensive Care* 2020; **8**: 36 [PMID: 32483488 DOI: 10.1186/s40560-020-00453-4]

39 **Wagner J**, DuPont A, Larson S, Cash B, Farooq A. Absolute lymphocyte count is a prognostic marker in Covid-19: A retrospective cohort review. *Int J Lab Hematol* 2020; **42**: 761-765 [PMID: 32779838 DOI: 10.1111/ijlh.13288]

40 **Fathi N**, Rezaei N. Lymphopenia in COVID-19: Therapeutic opportunities. *Cell Biol Int* 2020; **44**: 1792-1797 [PMID: 32458561 DOI: 10.1002/cbin.11403]

41 **Qin S**, Jiang Y, Wei X, Liu X, Guan J, Chen Y, Lu H, Qian J, Wang Z, Lin X. Dynamic changes in monocytes subsets in COVID-19 patients. *Hum Immunol* 2021; **82**: 170-176 [PMID: 33531264 DOI: 10.1016/j.humimm.2020.12.010]

42 **Bermejo-Martin JF**, González-Rivera M, Almansa R, Micheloud D, Tedim AP, Domínguez-Gil M, Resino S, Martín-Fernández M, Ryan Murua P, Pérez-García F, Tamayo L, Lopez-Izquierdo R, Bustamante E, Aldecoa C, Gómez JM, Rico-Feijoo J, Orduña A, Méndez R, Fernández Natal I, Megías G, González-Estecha M, Carriedo D, Doncel C, Jorge N, Ortega A, de la Fuente A, Del Campo F, Fernández-Ratero JA, Trapiello W, González-Jiménez P, Ruiz G, Kelvin AA, Ostadgavahi AT, Oneizat R, Ruiz LM, Miguéns I, Gargallo E, Muñoz I, Pelegrin S, Martín S, García Olivares P, Cedeño JA, Ruiz Albi T, Puertas C, Berezo JÁ, Renedo G, Herrán R, Bustamante-Munguira J, Enríquez P, Cicuendez R, Blanco J, Abadia J, Gómez Barquero J, Mamolar N, Blanca-López N, Valdivia LJ, Fernández Caso B, Mantecón MÁ, Motos A, Fernandez-Barat L, Ferrer R, Barbé F, Torres A, Menéndez R, Eiros JM, Kelvin DJ. Viral RNA load in plasma is associated with critical illness and a dysregulated host response in COVID-19. *Crit Care* 2020; **24**: 691 [PMID: 33317616 DOI: 10.1186/s13054-020-03398-0]

43 **Skendros P**, Mitsios A, Chrysanthopoulou A, Mastellos DC, Metallidis S, Rafailidis P, Ntinopoulou M, Sertaridou E, Tsironidou V, Tsigalou C, Tektonidou M, Konstantinidis T, Papagoras C, Mitroulis I, Germanidis G, Lambris JD, Ritis K. Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis. *J Clin Invest* 2020; **130**: 6151-6157 [PMID: 32759504 DOI: 10.1172/JCI141374]

44 **Java A**, Apicelli AJ, Liszewski MK, Coler-Reilly A, Atkinson JP, Kim AH, Kulkarni HS. The complement system in

COVID-19: friend and foe? *JCI Insight* 2020; **5** [PMID: 32554923 DOI: 10.1172/jci.insight.140711]

45 **Touret F**, de Lamballerie X. Of chloroquine and COVID-19. *Antiviral Res* 2020; **177**: 104762 [PMID: 32147496 DOI: 10.1016/j.antiviral.2020.104762]

46 **Devaux CA**, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents* 2020; **55**: 105938 [PMID: 32171740 DOI: 10.1016/j.ijantimicag.2020.105938]

47 **Gao J**, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020; **14**: 72-73 [PMID: 32074550 DOI: 10.5582/bst.2020.01047]

48 **Chen J**, Liu D, Liu L, Liu P, Xu Q, Xia L, Ling Y, Huang D, Song S, Zhang D, Qian Z, Li T, Shen Y, Lu H. A pilot study of hydroxychloroquine in the treatment of patients with common coronavirus disease-19 (COVID-19). *J Zhejiang Univ (Med Sci)* 2020

49 **Chen Z**, Hu J, Zhang Z, Jiang S, Han S, Yan D, Zhuang R, Hu B. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized trial. 2020 Preprint. Available from: MedRxiv:2020.03.22.20040758 [DOI: 10.1101/2020.03.22.20040758]

50 **Gautret P**, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Tissot Dupont H, Honoré S, Colson P, Chabrière E, La Scola B, Rolain JM, Brouqui P, Raoult D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020; **56**: 105949 [PMID: 32205204 DOI: 10.1016/j.ijantimicag.2020.105949]

51 **RECOVERY Collaborative Group**, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, Wiselka M, Ustianowski A, Elmahi E, Prudon B, Whitehouse T, Felton T, Williams J, Faccenda J, Underwood J, Baillie JK, Chappell LC, Faust SN, Jaki T, Jeffery K, Lim WS, Montgomery A, Rowan K, Tarning J, Watson JA, White NJ, Juszczak E, Haynes R, Landray MJ. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med* 2020; **383**: 2030-2040 [PMID: 33031652 DOI: 10.1056/NEJMoa2022926]

52 **WHO Solidarity Trial Consortium**, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, Alejandria MM, Hernández García C, Kieny MP, Malekzadeh R, Murthy S, Reddy KS, Roses Periago M, Abi Hanna P, Ader F, Al-Bader AM, Alhasawi A, Allum E, Alotaibi A, Alvarez-Moreno CA, Appadoo S, Asiri A, Aukrust P, Barratt-Due A, Bellani S, Branca M, Cappel-Porter HBC, Cerrato N, Chow TS, Como N, Eustace J, García PJ, Godbole S, Gotuzzo E, Griskevicius L, Hamra R, Hassan M, Hassany M, Hutton D, Irmansyah I, Jancoriene L, Kirwan J, Kumar S, Lennon P, Lopardo G, Lydon P, Magrini N, Maguire T, Manevska S, Manuel O, McGinty S, Medina MT, Mesa Rubio ML, Miranda-Montoya MC, Nel J, Nunes EP, Perola M, Portolés A, Rasmin MR, Raza A, Rees H, Reges PPS, Rogers CA, Salami K, Salvadori MI, Sinani N, Sterne JAC, Stevanovikj M, Tacconelli E, Tikkinen KAO, Trelle S, Zaid H, Røttingen JA, Swaminathan S. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med* 2021; **384**: 497-511 [PMID: 33264556 DOI: 10.1056/NEJMoa2023184]

53 **World Health Organization**. Ongoing Living Update of COVID-19 Therapeutic Options: Summary of Evidence. [cited 30 March 2021]. Available from: https://iris.paho.org/bitstream/handle/10665.2/52719/PAHOIMSEIHCOVID-19210002_eng.pdf?sequence=23&msclkid=7d6c3734bc6911ec8d71f4fe20799b01

54 **Axfors C**, Schmitt AM, Janiaud P, Van't Hooft J, Abd-Elsalam S, Abdo EF, Abella BS, Akram J, Amaravadi RK, Angus DC, Arabi YM, Azhar S, Baden LR, Baker AW, Belkhir L, Benfield T, Berrevoets MAH, Chen CP, Chen TC, Cheng SH, Cheng CY, Chung WS, Cohen YZ, Cowan LN, Dalgard O, de Almeida E Val FF, de Lacerda MVG, de Melo GC, Derde L, Dubee V, Elfakir A, Gordon AC, Hernandez-Cardenas CM, Hills T, Hoepelman AIM, Huang YW, Igau B, Jin R, Jurado-Camacho F, Khan KS, Kremsner PG, Kreuels B, Kuo CY, Le T, Lin YC, Lin WP, Lin TH, Lyngbakken MN, McArthur C, McVerry BJ, Meza-Meneses P, Monteiro WM, Morpeth SC, Mourad A, Mulligan MJ, Murthy S, Naggie S, Narayanasamy S, Nichol A, Novack LA, O'Brien SM, Okeke NL, Perez L, Perez-Padilla R, Perrin L, Remigio-Luna A, Rivera-Martinez NE, Rockhold FW, Rodriguez-Llamazares S, Rolfe R, Rosa R, Røsjø H, Sampaio VS, Seto TB, Shahzad M, Soliman S, Stout JE, Thirion-Romero I, Troxel AB, Tseng TY, Turner NA, Ulrich RJ, Walsh SR, Webb SA, Weehuizen JM, Velinova M, Wong HL, Wrenn R, Zampieri FG, Zhong W, Moher D, Goodman SN, Ioannidis JPA, Hemkens LG. Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials. *Nat Commun* 2021; **12**: 2349 [PMID: 33859192 DOI: 10.1038/s41467-021-22446-z]

55 **COVID-19 RISK and Treatments (CORIST) Collaboration**. Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: Findings from the observational multicentre Italian CORIST study. *Eur J Intern Med* 2020; **82**: 38-47 [PMID: 32859477 DOI: 10.1016/j.ejim.2020.08.019]

56 **Schlesinger N**, Firestein BL, Brunetti L. Colchicine in COVID-19: an Old Drug, New Use. *Curr Pharmacol Rep* 2020; 1-9 [PMID: 32837853 DOI: 10.1007/s40495-020-00225-6]

57 **Salah HM**, Mehta JL. Meta-analysis of the Effect of Colchicine on Mortality and Mechanical Ventilation in COVID-19. *Am J Cardiol* 2021; **145**: 170-172 [PMID: 33617817 DOI: 10.1016/j.amjcard.2021.02.005]

58 **Scarsi M**, Piantoni S, Colombo E, Airó P, Richini D, Miclini M, Bertasi V, Bianchi M, Bottone D, Civelli P, Cotelli MS, Damiolini E, Galbassini G, Gatta D, Ghirardelli ML, Magri R, Malamani P, Mendeni M, Molinari S, Morotti A, Salada L, Turla M, Vender A, Tincani A, Brucato A, Franceschini F, Furloni R, Andreoli L. Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome. *Ann Rheum Dis* 2020; **79**: 1286-1289 [PMID: 32732245 DOI: 10.1136/annrheumdis-2020-217712]

59 **Brunetti L**, Diawara O, Tsai A, Firestein BL, Nahass RG, Poiani G, Schlesinger N. Colchicine to Weather the Cytokine Storm in Hospitalized Patients with COVID-19. *J Clin Med* 2020; **9** [PMID: 32937800 DOI: 10.3390/jcm9092961]

60 **Deftereos SG**, Giannopoulos G, Vrachatis DA, Siasos GD, Giotaki SG, Gargalianos P, Metallidis S, Sianos G, Baltagiannis S, Panagopoulos P, Dolianitis K, Randou E, Syrigos K, Kotanidou A, Koulouris NG, Milionis H, Sipsas N, Gogos C, Tsoukalas G, Olympios CD, Tsagalou E, Migdalis I, Gerakari S, Angelidis C, Alexopoulos D, Davlouros P, Hahalis G, Kanonidis I, Katritsis D, Kolettis T, Manolis AS, Michalis L, Naka KK, Pyrgakis VN, Toutouzas KP, Triposkiadis F, Tsioufis K, Vavouranakis E, Martinèz-Dolz L, Reimers B, Stefanini GG, Cleman M, Goudevenos J,

Tsiodras S, Tousoulis D, Iliodromitis E, Mehran R, Dangas G, Stefanadis C; GRECCO-19 investigators. Effect of Colchicine *vs* Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial. *JAMA Netw Open* 2020; **3**: e2013136 [PMID: 32579195 DOI: 10.1001/jamanetworkopen.2020.13136]

61 **Randomised Evaluation of COVID-19 Therapy**. RECOVERY trial closes recruitment to colchicine treatment for patients hospitalised with COVID-19. [cited 14 March 2021]. Available from: https://www.recoverytrial.net/news/recovery-trial-closes-recruitment-to-colchicine-treatment-for-patients-hospitalised-with-covid-19?msclkid=0a598f21bc6211ec8cc61eebaf60e78e

62 **Schoot TS**, Kerckhoffs APM, Hilbrands LB, van Marum RJ. Immunosuppressive Drugs and COVID-19: A Review. *Front Pharmacol* 2020; **11**: 1333 [PMID: 32982743 DOI: 10.3389/fphar.2020.01333]

63 **Lai Q**, Spoletini G, Bianco G, Graceffa D, Agnes S, Rossi M, Lerut J. SARS-CoV2 and immunosuppression: A double-edged sword. *Transpl Infect Dis* 2020; **22**: e13404 [PMID: 32639598 DOI: 10.1111/tid.13404]

64 **Tanaka Y**, Sato Y, Sasaki T. Suppression of coronavirus replication by cyclophilin inhibitors. *Viruses* 2013; **5**: 1250-1260 [PMID: 23698397 DOI: 10.3390/v5051250]

65 **Alijotas-Reig J**, Esteve-Valverde E, Belizna C, Selva-O'Callaghan A, Pardos-Gea J, Quintana A, Mekinian A, Anunciacion-Llunell A, Miró-Mur F. Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: A comprehensive review. *Autoimmun Rev* 2020; **19**: 102569 [PMID: 32376394 DOI: 10.1016/j.autrev.2020.102569]

66 **Hage R**, Steinack C, Schuurmans MM. Calcineurin inhibitors revisited: A new paradigm for COVID-19? *Braz J Infect Dis* 2020; **24**: 365-367 [PMID: 32603679 DOI: 10.1016/j.bjid.2020.06.005]

67 **Poulsen NN**, von Brunn A, Hornum M, Blomberg Jensen M. Cyclosporine and COVID-19: Risk or favorable? *Am J Transplant* 2020; **20**: 2975-2982 [PMID: 32777170 DOI: 10.1111/ajt.16250]

68 **Cour M**, Ovize M, Argaud L. Cyclosporine A: a valid candidate to treat COVID-19 patients with acute respiratory failure? *Crit Care* 2020; **24**: 276 [PMID: 32487139 DOI: 10.1186/s13054-020-03014-1]

69 **Shakoory B**, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, Cron RQ, Opal SM. Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. *Crit Care Med* 2016; **44**: 275-281 [PMID: 26584195 DOI: 10.1097/CCM.0000000000001402]

70 **Schulert GS**, Grom AA. Pathogenesis of macrophage activation syndrome and potential for cytokine- directed therapies. *Annu Rev Med* 2015; **66**: 145-159 [PMID: 25386930 DOI: 10.1146/annurev-med-061813-012806]

71 **Carter SJ**, Tattersall RS, Ramanan AV. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. *Rheumatology (Oxford)* 2019; **58**: 5-17 [PMID: 29481673 DOI: 10.1093/rheumatology/key006]

72 **Ruan Q**, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020; **46**: 846-848 [PMID: 32125452 DOI: 10.1007/s00134-020-05991-x]

73 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]

74 **CORIMUNO-19 Collaborative group**. Effect of anakinra *vs* usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. *Lancet Respir Med* 2021; **9**: 295-304 [PMID: 33493450 DOI: 10.1016/S2213-2600(20)30556-7]

75 **Cavalli G**, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, Oltolini C, Castiglioni B, Tassan Din C, Boffini N, Tomelleri A, Farina N, Ruggeri A, Rovere-Querini P, Di Lucca G, Martinenghi S, Scotti R, Tresoldi M, Ciceri F, Landoni G, Zangrillo A, Scarpellini P, Dagna L. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020; **2**: e325-e331 [PMID: 32501454 DOI: 10.1016/S2665-9913(20)30127-2]

76 **Huet T**, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I, Sacco E, Naccache JM, Bézie Y, Laplanche S, Le Berre A, Le Pavec J, Salmeron S, Emmerich J, Mourad JJ, Chatellier G, Hayem G. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* 2020; **2**: e393-e400 [PMID: 32835245 DOI: 10.1016/S2665-9913(20)30164-8]

77 **Kooistra EJ**, Waalders NJB, Grondman I, Janssen NAF, de Nooijer AH, Netea MG, van de Veerdonk FL, Ewalds E, van der Hoeven JG, Kox M, Pickkers P; RCI-COVID-19 Study Group. Anakinra treatment in critically ill COVID-19 patients: a prospective cohort study. *Crit Care* 2020; **24**: 688 [PMID: 33302991 DOI: 10.1186/s13054-020-03364-w]

78 **Dimopoulos G**, de Mast Q, Markou N, Theodorakopoulou M, Komnos A, Mouktaroudi M, Netea MG, Spyridopoulos T, Verheggen RJ, Hoogerwerf J, Lachana A, van de Veerdonk FL, Giamarellos-Bourboulis EJ. Favorable Anakinra Responses in Severe Covid-19 Patients with Secondary Hemophagocytic Lymphohistiocytosis. *Cell Host Microbe* 2020; **28**: 117-123.e1 [PMID: 32411313 DOI: 10.1016/j.chom.2020.05.007]

79 **Rothman AM**, Morton AC, Crossman DC; MRC-ILA Heart investigators. Canakinumab for Atherosclerotic Disease. *N Engl J Med* 2018; **378**: 197-198 [PMID: 29322756 DOI: 10.1056/NEJMc1714635]

80 **Ucciferri C**, Auricchio A, Di Nicola M, Potere N, Abbate A, Cipollone F, Vecchiet J, Falasca K. Canakinumab in a subgroup of patients with COVID-19. *Lancet Rheumatol* 2020; **2**: e457-ee458 [PMID: 32835251 DOI: 10.1016/S2665-9913(20)30167-3]

81 **Tanaka T**, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol* 2014; **6**: a016295 [PMID: 25190079 DOI: 10.1101/cshperspect.a016295]

82 **Del Valle DM**, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, Lavin Y, Swartz TH, Madduri D, Stock A, Marron TU, Xie H, Patel M, Tuballes K, Van Oekelen O, Rahman A, Kovatch P, Aberg JA, Schadt E, Jagannath S, Mazumdar M, Charney AW, Firpo-Betancourt A, Mendu DR, Jhang J, Reich D, Sigel K, Cordon-Cardo C, Feldmann M, Parekh S, Merad M, Gnjatic S. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 2020; **26**: 1636-1643 [PMID: 32839624 DOI: 10.1038/s41591-020-1051-9]

83 **Chen X**, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y, Men D, Huang Q, Liu Y, Yang B, Ding J, Li F. Detectable Serum Severe Acute Respiratory Syndrome Coronavirus 2 Viral Load (RNAemia) Is Closely Correlated With Drastically Elevated Interleukin 6 Level in Critically Ill Patients With Coronavirus Disease 2019. *Clin Infect Dis* 2020; **71**: 1937-1942 [PMID: 32301997 DOI: 10.1093/cid/ciaa449]

84 **Lin A**, He ZB, Zhang S, Zhang JG, Zhang X, Yan WH. Early Risk Factors for the Duration of Severe Acute Respiratory Syndrome Coronavirus 2 Viral Positivity in Patients With Coronavirus Disease 2019. *Clin Infect Dis* 2020; **71**: 2061-2065 [PMID: 32337591 DOI: 10.1093/cid/ciaa490]

85 **Brasen CL**, Christensen H, Olsen DA, Kahns S, Andersen RF, Madsen JB, Lassen A, Kierkegaard H, Jensen A, Sydenham TV, Madsen JS, Møller JK, Brandslund I. Daily monitoring of viral load measured as SARS-CoV-2 antigen and RNA in blood, IL-6, CRP and complement C3d predicts outcome in patients hospitalized with COVID-19. *Clin Chem Lab Med* 2021; **59**: 1988-1997 [PMID: 34455731 DOI: 10.1515/cclm-2021-0694]

86 **Herold T**, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M, Klein M, Weinberger T. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol* 2020; **146**: 128-136.e4 [PMID: 32425269 DOI: 10.1016/j.jaci.2020.05.008]

87 **Zeng F**, Huang Y, Guo Y, Yin M, Chen X, Xiao L, Deng G. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. *Int J Infect Dis* 2020; **96**: 467-474 [PMID: 32425643 DOI: 10.1016/j.ijid.2020.05.055]

88 **Leisman DE**, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, Hirayama AV, Mastroiani F, Turtle CJ, Harhay MO, Legrand M, Deutschman CS. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet Respir Med* 2020; **8**: 1233-1244 [PMID: 33075298 DOI: 10.1016/S2213-2600(20)30404-5]

89 **EMC**. RoActemra 20mg/mL Concentrate for Solution for Infusion. [cited 28 March 2021]. Available from: https://www.medicines.org.uk/emc/product/6673

90 **Stone JH**, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, Horick NK, Healy BC, Shah R, Bensaci AM, Woolley AE, Nikiforow S, Lin N, Sagar M, Schrager H, Huckins DS, Axelrod M, Pincus MD, Fleisher J, Sacks CA, Dougan M, North CM, Halvorsen YD, Thurber TK, Dagher Z, Scherer A, Wallwork RS, Kim AY, Schoenfeld S, Sen P, Neilan TG, Perugino CA, Unizony SH, Collier DS, Matza MA, Yinh JM, Bowman KA, Meyerowitz E, Zafar A, Drobni ZD, Bolster MB, Kohler M, D'Silva KM, Dau J, Lockwood MM, Cubbison C, Weber BN, Mansour MK; BACC Bay Tocilizumab Trial Investigators. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. *N Engl J Med* 2020; **383**: 2333-2344 [PMID: 33085857 DOI: 10.1056/NEJMoa2028836]

91 **Xu X**, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, Zhang X, Pan A, Wei H. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A* 2020; **117**: 10970-10975 [PMID: 32350134 DOI: 10.1073/pnas.2005615117]

92 **Antony SJ**, Davis MA, Davis MG, Almaghlouth NK, Guevara R, Omar F, Del Rey F, Hassan A, Arian MU, Antony N, Prakash BV. Early use of tocilizumab in the prevention of adult respiratory failure in SARS-CoV-2 infections and the utilization of interleukin-6 Levels in the management. *J Med Virol* 2021; **93**: 491-498 [PMID: 32644254 DOI: 10.1002/jmv.26288]

93 **Alattar R**, Ibrahim TBH, Shaar SH, Abdalla S, Shukri K, Daghfal JN, Khatib MY, Aboukamar M, Abukhattab M, Alsoub HA, Almaslamani MA, Omrani AS. Tocilizumab for the treatment of severe coronavirus disease 2019. *J Med Virol* 2020; **92**: 2042-2049 [PMID: 32369191 DOI: 10.1002/jmv.25964]

94 **Price CC**, Altice FL, Shyr Y, Koff A, Pischel L, Goshua G, Azar MM, Mcmanus D, Chen SC, Gleeson SE, Britto CJ, Azmy V, Kaman K, Gaston DC, Davis M, Burrello T, Harris Z, Villanueva MS, Aoun-Barakat L, Kang I, Seropian S, Chupp G, Bucala R, Kaminski N, Lee AI, LoRusso PM, Topal JE, Dela Cruz C, Malinis M. Tocilizumab Treatment for Cytokine Release Syndrome in Hospitalized Patients With Coronavirus Disease 2019: Survival and Clinical Outcomes. *Chest* 2020; **158**: 1397-1408 [PMID: 32553536 DOI: 10.1016/j.chest.2020.06.006]

95 **Knorr JP**, Colomy V, Mauriello CM, Ha S. Tocilizumab in patients with severe COVID-19: A single-center observational analysis. *J Med Virol* 2020; **92**: 2813-2820 [PMID: 32628003 DOI: 10.1002/jmv.26191]

96 **Toniati P**, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, Franceschini F, Airò P, Bazzani C, Beindorf EA, Berlendis M, Bezzi M, Bossini N, Castellano M, Cattaneo S, Cavazzana I, Contessi GB, Crippa M, Delbarba A, De Peri E, Faletti A, Filippini M, Frassi M, Gaggiotti M, Gorla R, Lanspa M, Lorenzotti S, Marino R, Maroldi R, Metra M, Matteelli A, Modina D, Moioli G, Montani G, Muiesan ML, Odolini S, Peli E, Pesenti S, Pezzoli MC, Pirola I, Pozzi A, Proto A, Rasulo FA, Renisi G, Ricci C, Rizzoni D, Romanelli G, Rossi M, Salvetti M, Scolari F, Signorini L, Taglietti M, Tomasoni G, Tomasoni LR, Turla F, Valsecchi A, Zani D, Zuccalà F, Zunica F, Focà E, Andreoli L, Latronico N. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. *Autoimmun Rev* 2020; **19**: 102568 [PMID: 32376398 DOI: 10.1016/j.autrev.2020.102568]

97 **Jordan SC**, Zakowski P, Tran HP, Smith EA, Gaultier C, Marks G, Zabner R, Lowenstein H, Oft J, Bluen B, Le C, Shane R, Ammerman N, Vo A, Chen P, Kumar S, Toyoda M, Ge S, Huang E. Compassionate Use of Tocilizumab for Treatment of SARS-CoV-2 Pneumonia. *Clin Infect Dis* 2020; **71**: 3168-3173 [PMID: 32575124 DOI: 10.1093/cid/ciaa812]

98 **Colaneri M**, Bogliolo L, Valsecchi P, Sacchi P, Zuccaro V, Brandolino F, Montecucco C, Mojoli F, Giusti EM, Bruno R, The Covid Irccs San Matteo Pavia Task Force. Tocilizumab for Treatment of Severe COVID-19 Patients: Preliminary Results from SMAtteo COvid19 REgistry (SMACORE). *Microorganisms* 2020; **8** [PMID: 32397399 DOI: 10.3390/microorganisms8050695]

99 **Campochiaro C**, Della-Torre E, Cavalli G, De Luca G, Ripa M, Boffini N, Tomelleri A, Baldissera E, Rovere-Querini P, Ruggeri A, Monti G, De Cobelli F, Zangrillo A, Tresoldi M, Castagna A, Dagna L; TOCI-RAF Study Group. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. *Eur J Intern Med* 2020; **76**: 43-49 [PMID: 32482597 DOI: 10.1016/j.ejim.2020.05.021]

100 **Potere N**, Di Nisio M, Cibelli D, Scurti R, Frattari A, Porreca E, Abbate A, Parruti G. Interleukin-6 receptor blockade with subcutaneous tocilizumab in severe COVID-19 pneumonia and hyperinflammation: a case-control study. *Ann Rheum Dis* 2021; **80**: 1-2 [PMID: 32647027 DOI: 10.1136/annrheumdis-2020-218243]

101 **Guaraldi G**, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, Franceschini E, Cuomo G, Orlando G, Borghi V, Santoro A, Di Gaetano M, Puzzolante C, Carli F, Bedini A, Corradi L, Fantini R, Castaniere I, Tabbì L, Girardis M, Tedeschi S, Giannella M, Bartoletti M, Pascale R, Dolci G, Brugioni L, Pietrangelo A, Cossarizza A, Pea F, Clini E, Salvarani C, Massari M, Viale PL, Mussini C. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol* 2020; **2**: e474-e484 [PMID: 32835257 DOI: 10.1016/S2665-9913(20)30173-9]

102 **Biran N**, Ip A, Ahn J, Go RC, Wang S, Mathura S, Sinclaire BA, Bednarz U, Marafelias M, Hansen E, Siegel DS, Goy AH, Pecora AL, Sawczuk IS, Koniaris LS, Simwenyi M, Varga DW, Tank LK, Stein AA, Allusson V, Lin GS, Oser WF, Tuma RA, Reichman J, Brusco L Jr, Carpenter KL, Costanzo EJ, Vivona V, Goldberg SL. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. *Lancet Rheumatol* 2020; **2**: e603-e612 [PMID: 32838323 DOI: 10.1016/S2665-9913(20)30277-0]

103 **Klopfenstein T**, Zayet S, Lohse A, Balblanc JC, Badie J, Royer PY, Toko L, Mezher C, Kadiane-Oussou NJ, Bossert M, Bozgan AM, Charpentier A, Roux MF, Contreras R, Mazurier I, Dussert P, Gendrin V, Conrozier T; HNF Hospital Tocilizumab multidisciplinary team. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. *Med Mal Infect* 2020; **50**: 397-400 [PMID: 32387320 DOI: 10.1016/j.medmal.2020.05.001]

104 **Castelnovo L**, Tamburello A, Lurati A, Zaccara E, Marrazza MG, Olivetti M, Mumoli N, Mastroiacovo D, Colombo D, Ricchiuti E, Vigano' P, Paola F, Mazzone A. Anti-IL6 treatment of serious COVID-19 disease: A monocentric retrospective experience. *Medicine (Baltimore)* 2021; **100**: e23582 [PMID: 33429732 DOI: 10.1097/MD.0000000000023582]

105 **Rossotti R**, Travi G, Ughi N, Corradin M, Baiguera C, Fumagalli R, Bottiroli M, Mondino M, Merli M, Bellone A, Basile A, Ruggeri R, Colombo F, Moreno M, Pastori S, Perno CF, Tarsia P, Epis OM, Puoti M; Niguarda COVID-19 Working Group. Safety and efficacy of anti-il6-receptor tocilizumab use in severe and critical patients affected by coronavirus disease 2019: A comparative analysis. *J Infect* 2020; **81**: e11-e17 [PMID: 32652164 DOI: 10.1016/j.jinf.2020.07.008]

106 **Gupta S**, Wang W, Hayek SS, Chan L, Mathews KS, Melamed ML, Brenner SK, Leonberg-Yoo A, Schenck EJ, Radbel J, Reiser J, Bansal A, Srivastava A, Zhou Y, Finkel D, Green A, Mallappallil M, Faugno AJ, Zhang J, Velez JCQ, Shaefi S, Parikh CR, Charytan DM, Athavale AM, Friedman AN, Redfern RE, Short SAP, Correa S, Pokharel KK, Admon AJ, Donnelly JP, Gershengorn HB, Douin DJ, Semler MW, Hernán MA, Leaf DE; STOP-COVID Investigators. Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19. *JAMA Intern Med* 2021; **181**: 41-51 [PMID: 33080002 DOI: 10.1001/jamainternmed.2020.6252]

107 **Rojas-Marte G**, Khalid M, Mukhtar O, Hashmi AT, Waheed MA, Ehrlich S, Aslam A, Siddiqui S, Agarwal C, Malyshev Y, Henriquez-Felipe C, Sharma D, Sharma S, Chukwuka N, Rodriguez DC, Alliu S, Le J, Shani J. Outcomes in patients with severe COVID-19 disease treated with tocilizumab: a case-controlled study. *QJM* 2020; **113**: 546-550 [PMID: 32569363 DOI: 10.1093/qjmed/hcaa206]

108 **Somers EC**, Eschenauer GA, Troost JP, Golob JL, Gandhi TN, Wang L, Zhou N, Petty LA, Baang JH, Dillman NO, Frame D, Gregg KS, Kaul DR, Nagel J, Patel TS, Zhou S, Lauring AS, Hanauer DA, Martin E, Sharma P, Fung CM, Pogue JM. Tocilizumab for Treatment of Mechanically Ventilated Patients With COVID-19. *Clin Infect Dis* 2021; **73**: e445-e454 [PMID: 32651997 DOI: 10.1093/cid/ciaa954]

109 **Fisher MJ**, Marcos Raymundo LA, Monteforte M, Taub EM, Go R. Tocilizumab in the treatment of critical COVID-19 pneumonia: A retrospective cohort study of mechanically ventilated patients. *Int J Infect Dis* 2021; **103**: 536-539 [PMID: 33333252 DOI: 10.1016/j.ijid.2020.12.021]

110 **Salama C**, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, Criner GJ, Kaplan-Lewis E, Baden R, Pandit L, Cameron ML, Garcia-Diaz J, Chávez V, Mekebeb-Reuter M, Lima de Menezes F, Shah R, González-Lara MF, Assman B, Freedman J, Mohan SV. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. *N Engl J Med* 2021; **384**: 20-30 [PMID: 33332779 DOI: 10.1056/NEJMoa2030340]

111 **Salvarani C**, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, Bruzzi P, Boni F, Braglia L, Turrà C, Ballerini PF, Sciascia R, Zammarchi L, Para O, Scotton PG, Inojosa WO, Ravagnani V, Salerno ND, Sainaghi PP, Brignone A, Codeluppi M, Teopompi E, Milesi M, Bertomoro P, Claudio N, Salio M, Falcone M, Cenderello G, Donghi L, Del Bono V, Colombelli PL, Angheben A, Passaro A, Secondo G, Pascale R, Piazza I, Facciolongo N, Costantini M; RCT-TCZ-COVID-19 Study Group. Effect of Tocilizumab *vs* Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med* 2021; **181**: 24-31 [PMID: 33080005 DOI: 10.1001/jamainternmed.2020.6615]

112 **Mariette X**, Hermine O, Tharaux PL, Resche-Rigon M, Steg PG, Porcher R, Ravaud P. Effectiveness of Tocilizumab in Patients Hospitalized With COVID-19: A Follow-up of the CORIMUNO-TOCI-1 Randomized Clinical Trial. *JAMA Intern Med* 2021; **181**: 1241-1243 [PMID: 34028504 DOI: 10.1001/jamainternmed.2021.2209]

113 **Rosas IO**, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, Skiest D, Aziz MS, Cooper N, Douglas IS, Savic S, Youngstein T, Del Sorbo L, Cubillo Gracian A, De La Zerda DJ, Ustianowski A, Bao M, Dimonaco S, Graham E, Matharu B, Spotswood H, Tsai L, Malhotra A. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. *N Engl J Med* 2021; **384**: 1503-1516 [PMID: 33631066 DOI: 10.1056/NEJMoa2028700]

114 **Veiga VC**, Prats JAGG, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, Machado FR, Lopes RD, Berwanger O, Azevedo LCP, Avezum Á, Lisboa TC, Rojas SSO, Coelho JC, Leite RT, Carvalho JC, Andrade LEC, Sandes AF, Pintão MCT, Castro CG Jr, Santos SV, de Almeida TML, Costa AN, Gebara OCE, de Freitas FGR, Pacheco ES, Machado DJB, Martin J, Conceição FG, Siqueira SRR, Damiani LP, Ishihara LM, Schneider D, de Souza D, Cavalcanti AB, Scheinberg P; Coalition covid-19 Brazil VI Investigators. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ* 2021; **372**: n84 [PMID: 33472855 DOI: 10.1136/bmj.n84]

115 **RECOVERY Collaborative Group**. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397**: 1637-1645 [PMID: 33933206 DOI: 10.1016/S0140-6736(21)00676-0]

116 **REMAP-CAP Investigators**, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, Berry LR, Bhimani Z, Bonten MJM, Bradbury CA, Brunkhorst FM, Buzgau A, Cheng

AC, Detry MA, Duffy EJ, Estcourt LJ, Fitzgerald M, Goossens H, Haniffa R, Higgins AM, Hills TE, Horvat CM, Lamontagne F, Lawler PR, Leavis HL, Linstrum KM, Litton E, Lorenzi E, Marshall JC, Mayr FB, McAuley DF, McGlothlin A, McGuinness SP, McVerry BJ, Montgomery SK, Morpeth SC, Murthy S, Orr K, Parke RL, Parker JC, Patanwala AE, Pettilä V, Rademaker E, Santos MS, Saunders CT, Seymour CW, Shankar-Hari M, Sligl WI, Turgeon AF, Turner AM, van de Veerdonk FL, Zarychanski R, Green C, Lewis RJ, Angus DC, McArthur CJ, Berry S, Webb SA, Derde LPG. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *N Engl J Med* 2021; **384**: 1491-1502 [PMID: 33631065 DOI: 10.1056/NEJMoa2100433]

117 **Gremese E**, Cingolani A, Bosello SL, Alivernini S, Tolusso B, Perniola S, Landi F, Pompili M, Murri R, Santoliquido A, Garcovich M, Sali M, De Pascale G, Gabrielli M, Biscetti F, Montalto M, Tosoni A, Gambassi G, Rapaccini GL, Iaconelli A, Zileri Del Verme L, Petricca L, Fedele AL, Lizzio MM, Tamburrini E, Natalello G, Gigante L, Bruno D, Verardi L, Taddei E, Calabrese A, Lombardi F, Bernabei R, Cauda R, Franceschi F, Landolfi R, Richeldi L, Sanguinetti M, Fantoni M, Antonelli M, Gasbarrini A; GEMELLI AGAINST COVID-19 Group. Sarilumab use in severe SARS-CoV-2 pneumonia. *EClinicalMedicine* 2020; **27**: 100553 [PMID: 33043284 DOI: 10.1016/j.eclinm.2020.100553]

118 **Sinha P**, Mostaghim A, Bielick CG, McLaughlin A, Hamer DH, Wetzler LM, Bhadelia N, Fagan MA, Linas BP, Assoumou SA, Ieong MH, Lin NH, Cooper ER, Brade KD, White LF, Barlam TF, Sagar M; Boston Medical Center Covid-19 Treatment Panel. Early administration of interleukin-6 inhibitors for patients with severe COVID-19 disease is associated with decreased intubation, reduced mortality, and increased discharge. *Int J Infect Dis* 2020; **99**: 28-33 [PMID: 32721528 DOI: 10.1016/j.ijid.2020.07.023]

119 **Montesarchio V**, Parrela R, Iommelli C, Bianco A, Manzillo E, Fraganza F, Palumbo C, Rea G, Murino P, De Rosa R, Atripaldi L, D'Abbraccio M, Curvietto M, Mallardo D, Celentano E, Grimaldi AM, Palla M, Trojaniello C, Vitale MG, Million-Weaver SL, Ascierto PA. Outcomes and biomarker analyses among patients with COVID-19 treated with interleukin 6 (IL-6) receptor antagonist sarilumab at a single institution in Italy. *J Immunother Cancer* 2020; **8** [PMID: 32784217 DOI: 10.1136/jitc-2020-001089]

120 **Della-Torre E**, Campochiaro C, Cavalli G, De Luca G, Napolitano A, La Marca S, Boffini N, Da Prat V, Di Terlizzi G, Lanzillotta M, Rovere Querini P, Ruggeri A, Landoni G, Tresoldi M, Ciceri F, Zangrillo A, De Cobelli F, Dagna L; SARI-RAF Study Group; SARI-RAF Study Group members. Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: an open-label cohort study. *Ann Rheum Dis* 2020; **79**: 1277-1285 [PMID: 32620597 DOI: 10.1136/annrheumdis-2020-218122]

121 **Tleyjeh IM**, Kashour Z, Damlaj M, Riaz M, Tlayjeh H, Altannir M, Altannir Y, Al-Tannir M, Tleyjeh R, Hassett L, Kashour T. Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis. *Clin Microbiol Infect* 2021; **27**: 215-227 [PMID: 33161150 DOI: 10.1016/j.cmi.2020.10.036]

122 **Magro G**. COVID-19: Review on latest available drugs and therapies against SARS-CoV-2. Coagulation and inflammation cross-talking. *Virus Res* 2020; **286**: 198070 [PMID: 32569708 DOI: 10.1016/j.virusres.2020.198070]

123 **Jamilloux Y**, Henry T, Belot A, Viel S, Fauter M, El Jammal T, Walzer T, François B, Sève P. Should we stimulate or suppress immune responses in COVID-19? *Autoimmun Rev* 2020; **19**: 102567 [PMID: 32376392 DOI: 10.1016/j.autrev.2020.102567]

124 **Satarker S**, Tom AA, Shaji RA, Alosious A, Luvis M, Nampoothiri M. JAK-STAT Pathway Inhibition and their Implications in COVID-19 Therapy. *Postgrad Med* 2021; **133**: 489-507 [PMID: 33245005 DOI: 10.1080/00325481.2020.1855921]

125 **Stebbing J**, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, Richardson P. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis* 2020; **20**: 400-402 [PMID: 32113509 DOI: 10.1016/S1473-3099(20)30132-8]

126 **Richardson P**, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, Rawling M, Savory E, Stebbing J. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet* 2020; **395**: e30-e31 [PMID: 32032529 DOI: 10.1016/S0140-6736(20)30304-4]

127 **Favalli EG**, Biggioggero M, Maioli G, Caporali R. Baricitinib for COVID-19: a suitable treatment? *Lancet Infect Dis* 2020; **20**: 1012-1013 [PMID: 32251638 DOI: 10.1016/S1473-3099(20)30262-0]

128 **Zhang X**, Zhang Y, Qiao W, Zhang J, Qi Z. Baricitinib, a drug with potential effect to prevent SARS-COV-2 from entering target cells and control cytokine storm induced by COVID-19. *Int Immunopharmacol* 2020; **86**: 106749 [PMID: 32645632 DOI: 10.1016/j.intimp.2020.106749]

129 **Seif F**, Aazami H, Khoshmirsafa M, Kamali M, Mohsenzadegan M, Pornour M, Mansouri D. JAK Inhibition as a New Treatment Strategy for Patients with COVID-19. *Int Arch Allergy Immunol* 2020; **181**: 467-475 [PMID: 32392562 DOI: 10.1159/000508247]

130 **Bronte V**, Ugel S, Tinazzi E, Vella A, De Sanctis F, Canè S, Batani V, Trovato R, Fiore A, Petrova V, Hofer F, Barouni RM, Musiu C, Caligola S, Pinton L, Torroni L, Polati E, Donadello K, Friso S, Pizzolo F, Iezzi M, Facciotti F, Pelicci PG, Righetti D, Bazzoni P, Rampudda M, Comel A, Mosaner W, Lunardi C, Olivieri O. Baricitinib restrains the immune dysregulation in patients with severe COVID-19. *J Clin Invest* 2020; **130**: 6409-6416 [PMID: 32809969 DOI: 10.1172/JCI141772]

131 **Kubo S**, Nakayamada S, Tanaka Y. Baricitinib for the treatment of rheumatoid arthritis and systemic lupus erythematosus: a 2019 update. *Expert Rev Clin Immunol* 2019; **15**: 693-700 [PMID: 30987474 DOI: 10.1080/1744666X.2019.1608821]

132 **Zhang W**, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, Wang J, Qin Y, Zhang X, Yan X, Zeng X, Zhang S. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. *Clin Immunol* 2020; **214**: 108393 [PMID: 32222466 DOI: 10.1016/j.clim.2020.108393]

133 **Cantini F**, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. *J Infect* 2020; **81**: 318-356 [PMID: 32333918 DOI: 10.1016/j.jinf.2020.04.017]

134 **Kalil AC**, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, Marconi VC, Ruiz-Palacios GM, Hsieh L, Kline S, Tapson V, Iovine NM, Jain MK, Sweeney DA, El Sahly HM, Branche AR, Regalado Pineda J, Lye DC, Sandkovsky U, Luetkemeyer AF, Cohen SH, Finberg RW, Jackson PEH, Taiwo B, Paules CI, Arguinchona H, Erdmann

N, Ahuja N, Frank M, Oh MD, Kim ES, Tan SY, Mularski RA, Nielsen H, Ponce PO, Taylor BS, Larson L, Rouphael NG, Saklawi Y, Cantos VD, Ko ER, Engemann JJ, Amin AN, Watanabe M, Billings J, Elie MC, Davey RT, Burgess TH, Ferreira J, Green M, Makowski M, Cardoso A, de Bono S, Bonnett T, Proschan M, Deye GA, Dempsey W, Nayak SU, Dodd LE, Beigel JH; ACTT-2 Study Group Members. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med* 2021; **384**: 795-807 [PMID: 33306283 DOI: 10.1056/NEJMoa2031994]

135 **Rizk JG**, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, Forthal DN. Pharmaco-Immunomodulatory Therapy in COVID-19. *Drugs* 2020; **80**: 1267-1292 [PMID: 32696108 DOI: 10.1007/s40265-020-01367-z]

136 **Yeleswaram S**, Smith P, Burn T, Covington M, Juvekar A, Li Y, Squier P, Langmuir P. Inhibition of cytokine signaling by ruxolitinib and implications for COVID-19 treatment. *Clin Immunol* 2020; **218**: 108517 [PMID: 32585295 DOI: 10.1016/j.clim.2020.108517]

137 **Goker Bagca B**, Biray Avci C. The potential of JAK/STAT pathway inhibition by ruxolitinib in the treatment of COVID-19. *Cytokine Growth Factor Rev* 2020; **54**: 51-62 [PMID: 32636055 DOI: 10.1016/j.cytogfr.2020.06.013]

138 **Shi JG**, Chen X, McGee RF, Landman RR, Emm T, Lo Y, Scherle PA, Punwani NG, Williams WV, Yeleswaram S. The pharmacokinetics, pharmacodynamics, and safety of orally dosed INCB018424 phosphate in healthy volunteers. *J Clin Pharmacol* 2011; **51**: 1644-1654 [PMID: 21257798 DOI: 10.1177/0091270010389469]

139 **D'Alessio A**, Del Poggio P, Bracchi F, Cesana G, Sertori N, Di Mauro D, Fargnoli A, Motta M, Giussani C, Moro P, Vitale G, Giacomini M, Borra G. Low-dose ruxolitinib plus steroid in severe SARS-CoV-2 pneumonia. *Leukemia* 2021; **35**: 635-638 [PMID: 33173161 DOI: 10.1038/s41375-020-01087-z]

140 **La Rosée F**, Bremer HC, Gehrke I, Kehr A, Hochhaus A, Birndt S, Fellhauer M, Henkes M, Kumle B, Russo SG, La Rosée P. The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation. *Leukemia* 2020; **34**: 1805-1815 [PMID: 32518419 DOI: 10.1038/s41375-020-0891-0]

141 **Cao Y**, Wei J, Zou L, Jiang T, Wang G, Chen L, Huang L, Meng F, Wang N, Zhou X, Luo H, Mao Z, Chen X, Xie J, Liu J, Cheng H, Zhao J, Huang G, Wang W, Zhou J. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol* 2020; **146**: 137-146.e3 [PMID: 32470486 DOI: 10.1016/j.jaci.2020.05.019]

142 **Buttgereit F**. Glucocorticoids: surprising new findings on their mechanisms of actions. *Ann Rheum Dis* 2021; **80**: 137-139 [PMID: 33162396 DOI: 10.1136/annrheumdis-2020-218798]

143 **Cavalcanti DM**, Lotufo CM, Borelli P, Ferreira ZS, Markus RP, Farsky SH. Endogenous glucocorticoids control neutrophil mobilization from bone marrow to blood and tissues in non-inflammatory conditions. *Br J Pharmacol* 2007; **152**: 1291-1300 [PMID: 17982481 DOI: 10.1038/sj.bjp.0707512]

144 **Liles WC**, Dale DC, Klebanoff SJ. Glucocorticoids inhibit apoptosis of human neutrophils. *Blood* 1995; **86**: 3181-3188 [PMID: 7579413 DOI: 10.1182/blood.V86.8.3181.bloodjournal8683181]

145 **Dandona P**, Mohanty P, Hamouda W, Aljada A, Kumbkarni Y, Garg R. Effect of dexamethasone on reactive oxygen species generation by leukocytes and plasma interleukin-10 concentrations: a pharmacodynamic study. *Clin Pharmacol Ther* 1999; **66**: 58-65 [PMID: 10430110 DOI: 10.1016/S0009-9236(99)70054-8]

146 **Llewellyn-Jones CG**, Hill SL, Stockley RA. Effect of fluticasone propionate on neutrophil chemotaxis, superoxide generation, and extracellular proteolytic activity in vitro. *Thorax* 1994; **49**: 207-212 [PMID: 8202875 DOI: 10.1136/thx.49.3.207]

147 **Rozkova D**, Horvath R, Bartunkova J, Spisek R. Glucocorticoids severely impair differentiation and antigen presenting function of dendritic cells despite upregulation of Toll-like receptors. *Clin Immunol* 2006; **120**: 260-271 [PMID: 16765091 DOI: 10.1016/j.clim.2006.04.567]

148 **Piemonti L**, Monti P, Allavena P, Sironi M, Soldini L, Leone BE, Socci C, Di Carlo V. Glucocorticoids affect human dendritic cell differentiation and maturation. *J Immunol* 1999; **162**: 6473-6481 [PMID: 10352262]

149 **Zaza G**, Leventhal J, Signorini L, Gambaro G, Cravedi P. Effects of Antirejection Drugs on Innate Immune Cells After Kidney Transplantation. *Front Immunol* 2019; **10**: 2978 [PMID: 31921213 DOI: 10.3389/fimmu.2019.02978]

150 **Stahn C**, Buttgereit F. Genomic and nongenomic effects of glucocorticoids. *Nat Clin Pract Rheumatol* 2008; **4**: 525-533 [PMID: 18762788 DOI: 10.1038/ncprheum0898]

151 **Ruiz-Irastorza G**, Danza A, Khamashta M. Glucocorticoid use and abuse in SLE. *Rheumatology (Oxford)* 2012; **51**: 1145-1153 [PMID: 22271756 DOI: 10.1093/rheumatology/ker410]

152 **Roujeau JC**. Pulse glucocorticoid therapy. The 'big shot' revisited. *Arch Dermatol* 1996; **132**: 1499-1502 [PMID: 8961881]

153 **Meduri GU**, Chrousos GP. Effectiveness of prolonged glucocorticoid treatment in acute respiratory distress syndrome: the right drug, the right way? *Crit Care Med* 2006; **34**: 236-238 [PMID: 16374183 DOI: 10.1097/01.CCM.0000196088.75067.4C]

154 **Luce JM**, Montgomery AB, Marks JD, Turner J, Metz CA, Murray JF. Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. *Am Rev Respir Dis* 1988; **138**: 62-68 [PMID: 3202402 DOI: 10.1164/ajrccm/138.1.62]

155 **Steinberg KP**, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, Thompson BT, Ancukiewicz M; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; **354**: 1671-1684 [PMID: 16625008 DOI: 10.1056/NEJMoa051693]

156 **Moreno G**, Rodríguez A, Reyes LF, Gomez J, Sole-Violan J, Díaz E, Bodí M, Trefler S, Guardiola J, Yébenes JC, Soriano A, Garnacho-Montero J, Socias L, Del Valle Ortíz M, Correig E, Marín-Corral J, Vallverdú-Vidal M, Restrepo MI, Torres A, Martín-Loeches I; GETGAG Study Group. Corticosteroid treatment in critically ill patients with severe influenza pneumonia: a propensity score matching study. *Intensive Care Med* 2018; **44**: 1470-1482 [PMID: 30074052 DOI: 10.1007/s00134-018-5332-4]

157 **Cao B**, Gao H, Zhou B, Deng X, Hu C, Deng C, Lu H, Li Y, Gan J, Liu J, Li H, Zhang Y, Yang Y, Fang Q, Shen Y, Gu Q, Zhou X, Zhao W, Pu Z, Chen L, Sun B, Liu X, Hamilton CD, Li L. Adjuvant Corticosteroid Treatment in Adults With Influenza A (H7N9) Viral Pneumonia. *Crit Care Med* 2016; **44**: e318-e328 [PMID: 26934144 DOI:

10.1097/CCM.0000000000001616]

158 **Li H**, Yang SG, Gu L, Zhang Y, Yan XX, Liang ZA, Zhang W, Jia HY, Chen W, Liu M, Yu KJ, Xue CX, Hu K, Zou Q, Li LJ, Cao B, Wang C; National Influenza A(H1N1)pdm09 Clinical Investigation Group of China. Effect of low-to-moderate-dose corticosteroids on mortality of hospitalized adolescents and adults with influenza A(H1N1)pdm09 viral pneumonia. *Influenza Other Respir Viruses* 2017; **11**: 345-354 [PMID: 28464462 DOI: 10.1111/irv.12456]

159 **Brun-Buisson C**, Richard JC, Mercat A, Thiébaut AC, Brochard L; REVA-SRLF A/H1N1v 2009 Registry Group. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2011; **183**: 1200-1206 [PMID: 21471082 DOI: 10.1164/rccm.201101-0135OC]

160 **Diaz E**, Martin-Loeches I, Canadell L, Vidaur L, Suarez D, Socias L, Estella A, Gil Rueda B, Guerrero JE, Valverdú-Vidal M, Vergara JC, López-Pueyo MJ, Magret M, Recio T, López D, Rello J, Rodriguez A; H1N1 SEMICYUC-CIBERES-REIPI Working Group (GETGAG). Corticosteroid therapy in patients with primary viral pneumonia due to pandemic (H1N1) 2009 influenza. *J Infect* 2012; **64**: 311-318 [PMID: 22240033 DOI: 10.1016/j.jinf.2011.12.010]

161 **Viasus D**, Paño-Pardo JR, Cordero E, Campins A, López-Medrano F, Villoslada A, Fariñas MC, Moreno A, Rodríguez-Baño J, Oteo JA, Martínez-Montauti J, Torre-Cisneros J, Segura F, Carratalà J; Novel Influenza A (H1N1) Study Group, Spanish Network for Research in Infectious Diseases. Effect of immunomodulatory therapies in patients with pandemic influenza A (H1N1) 2009 complicated by pneumonia. *J Infect* 2011; **62**: 193-199 [PMID: 21295604 DOI: 10.1016/j.jinf.2011.01.014]

162 **Meduri GU**, Headley AS, Golden E, Carson SJ, Umberger RA, Kelso T, Tolley EA. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1998; **280**: 159-165 [PMID: 9669790 DOI: 10.1001/jama.280.2.159]

163 **Keel JB**, Hauser M, Stocker R, Baumann PC, Speich R. Established acute respiratory distress syndrome: benefit of corticosteroid rescue therapy. *Respiration* 1998; **65**: 258-264 [PMID: 9730790 DOI: 10.1159/000029273]

164 **Bone RC**, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA. Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome. *Chest* 1987; **92**: 1032-1036 [PMID: 3315478 DOI: 10.1378/chest.92.6.1032]

165 **Bernard GR**, Luce JM, Sprung CL, Rinaldo JE, Tate RM, Sibbald WJ, Kariman K, Higgins S, Bradley R, Metz CA. High-dose corticosteroids in patients with the adult respiratory distress syndrome. *N Engl J Med* 1987; **317**: 1565-1570 [PMID: 3317054 DOI: 10.1056/NEJM198712173172504]

166 **Meduri GU**, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, Gibson M, Umberger R. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest* 2007; **131**: 954-963 [PMID: 17426195 DOI: 10.1378/chest.06-2100]

167 **Weigelt JA**, Norcross JF, Borman KR, Snyder WH 3rd. Early steroid therapy for respiratory failure. *Arch Surg* 1985; **120**: 536-540 [PMID: 3885915 DOI: 10.1001/archsurg.1985.01390290018003]

168 **Wu C**, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020; **180**: 934-943 [PMID: 32167524 DOI: 10.1001/jamainternmed.2020.0994]

169 **Georgiev T**. Coronavirus disease 2019 (COVID-19) and anti-rheumatic drugs. *Rheumatol Int* 2020; **40**: 825-826 [PMID: 32232552 DOI: 10.1007/s00296-020-04570-z]

170 **Zhou W**, Liu Y, Tian D, Wang C, Wang S, Cheng J, Hu M, Fang M, Gao Y. Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia. *Signal Transduct Target Ther* 2020; **5**: 18 [PMID: 32296012 DOI: 10.1038/s41392-020-0127-9]

171 **Russell CD**, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 2020; **395**: 473-475 [PMID: 32043983 DOI: 10.1016/S0140-6736(20)30317-2]

172 **WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group**, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, Annane D, Azevedo LCP, Berwanger O, Cavalcanti AB, Dequin PF, Du B, Emberson J, Fisher D, Giraudeau B, Gordon AC, Granholm A, Green C, Haynes R, Heming N, Higgins JPT, Horby P, Jüni P, Landray MJ, Le Gouge A, Leclerc M, Lim WS, Machado FR, McArthur C, Meziani F, Møller MH, Perner A, Petersen MW, Savovic J, Tomazini B, Veiga VC, Webb S, Marshall JC. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA* 2020; **324**: 1330-1341 [PMID: 32876694 DOI: 10.1001/jama.2020.17023]

173 **World Health Organization**. WHO Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance. [cited 22 June 2021]. Available from: https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf?sfvrsn=bc7da517_2&msclkid=b8ae9dc9bc5911ec94d5e9144972ec07

174 **Peng F**, Tu L, Yang Y, Hu P, Wang R, Hu Q, Cao F, Jiang T, Sun J, Xu G, Chang C. Management and Treatment of COVID-19: The Chinese Experience. *Can J Cardiol* 2020; **36**: 915-930 [PMID: 32439306 DOI: 10.1016/j.cjca.2020.04.010]

175 **Lu X**, Chen T, Wang Y, Wang J, Yan F. Adjuvant corticosteroid therapy for critically ill patients with COVID-19. *Crit Care* 2020; **24**: 241 [PMID: 32430057 DOI: 10.1186/s13054-020-02964-w]

176 **Tomazini BM**, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, Avezum A, Lopes RD, Bueno FR, Silva MVAO, Baldassare FP, Costa ELV, Moura RAB, Honorato MO, Costa AN, Damiani LP, Lisboa T, Kawano-Dourado L, Zampieri FG, Olivato GB, Righy C, Amendola CP, Roepke RML, Freitas DHM, Forte DN, Freitas FGR, Fernandes CCF, Melro LMG, Junior GFS, Morais DC, Zung S, Machado FR, Azevedo LCP; COALITION COVID-19 Brazil III Investigators. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. *JAMA* 2020; **324**: 1307-1316 [PMID: 32876695 DOI: 10.1001/jama.2020.17021]

177 **RECOVERY Collaborative Group**, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in

Hospitalized Patients with Covid-19. *N Engl J Med* 2021; **384**: 693-704 [PMID: 32678530 DOI: 10.1056/NEJMoa2021436]

178 **Jeronimo CMP**, Farias MEL, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Safe IP, Borba MGS, Netto RLA, Maciel ABS, Neto JRS, Oliveira LB, Figueiredo EFG, Oliveira Dinelly KM, de Almeida Rodrigues MG, Brito M, Mourão MPG, Pivoto João GA, Hajjar LA, Bassat Q, Romero GAS, Naveca FG, Vasconcelos HL, de Araújo Tavares M, Brito-Sousa JD, Costa FTM, Nogueira ML, Baía-da-Silva DC, Xavier MS, Monteiro WM, Lacerda MVG; Metcovid Team. Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With Coronavirus Disease 2019 (COVID-19; Metcovid): A Randomized, Double-blind, Phase IIb, Placebo-controlled Trial. *Clin Infect Dis* 2021; **72**: e373-e381 [PMID: 32785710 DOI: 10.1093/cid/ciaa1177]

179 **Dequin PF**, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J, François B, Aubron C, Ricard JD, Ehrmann S, Jouan Y, Guillon A, Leclerc M, Coffre C, Bourgoin H, Lengellé C, Caille-Fénérol C, Tavernier E, Zohar S, Giraudeau B, Annane D, Le Gouge A; CAPE COVID Trial Group and the CRICS-TriGGERSep Network. Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial. *JAMA* 2020; **324**: 1298-1306 [PMID: 32876689 DOI: 10.1001/jama.2020.16761]

180 **Angus DC**, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, van Bentum-Puijk W, Berry L, Bhimani Z, Bonten M, Bradbury C, Brunkhorst F, Buxton M, Buzgau A, Cheng AC, de Jong M, Detry M, Estcourt L, Fitzgerald M, Goossens H, Green C, Haniffa R, Higgins AM, Horvat C, Hullegie SJ, Kruger P, Lamontagne F, Lawler PR, Linstrum K, Litton E, Lorenzi E, Marshall J, McAuley D, McGlothin A, McGuinness S, McVerry B, Montgomery S, Mouncey P, Murthy S, Nichol A, Parke R, Parker J, Rowan K, Sanil A, Santos M, Saunders C, Seymour C, Turner A, van de Veerdonk F, Venkatesh B, Zarychanski R, Berry S, Lewis RJ, McArthur C, Webb SA, Gordon AC; Writing Committee for the REMAP-CAP Investigators, Al-Beidh F, Angus D, Annane D, Arabi Y, van Bentum-Puijk W, Berry S, Beane A, Bhimani Z, Bonten M, Bradbury C, Brunkhorst F, Buxton M, Cheng A, De Jong M, Derde L, Estcourt L, Goossens H, Gordon A, Green C, Haniffa R, Lamontagne F, Lawler P, Litton E, Marshall J, McArthur C, McAuley D, McGuinness S, McVerry B, Montgomery S, Mouncey P, Murthy S, Nichol A, Parke R, Rowan K, Seymour C, Turner A, van de Veerdonk F, Webb S, Zarychanski R, Campbell L, Forbes A, Gattas D, Heritier S, Higgins L, Kruger P, Peake S, Presneill J, Seppelt I, Trapani T, Young P, Bagshaw S, Daneman N, Ferguson N, Misak C, Santos M, Hullegie S, Pletz M, Rohde G, Rowan K, Alexander B, Basile K, Girard T, Horvat C, Huang D, Linstrum K, Vates J, Beasley R, Fowler R, McGloughlin S, Morpeth S, Paterson D, Venkatesh B, Uyeki T, Baillie K, Duffy E, Fowler R, Hills T, Orr K, Patanwala A, Tong S, Netea M, Bihari S, Carrier M, Fergusson D, Goligher E, Haidar G, Hunt B, Kumar A, Laffan M, Lawless P, Lother S, McCallum P, Middeldopr S, McQuilten Z, Neal M, Pasi J, Schutgens R, Stanworth S, Turgeon A, Weissman A, Adhikari N, Anstey M, Brant E, de Man A, Lamonagne F, Masse MH, Udy A, Arnold D, Begin P, Charlewood R, Chasse M, Coyne M, Cooper J, Daly J, Gosbell I, Harvala-Simmonds H, Hills T, MacLennan S, Menon D, McDyer J, Pridee N, Roberts D, Shankar-Hari M, Thomas H, Tinmouth A, Triulzi D, Walsh T, Wood E, Calfee C, O'Kane C, Shyamsundar M, Sinha P, Thompson T, Young I, Bihari S, Hodgson C, Laffey J, McAuley D, Orford N, Neto A, Detry M, Fitzgerald M, Lewis R, McGlothlin A, Sanil A, Saunders C, Berry L, Lorenzi E, Miller E, Singh V, Zammit C, van Bentum Puijk W, Bouwman W, Mangindaan Y, Parker L, Peters S, Rietveld I, Raymakers K, Ganpat R, Brillinger N, Markgraf R, Ainscough K, Brickell K, Anjum A, Lane JB, Richards-Belle A, Saull M, Wiley D, Bion J, Connor J, Gates S, Manax V, van der Poll T, Reynolds J, van Beurden M, Effelaar E, Schotsman J, Boyd C, Harland C, Shearer A, Wren J, Clermont G, Garrard W, Kalchthaler K, King A, Ricketts D, Malakoutis S, Marroquin O, Music E, Quinn K, Cate H, Pearson K, Collins J, Hanson J, Williams P, Jackson S, Asghar A, Dyas S, Sutu M, Murphy S, Williamson D, Mguni N, Potter A, Porter D, Goodwin J, Rook C, Harrison S, Williams H, Campbell H, Lomme K, Williamson J, Sheffield J, van't Hoff W, McCracken P, Young M, Board J, Mart E, Knott C, Smith J, Boschert C, Affleck J, Ramanan M, D'Souza R, Pateman K, Shakih A, Cheung W, Kol M, Wong H, Shah A, Wagh A, Simpson J, Duke G, Chan P, Cartner B, Hunter S, Laver R, Shrestha T, Regli A, Pellicano A, McCullough J, Tallott M, Kumar N, Panwar R, Brinkerhoff G, Koppen C, Cazzola F, Brain M, Mineall S, Fischer R, Biradar V, Soar N, White H, Estensen K, Morrison L, Smith J, Cooper M, Health M, Shehabi Y, Al-Bassam W, Hulley A, Whitehead C, Lowrey J, Gresha R, Walsham J, Meyer J, Harward M, Venz E, Williams P, Kurenda C, Smith K, Smith M, Garcia R, Barge D, Byrne D, Byrne K, Driscoll A, Fortune L, Janin P, Yarad E, Hammond N, Bass F, Ashelford A, Waterson S, Wedd S, McNamara R, Buhr H, Coles J, Schweikert S, Wibrow B, Rauniyar R, Myers E, Fysh E, Dawda A, Mevavala B, Litton E, Ferrier J, Nair P, Buscher H, Reynolds C, Santamaria J, Barbazza L, Homes J, Smith R, Murray L, Brailsford J, Forbes L, Maguire T, Mariappa V, Smith J, Simpson S, Maiden M, Bone A, Horton M, Salerno T, Sterba M, Geng W, Depuydt P, De Waele J, De Bus L, Fierens J, Bracke S, Reeve B, Dechert W, Chassé M, Carrier FM, Boumahni D, Benettaib F, Ghamraoui A, Bellemare D, Cloutier È, Francoeur C, Lamontagne F, D'Aragon F, Carbonneau E, Leblond J, Vazquez-Grande G, Marten N, Wilson M, Albert M, Serri K, Cavayas A, Duplaix M, Williams V, Rochwerg B, Karachi T, Oczkowski S, Centofanti J, Millen T, Duan E, Tsang J, Patterson L, English S, Watpool I, Porteous R, Miezitis S, McIntyre L, Brochard L, Burns K, Sandhu G, Khalid I, Binnie A, Powell E, McMillan A, Luk T, Aref N, Andric Z, Cviljevic S, Đimoti R, Zapalac M, Mirković G, Baršić B, Kutleša M, Kotarski V, Vujaklija Brajković A, Babel J, Sever H, Dragija L, Kušan I, Vaara S, Pettilä L, Heinonen J, Kuitunen A, Karlsson S, Vahtera A, Kiiski H, Ristimäki S, Azaiz A, Charron C, Godement M, Geri G, Vieillard-Baron A, Pourcine F, Monchi M, Luis D, Mercier R, Sagnier A, Verrier N, Caplin C, Siami S, Aparicio C, Vautier S, Jeblaoui A, Fartoukh M, Courtin L, Labbe V, Leparco C, Muller G, Nay MA, Kamel T, Benzekri D, Jacquier S, Mercier E, Chartier D, Salmon C, Dequin P, Schneider F, Morel G, L'Hotellier S, Badie J, Berdaguer FD, Malfroy S, Mezher C, Bourgoin C, Megarbane B, Voicu S, Deye N, Malissin I, Sutterlin L, Guitton C, Darreau C, Landais M, Chudeau N, Robert A, Moine P, Heming N, Maxime V, Bossard I, Nicholier TB, Colin G, Zinzoni V, Maquigneau N, Finn A, Kreß G, Hoff U, Friedrich Hinrichs C, Nee J, Pletz M, Hagel S, Ankert J, Kolanos S, Bloos F, Petros S, Pasieka B, Kunz K, Appelt P, Schütze B, Kluge S, Nierhaus A, Jarczak D, Roedl K, Weismann D, Frey A, Klinikum Neukölln V, Reill L, Distler M, Maselli A, Bélteczki J, Magyar I, Fazekas Á, Kovács S, Szőke V, Szigligeti G, Leszkoven J, Collins D, Breen P, Frohlich S, Whelan R, McNicholas B, Scully M, Casey S, Kernan M, Doran P, O'Dywer M, Smyth M, Hayes L, Hoiting O, Peters M, Rengers E, Evers M, Prinssen A, Bosch Ziekenhuis J, Simons K, Rozendaal W, Polderman F, de Jager P, Moviat M, Paling A, Salet A, Rademaker E, Peters AL, de Jonge E, Wigbers J, Guilder E, Butler M, Cowdrey KA, Newby L, Chen Y, Simmonds C, McConnochie R, Ritzema

Carter J, Henderson S, Van Der Heyden K, Mehrtens J, Williams T, Kazemi A, Song R, Lai V, Girijadevi D, Everitt R, Russell R, Hacking D, Buehner U, Williams E, Browne T, Grimwade K, Goodson J, Keet O, Callender O, Martynoga R, Trask K, Butler A, Schischka L, Young C, Lesona E, Olatunji S, Robertson Y, José N, Amaro dos Santos Catorze T, de Lima Pereira TNA, Neves Pessoa LM, Castro Ferreira RM, Pereira Sousa Bastos JM, Aysel Florescu S, Stanciu D, Zaharia MF, Kosa AG, Codreanu D, Marabi Y, Al Qasim E, Moneer Hagazy M, Al Swaidan L, Arishi H, Muñoz-Bermúdez R, Marin-Corral J, Salazar Degracia A, Parrilla Gómez F, Mateo López MI, Rodriguez Fernandez J, Cárcel Fernández S, Carmona Flores R, León López R, de la Fuente Martos C, Allan A, Polgarova P, Farahi N, McWilliam S, Hawcutt D, Rad L, O'Malley L, Whitbread J, Kelsall O, Wild L, Thrush J, Wood H, Austin K, Donnelly A, Kelly M, O'Kane S, McClintock D, Warnock M, Johnston P, Gallagher LJ, Mc Goldrick C, Mc Master M, Strzelecka A, Jha R, Kalogirou M, Ellis C, Krishnamurthy V, Deelchand V, Silversides J, McGuigan P, Ward K, O'Neill A, Finn S, Phillips B, Mullan D, Oritz-Ruiz de Gordoa L, Thomas M, Sweet K, Grimmer L, Johnson R, Pinnell J, Robinson M, Gledhill L, Wood T, Morgan M, Cole J, Hill H, Davies M, Antcliffe D, Templeton M, Rojo R, Coghlan P, Smee J, Mackay E, Cort J, Whileman A, Spencer T, Spittle N, Kasipandian V, Patel A, Allibone S, Genetu RM, Ramali M, Ghosh A, Bamford P, London E, Cawley K, Faulkner M, Jeffrey H, Smith T, Brewer C, Gregory J, Limb J, Cowton A, O'Brien J, Nikitas N, Wells C, Lankester L, Pulletz M, Williams P, Birch J, Wiseman S, Horton S, Alegria A, Turki S, Elsefi T, Crisp N, Allen L, McCullagh I, Robinson P, Hays C, Babio-Galan M, Stevenson H, Khare D, Pinder M, Selvamoni S, Gopinath A, Pugh R, Menzies D, Mackay C, Allan E, Davies G, Puxty K, McCue C, Cathcart S, Hickey N, Ireland J, Yusuff H, Isgro G, Brightling C, Bourne M, Craner M, Watters M, Prout R, Davies L, Pegler S, Kyeremeh L, Arbane G, Wilson K, Gomm L, Francia F, Brett S, Sousa Arias S, Elin Hall R, Budd J, Small C, Birch J, Collins E, Henning J, Bonner S, Hugill K, Cirstea E, Wilkinson D, Karlikowski M, Sutherland H, Wilhelmsen E, Woods J, North J, Sundaran D, Hollos L, Coburn S, Walsh J, Turns M, Hopkins P, Smith J, Noble H, Depante MT, Clarey E, Laha S, Verlander M, Williams A, Huckle A, Hall A, Cooke J, Gardiner-Hill C, Maloney C, Qureshi H, Flint N, Nicholson S, Southin S, Nicholson A, Borgatta B, Turner-Bone I, Reddy A, Wilding L, Chamara Warnapura L, Agno Sathianathan R, Golden D, Hart C, Jones J, Bannard-Smith J, Henry J, Birchall K, Pomeroy F, Quayle R, Makowski A, Misztal B, Ahmed I, KyereDiabour T, Naiker K, Stewart R, Mwaura E, Mew L, Wren L, Willams F, Innes R, Doble P, Hutter J, Shovelton C, Plumb B, Szakmany T, Hamlyn V, Hawkins N, Lewis S, Dell A, Gopal S, Ganguly S, Smallwood A, Harris N, Metherell S, Lazaro JM, Newman T, Fletcher S, Nortje J, Fottrell-Gould D, Randell G, Zaman M, Elmahi E, Jones A, Hall K, Mills G, Ryalls K, Bowler H, Sall J, Bourne R, Borrill Z, Duncan T, Lamb T, Shaw J, Fox C, Moreno Cuesta J, Xavier K, Purohit D, Elhassan M, Bakthavatsalam D, Rowland M, Hutton P, Bashyal A, Davidson N, Hird C, Chhablani M, Phalod G, Kirkby A, Archer S, Netherton K, Reschreiter H, Camsooksai J, Patch S, Jenkins S, Pogson D, Rose S, Daly Z, Brimfield L, Claridge H, Parekh D, Bergin C, Bates M, Dasgin J, McGhee C, Sim M, Hay SK, Henderson S, Phull MK, Zaidi A, Pogreban T, Rosaroso LP, Harvey D, Lowe B, Meredith M, Ryan L, Hormis A, Walker R, Collier D, Kimpton S, Oakley S, Rooney K, Rodden N, Hughes E, Thomson N, McGlynn D, Walden A, Jacques N, Coles H, Tilney E, Vowell E, Schuster-Bruce M, Pitts S, Miln R, Purandare L, Vamplew L, Spivey M, Bean S, Burt K, Moore L, Day C, Gibson C, Gordon E, Zitter L, Keenan S, Baker E, Cherian S, Cutler S, Roynon-Reed A, Harrington K, Raithatha A, Bauchmuller K, Ahmad N, Grecu I, Trodd D, Martin J, Wrey Brown C, Arias AM, Craven T, Hope D, Singleton J, Clark S, Rae N, Welters I, Hamilton DO, Williams K, Waugh V, Shaw D, Puthucheary Z, Martin T, Santos F, Uddin R, Somerville A, Tatham KC, Jhanji S, Black E, Dela Rosa A, Howle R, Tully R, Drummond A, Dearden J, Philbin J, Munt S, Vuylsteke A, Chan C, Victor S, Matsa R, Gellamucho M, Creagh-Brown B, Tooley J, Montague L, De Beaux F, Bullman L, Kersiake I, Demetriou C, Mitchard S, Ramos L, White K, Donnison P, Johns M, Casey R, Mattocks L, Salisbury S, Dark P, Claxton A, McLachlan D, Slevin K, Lee S, Hulme J, Joseph S, Kinney F, Senya HJ, Oborska A, Kayani A, Hadebe B, Orath Prabakaran R, Nichols L, Thomas M, Worner R, Faulkner B, Gendall E, Hayes K, Hamilton-Davies C, Chan C, Mfuko C, Abbass H, Mandadapu V, Leaver S, Forton D, Patel K, Paramasivam E, Powell M, Gould R, Wilby E, Howcroft C, Banach D, Fernández de Pinedo Artaraz Z, Cabreros L, White I, Croft M, Holland N, Pereira R, Zaki A, Johnson D, Jackson M, Garrard H, Juhaz V, Roy A, Rostron A, Woods L, Cornell S, Pillai S, Harford R, Rees T, Ivatt H, Sundara Raman A, Davey M, Lee K, Barber R, Chablani M, Brohi F, Jagannathan V, Clark M, Purvis S, Wetherill B, Dushianthan A, Cusack R, de Courcy-Golder K, Smith S, Jackson S, Attwood B, Parsons P, Page V, Zhao XB, Oza D, Rhodes J, Anderson T, Morris S, Xia Le Tai C, Thomas A, Keen A, Digby S, Cowley N, Wild L, Southern D, Reddy H, Campbell A, Watkins C, Smuts S, Touma O, Barnes N, Alexander P, Felton T, Ferguson S, Sellers K, Bradley-Potts J, Yates D, Birkinshaw I, Kell K, Marshall N, Carr-Knott L, Summers C. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. *JAMA* 2020; **324**: 1317-1329 [PMID: 32876697 DOI: 10.1001/jama.2020.17022]

181 **Edalatifard M**, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S, Najafizadeh SR, Farhadi E, Jalili N, Esfahani M, Rahimi B, Kazemzadeh H, Mahmoodi Aliabadi M, Ghazanfari T, Sattarian M, Ebrahimi Louyeh H, Raeeskarami SR, Jamalimoghadamsiahkali S, Khajavirad N, Mahmoudi M, Rostamian A. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. *Eur Respir J* 2020; **56** [PMID: 32943404 DOI: 10.1183/13993003.02808-2020]

182 **Callejas Rubio JL**, Luna Del Castillo JD, de la Hera Fernández J, Guirao Arrabal E, Colmenero Ruiz M, Ortego Centeno N. [Effectiveness of corticoid pulses in patients with cytokine storm syndrome induced by SARS-CoV-2 infection]. *Med Clin (Barc)* 2020; **155**: 159-161 [PMID: 32532461 DOI: 10.1016/j.medcli.2020.04.018]

183 **Ruiz-Irastorza G**, Pijoan JI, Bereciartua E, Dunder S, Dominguez J, Garcia-Escudero P, Rodrigo A, Gomez-Carballo C, Varona J, Guio L, Ibarrola M, Ugarte A, Martinez-Berriotxoa A; Cruces COVID Study Group. Second week methyl-prednisolone pulses improve prognosis in patients with severe coronavirus disease 2019 pneumonia: An observational comparative study using routine care data. *PLoS One* 2020; **15**: e0239401 [PMID: 32960899 DOI: 10.1371/journal.pone.0239401]

184 **Cusacovich I**, Aparisi Á, Marcos M, Ybarra-Falcón C, Iglesias-Echevarria C, Lopez-Veloso M, Barraza-Vengoechea J, Dueñas C, Juarros Martínez SA, Rodríguez-Alonso B, Martín-Oterino JÁ, Montero-Baladia M, Moralejo L, Andaluz-Ojeda D, Gonzalez-Fuentes R. Corticosteroid Pulses for Hospitalized Patients with COVID-19: Effects on Mortality. *Mediators Inflamm* 2021; **2021**: 6637227 [PMID: 33776574 DOI: 10.1155/2021/6637227]

185 **Corral-Gudino L**. MP3-pulses-COVID-19. Methylprednisolone Pulses Versus Dexamethasone According RECOVERY Protocol in Patients With Pneumonia Due to SARS-COV-2 Coronavirus Infection. [accessed 2021 Jul 5]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/history/NCT04780581?V_2=View&msclkid=7fc298a1bc5811ecb7fef0bd1162a159 ClinicalTrials.gov Identifier: NCT04780581

186 **Kim MS**, An MH, Kim WJ, Hwang TH. Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis. *PLoS Med* 2020; **17**: e1003501 [PMID: 33378357 DOI: 10.1371/journal.pmed.1003501]

187 **van Paassen J**, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. *Crit Care* 2020; **24**: 696 [PMID: 33317589 DOI: 10.1186/s13054-020-03400-9]

188 **Corral-Gudino L**, Bahamonde A, Arnaiz-Revillas F, Gómez-Barquero J, Abadía-Otero J, García-Ibarbia C, Mora V, Cerezo-Hernández A, Hernández JL, López-Muñíz G, Hernández-Blanco F, Cifrián JM, Olmos JM, Carrascosa M, Nieto L, Fariñas MC, Riancho JA; GLUCOCOVID investigators. Methylprednisolone in adults hospitalized with COVID-19 pneumonia: An open-label randomized trial (GLUCOCOVID). *Wien Klin Wochenschr* 2021; **133**: 303-311 [PMID: 33534047 DOI: 10.1007/s00508-020-01805-8]

189 **Gupta A**, Karki R, Dandu HR, Dhama K, Bhatt ML, Saxena SK. COVID-19: benefits and risks of passive immunotherapeutics. *Hum Vaccin Immunother* 2020; **16**: 2963-2972 [PMID: 32962524 DOI: 10.1080/21645515.2020.1808410]

190 **Mustafa S**, Balkhy H, Gabere MN. Current treatment options and the role of peptides as potential therapeutic components for Middle East Respiratory Syndrome (MERS): A review. *J Infect Public Health* 2018; **11**: 9-17 [PMID: 28864360 DOI: 10.1016/j.jiph.2017.08.009]

191 **Nguyen AA**, Habiballah SB, Platt CD, Geha RS, Chou JS, McDonald DR. Immunoglobulins in the treatment of COVID-19 infection: Proceed with caution! *Clin Immunol* 2020; **216**: 108459 [PMID: 32418917 DOI: 10.1016/j.clim.2020.108459]

192 **Moradimajd P**, Samaee H, Sedigh-Maroufi S, Kourosh-Aami M, Mohsenzadagan M. Administration of intravenous immunoglobulin in the treatment of COVID-19: A review of available evidence. *J Med Virol* 2021; **93**: 2675-2682 [PMID: 33314173 DOI: 10.1002/jmv.26727]

193 **Xie Y**, Cao S, Dong H, Li Q, Chen E, Zhang W, Yang L, Fu S, Wang R. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. *J Infect* 2020; **81**: 318-356 [PMID: 32283154 DOI: 10.1016/j.jinf.2020.03.044]

194 **Tabarsi P**, Barati S, Jamaati H, Haseli S, Marjani M, Moniri A, Abtahian Z, Dastan A, Yousefian S, Eskandari R, Saffaei A, Monjazebi F, Vahedi A, Dastan F. Evaluating the effects of Intravenous Immunoglobulin (IVIg) on the management of severe COVID-19 cases: A randomized controlled trial. *Int Immunopharmacol* 2021; **90**: 107205 [PMID: 33214093 DOI: 10.1016/j.intimp.2020.107205]

195 **Gharebaghi N**, Nejadrahim R, Mousavi SJ, Sadat-Ebrahimi SR, Hajizadeh R. The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial. *BMC Infect Dis* 2020; **20**: 786 [PMID: 33087047 DOI: 10.1186/s12879-020-05507-4]

196 **Perricone C**, Triggianese P, Bursi R, Cafaro G, Bartoloni E, Chimenti MS, Gerli R, Perricone R. Intravenous Immunoglobulins at the Crossroad of Autoimmunity and Viral Infections. *Microorganisms* 2021; **9** [PMID: 33430200 DOI: 10.3390/microorganisms9010121]

197 **Hung IFN**, To KKW, Lee CK, Lee KL, Yan WW, Chan K, Chan WM, Ngai CW, Law KI, Chow FL, Liu R, Lai KY, Lau CCY, Liu SH, Chan KH, Lin CK, Yuen KY. Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. *Chest* 2013; **144**: 464-473 [PMID: 23450336 DOI: 10.1378/chest.12-2907]

198 **Annamaria P**, Eugenia Q, Paolo S. Anti-SARS-CoV-2 hyperimmune plasma workflow. *Transfus Apher Sci* 2020; **59**: 102850 [PMID: 32540345 DOI: 10.1016/j.transci.2020.102850]

199 **Piechotta V**, Chai KL, Valk SJ, Doree C, Monsef I, Wood EM, Lamikanra A, Kimber C, McQuilten Z, So-Osman C, Estcourt LJ, Skoetz N. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database Syst Rev* 2020; **7**: CD013600 [PMID: 32648959 DOI: 10.1002/14651858.CD013600.pub2]

200 **Agarwal A**, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P; PLACID Trial Collaborators. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ* 2020; **371**: m3939 [PMID: 33093056 DOI: 10.1136/bmj.m3939]

201 **Li L**, Zhang W, Hu Y, Tong X, Zheng S, Yang J, Kong Y, Ren L, Wei Q, Mei H, Hu C, Tao C, Yang R, Wang J, Yu Y, Guo Y, Wu X, Xu Z, Zeng L, Xiong N, Chen L, Man N, Liu Y, Xu H, Deng E, Zhang X, Li C, Wang C, Su S, Zhang L, Wu Y, Liu Z. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. *JAMA* 2020; **324**: 460-470 [PMID: 32492084 DOI: 10.1001/jama.2020.10044]

202 **Shen C**, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J, Xiao H, Qu J, Qing L, Chen L, Xu Z, Peng L, Li Y, Zheng H, Chen F, Huang K, Jiang Y, Liu D, Zhang Z, Liu Y, Liu L. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA* 2020; **323**: 1582-1589 [PMID: 32219428 DOI: 10.1001/jama.2020.4783]

203 **Zhang B**, Liu S, Tan T, Huang W, Dong Y, Chen L, Chen Q, Zhang L, Zhong Q, Zhang X, Zou Y, Zhang S. Treatment With Convalescent Plasma for Critically Ill Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *Chest* 2020; **158**: e9-e13 [PMID: 32243945 DOI: 10.1016/j.chest.2020.03.039]

204 **Parihar SP**, Guler R, Brombacher F. Statins: a viable candidate for host-directed therapy against infectious diseases. *Nat Rev Immunol* 2019; **19**: 104-117 [PMID: 30487528 DOI: 10.1038/s41577-018-0094-3]

205 **Scheen AJ**. Statins and clinical outcomes with COVID-19: Meta-analyses of observational studies. *Diabetes Metab* 2021;

47: 101220 [PMID: 33359486 DOI: 10.1016/j.diabet.2020.101220]
206 **Aparisi Á**, Amat-Santos IJ, López Otero D, Marcos-Mangas M, González-Juanatey JR, San Román JA. Impact of statins in patients with COVID-19. *Rev Esp Cardiol (Engl Ed)* 2021; **74**: 637-640 [PMID: 33593686 DOI: 10.1016/j.rec.2021.01.005]
207 **Cariou B**, Goronflot T, Rimbert A, Boullu S, Le May C, Moulin P, Pichelin M, Potier L, Smati S, Sultan A, Tramunt B, Wargny M, Gourdy P, Hadjadj S; CORONADO investigators. Routine use of statins and increased COVID-19 related mortality in inpatients with type 2 diabetes: Results from the CORONADO study. *Diabetes Metab* 2021; **47**: 101202 [PMID: 33091555 DOI: 10.1016/j.diabet.2020.10.001]
208 **Saeed O**, Castagna F, Agalliu I, Xue X, Patel SR, Rochlani Y, Kataria R, Vukelic S, Sims DB, Alvarez C, Rivas-Lasarte M, Garcia MJ, Jorde UP. Statin Use and In-Hospital Mortality in Patients With Diabetes Mellitus and COVID-19. *J Am Heart Assoc* 2020; **9**: e018475 [PMID: 33092446 DOI: 10.1161/JAHA.120.018475]
209 **Lee HY**, Ahn J, Park J, Kyung Kang C, Won SH, Wook Kim D, Park JH, Chung KH, Joh JS, Bang JH, Hee Kang C, Bum Pyun W, Oh MD; Korean Society of Hypertension, National Committee for Clinical Management of Emerging Infectious Diseases. Beneficial Effect of Statins in COVID-19-Related Outcomes-Brief Report: A National Population-Based Cohort Study. *Arterioscler Thromb Vasc Biol* 2021; **41**: e175-e182 [PMID: 33535790 DOI: 10.1161/ATVBAHA.120.315551]
210 **Owji H**, Negahdaripour M, Hajighahramani N. Immunotherapeutic approaches to curtail COVID-19. *Int Immunopharmacol* 2020; **88**: 106924 [PMID: 32877828 DOI: 10.1016/j.intimp.2020.106924]
211 **Atri D**, Siddiqi HK, Lang JP, Nauffal V, Morrow DA, Bohula EA. COVID-19 for the Cardiologist: Basic Virology, Epidemiology, Cardiac Manifestations, and Potential Therapeutic Strategies. *JACC Basic Transl Sci* 2020; **5**: 518-536 [PMID: 32292848 DOI: 10.1016/j.jacbts.2020.04.002]
212 **Oesterle A**, Laufs U, Liao JK. Pleiotropic Effects of Statins on the Cardiovascular System. *Circ Res* 2017; **120**: 229-243 [PMID: 28057795 DOI: 10.1161/CIRCRESAHA.116.308537]
213 **Bangalore S**, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, Ibrahim H, Friedman GH, Thompson C, Alviar CL, Chadow HL, Fishman GI, Reynolds HR, Keller N, Hochman JS. ST-Segment Elevation in Patients with Covid-19 - A Case Series. *N Engl J Med* 2020; **382**: 2478-2480 [PMID: 32302081 DOI: 10.1056/NEJMc2009020]
214 **Oxley TJ**, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, De Leacy RA, Shigematsu T, Ladner TR, Yaeger KA, Skliut M, Weinberger J, Dangayach NS, Bederson JB, Tuhrim S, Fifi JT. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med* 2020; **382**: e60 [PMID: 32343504 DOI: 10.1056/NEJMc2009787]
215 **National Heart**, Lung, and Blood Institute ARDS Clinical Trials Network, Truwit JD, Bernard GR, Steingrub J, Matthay MA, Liu KD, Albertson TE, Brower RG, Shanholtz C, Rock P, Douglas IS, deBoisblanc BP, Hough CL, Hite RD, Thompson BT. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. *N Engl J Med* 2014; **370**: 2191-2200 [PMID: 24835849 DOI: 10.1056/NEJMoa1401520]
216 **McAuley DF**, Laffey JG, O'Kane CM, Perkins GD, Mullan B, Trinder TJ, Johnston P, Hopkins PA, Johnston AJ, McDowell C, McNally C; HARP-2 Investigators; Irish Critical Care Trials Group. Simvastatin in the acute respiratory distress syndrome. *N Engl J Med* 2014; **371**: 1695-1703 [PMID: 25268516 DOI: 10.1056/NEJMoa1403285]
217 **Xiong B**, Wang C, Tan J, Cao Y, Zou Y, Yao Y, Qian J, Rong S, Huang Y, Huang J. Statins for the prevention and treatment of acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis. *Respirology* 2016; **21**: 1026-1033 [PMID: 27221951 DOI: 10.1111/resp.12820]
218 **Calfee CS**, Delucchi KL, Sinha P, Matthay MA, Hackett J, Shankar-Hari M, McDowell C, Laffey JG, O'Kane CM, McAuley DF; Irish Critical Care Trials Group. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. *Lancet Respir Med* 2018; **6**: 691-698 [PMID: 30078618 DOI: 10.1016/S2213-2600(18)30177-2]
219 **Nägele MP**, Haubner B, Tanner FC, Ruschitzka F, Flammer AJ. Endothelial dysfunction in COVID-19: Current findings and therapeutic implications. *Atherosclerosis* 2020; **314**: 58-62 [PMID: 33161318 DOI: 10.1016/j.atherosclerosis.2020.10.014]
220 **Mackall CL**, Fry TJ, Gress RE. Harnessing the biology of IL-7 for therapeutic application. *Nat Rev Immunol* 2011; **11**: 330-342 [PMID: 21508983 DOI: 10.1038/nri2970]
221 **Barata JT**, Durum SK, Seddon B. Flip the coin: IL-7 and IL-7R in health and disease. *Nat Immunol* 2019; **20**: 1584-1593 [PMID: 31745336 DOI: 10.1038/s41590-019-0479-x]
222 **Laterre PF**, François B, Collienne C, Hantson P, Jeannet R, Remy KE, Hotchkiss RS. Association of Interleukin 7 Immunotherapy With Lymphocyte Counts Among Patients With Severe Coronavirus Disease 2019 (COVID-19). *JAMA Netw Open* 2020; **3**: e2016485 [PMID: 32697322 DOI: 10.1001/jamanetworkopen.2020.16485]
223 **Liu Y**, Pan Y, Hu Z, Wu M, Wang C, Feng Z, Mao C, Tan Y, Liu Y, Chen L, Li M, Wang G, Yuan Z, Diao B, Wu Y, Chen Y. Thymosin Alpha 1 Reduces the Mortality of Severe Coronavirus Disease 2019 by Restoration of Lymphocytopenia and Reversion of Exhausted T Cells. *Clin Infect Dis* 2020; **71**: 2150-2157 [PMID: 32442287 DOI: 10.1093/cid/ciaa630]
224 **Lim ZJ**, Subramaniam A, Ponnapa Reddy M, Blecher G, Kadam U, Afroz A, Billah B, Ashwin S, Kubicki M, Bilotta F, Curtis JR, Rubulotta F. Case Fatality Rates for Patients with COVID-19 Requiring Invasive Mechanical Ventilation. A Meta-analysis. *Am J Respir Crit Care Med* 2021; **203**: 54-66 [PMID: 33119402 DOI: 10.1164/rccm.202006-2405OC]
225 **Chang R**, Elhusseiny KM, Yeh YC, Sun WZ. COVID-19 ICU and mechanical ventilation patient characteristics and outcomes-A systematic review and meta-analysis. *PLoS One* 2021; **16**: e0246318 [PMID: 33571301 DOI: 10.1371/journal.pone.0246318]
226 **Penttilä PA**, Van Gassen S, Panovska D, Vanderbeke L, Van Herck Y, Quintelier K, Emmaneel A, Filtjens J, Malengier-Devlies B, Ahmadzadeh K, Van Mol P, Borràs DM, Antoranz A, Bosisio FM, Wauters E, Martinod K, Matthys P, Saeys Y, Garg AD, Wauters J, De Smet F; CONTAGIOUS consortium. High dimensional profiling identifies specific immune types along the recovery trajectories of critically ill COVID19 patients. *Cell Mol Life Sci* 2021; **78**: 3987-4002 [PMID: 33715015 DOI: 10.1007/s00018-021-03808-8]
227 **Rodríguez A**, Ruiz-Botella M, Martín-Loeches I, Jimenez Herrera M, Solé-Violan J, Gómez J, Bodí M, Trefler S, Papiol E, Díaz E, Suberviola B, Vallverdu M, Mayor-Vázquez E, Albaya Moreno A, Canabal Berlanga A, Sánchez M, Del Valle

Ortíz M, Ballesteros JC, Martín Iglesias L, Marín-Corral J, López Ramos E, Hidalgo Valverde V, Vidaur Tello LV, Sancho Chinesta S, Gonzáles de Molina FJ, Herrero García S, Sena Pérez CC, Pozo Laderas JC, Rodríguez García R, Estella A, Ferrer R; COVID-19 SEMICYUC Working Group. Deploying unsupervised clustering analysis to derive clinical phenotypes and risk factors associated with mortality risk in 2022 critically ill patients with COVID-19 in Spain. *Crit Care* 2021; **25**: 63 [PMID: 33588914 DOI: 10.1186/s13054-021-03487-8]

228 **Osuchowski MF**, Winkler MS, Skirecki T, Cajander S, Shankar-Hari M, Lachmann G, Monneret G, Venet F, Bauer M, Brunkhorst FM, Weis S, Garcia-Salido A, Kox M, Cavaillon JM, Uhle F, Weigand MA, Flohé SB, Wiersinga WJ, Almansa R, de la Fuente A, Martin-Loeches I, Meisel C, Spinetti T, Schefold JC, Cilloniz C, Torres A, Giamarellos-Bourboulis EJ, Ferrer R, Girardis M, Cossarizza A, Netea MG, van der Poll T, Bermejo-Martín JF, Rubio I. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. *Lancet Respir Med* 2021; **9**: 622-642 [PMID: 33965003 DOI: 10.1016/S2213-2600(21)00218-6]

229 **Chen H**, Xie J, Su N, Wang J, Sun Q, Li S, Jin J, Zhou J, Mo M, Wei Y, Chao Y, Hu W, Du B, Qiu H. Corticosteroid Therapy Is Associated With Improved Outcome in Critically Ill Patients With COVID-19 With Hyperinflammatory Phenotype. *Chest* 2021; **159**: 1793-1802 [PMID: 33316235 DOI: 10.1016/j.chest.2020.11.050]

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META-ANALYSIS

Association between early viral lower respiratory tract infections and subsequent asthma development

Sebastien Kenmoe, Etienne Atenguena Okobalemba, Guy Roussel Takuissu, Jean Thierry Ebogo-Belobo, Martin Gael Oyono, Jeannette Nina Magoudjou-Pekam, Ginette Irma Kame-Ngasse, Jean Bosco Taya-Fokou, Chris Andre Mbongue Mikangue, Raoul Kenfack-Momo, Donatien Serge Mbaga, Arnol Bowo-Ngandji, Cyprien Kengne-Ndé, Seraphine Nkie Esemu, Richard Njouom, Lucy Ndip

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Sebastien Kenmoe, Seraphine Nkie Esemu, Lucy Ndip, Department of Microbiology and Parasitology, University of Buea, Buea 00237, Cameroon

Sebastien Kenmoe, Richard Njouom, Department of Virology, Centre Pasteur of Cameroon, Yaounde 00237, Cameroon

Etienne Atenguena Okobalemba, Faculty of Medicine and Biomedical Science, The University of Yaounde I, Yaounde 00237, Cameroon

Guy Roussel Takuissu, Centre of Research in Food, Food Security and Nutrition, Institute of Medical Research and Medicinal Plants Studies, Yaounde 00237, Cameroon

Jean Thierry Ebogo-Belobo, Ginette Irma Kame-Ngasse, Medical Research Centre, Institute of Medical Research and Medicinal Plants Studies, Yaounde 00237, Cameroon

Martin Gael Oyono, Laboratory of Parasitology and Ecology, The University of Yaounde I, Yaounde 00237, Cameroon

Jeannette Nina Magoudjou-Pekam, Raoul Kenfack-Momo, Department of Biochemistry, The University of Yaounde I, Yaounde 00237, Cameroon

Jean Bosco Taya-Fokou, Chris Andre Mbongue Mikangue, Donatien Serge Mbaga, Arnol Bowo-Ngandji, Department of Microbiology, The University of Yaounde I, Yaounde 00237, Cameroon

Cyprien Kengne-Ndé, Epidemiological Surveillance, Evaluation and Research Unit, National Aids Control Committee, Douala 00237, Cameroon

Corresponding author: Sebastien Kenmoe, PhD, Assistant Lecturer, Department of Microbiology and Parasitology, University of Buea, Molyko to Buea Town Rd, Buea 00237, Cameroon. sebastien.kenmoe@ubuea.cm

Abstract

BACKGROUND

The association between hospitalization for human respiratory syncytial virus (HRSV) bronchiolitis in early childhood and subsequent asthma is well

established. The long-term prognosis for non-bronchiolitis lower respiratory tract infections (LRTI) caused by viruses different from HRSV and rhinovirus, on the other hand, has received less interest.

AIM

To investigate the relationship between infant LRTI and later asthma and examine the influence of confounding factors.

METHODS

The PubMed and Global Index Medicus bibliographic databases were used to search for articles published up to October 2021 for this systematic review. We included cohort studies comparing the incidence of asthma between patients with and without LRTI at ≤ 2 years regardless of the virus responsible. The meta-analysis was performed using the random effects model. Sources of heterogeneity were assessed by stratified analyses.

RESULTS

This review included 15 articles (18 unique studies) that met the inclusion criteria. LRTIs at ≤ 2 years were associated with an increased risk of subsequent asthma up to 20 years [odds ratio (OR) = 5.0, 95%CI: 3.3-7.5], with doctor-diagnosed asthma (OR = 5.3, 95%CI: 3.3-8.6), current asthma (OR = 5.4, 95%CI: 2.7-10.6), and current medication for asthma (OR = 1.2, 95%CI: 0.7-3.9). Our overall estimates were not affected by publication bias (P = 0.671), but there was significant heterogeneity [I^2 = 58.8% (30.6-75.5)]. Compared to studies with hospitalized controls without LRTI, those with ambulatory controls had a significantly higher strength of association between LRTIs and subsequent asthma. The strength of the association between LRTIs and later asthma varied significantly by country and age at the time of the interview. The sensitivity analyses including only studies with similar proportions of confounding factors (gender, age at LRTI development, age at interview, gestational age, birth weight, weight, height, smoking exposure, crowding, family history of atopy, and family history of asthma) between cases and controls did not alter the overall estimates.

CONCLUSION

Regardless of the causative virus and confounding factors, viral LRTIs in children < 2 years are associated with an increased risk of developing a subsequent asthma. Parents and pediatricians should be informed of this risk.

Key Words: Asthma; Lower respiratory tract infections; Respiratory viruses; Long term sequelae; Children

Core Tip: The results of this meta-analysis confirmed that viral lower respiratory tract infections (LRTIs) in children < 2 years increase the risk of developing asthma later until the age of 20 years. This indicates that pediatricians and parents should be vigilant with anticipating asthma preventive measures in children with viral LRTIs in childhood.

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INTRODUCTION

Asthma is a major contributor to the burden of non-communicable diseases and the most common chronic respiratory disease in the world[1]. The prevalence of asthma has increased by 12.6% in 25 years (1990-2015), and asthma causes the deaths of nearly half a million people each year[1]. Asthma also represents a considerable financial burden and costs about 19 billion Euros per year in Europe[2].

Multiple factors have been involved in the development of asthma. There is evidence that respiratory viruses, particularly human respiratory syncytial virus (HRSV)[3-7], human metapneumovirus[7-12], or

rhinovirus (RV)[12-22] (including mostly the recently described RV-C), were triggers for asthma and asthma exacerbation. The data also show that air pollutants were involved in the risk of developing asthma[23].

In addition, many studies have historically suggested that neonatal bronchiolitis due to HRSV, and RV recently, is a predisposing factor for asthma development later[3,5,10,24-39]. However, the involvement of other common respiratory viruses (influenza, human coronavirus, human parainfluenza virus) and non-bronchiolitis lower respiratory tract infections (LRTI) in the subsequent risk of developing asthma has not been synthesized to date.

Conflicting findings have been reported regarding the synergistic effect of early-life bronchiolitis and personal or family history of atopic sensitization or asthma, gender, maternal smoking in the onset of asthma later[6,34,40-53]. Some authors have suggested that bronchiolitis identifies children prone to developing asthma during adolescence[26,54-59]. Therefore, the causal role of early-onset bronchiolitis and the mechanisms underlying the development of subsequent asthma remain to be clarified[3,60].

Preventing or stopping the development of predictive factors would be a possible strategy for preventing asthma[61-63]. This systematic review was conducted to describe the risk of developing asthma following viral LRTI in childhood and associated factors. Our secondary objective was to evaluate the role of confounding factors of the association of neonatal LRTI and asthma during childhood using sensitivity analyses.

MATERIALS AND METHODS

Study design

We registered the protocol of this systematic review in the PROSPERO with access number CRD42018116955. This review has been done in accordance with the Centre for Reviews and Dissemination guidelines[64] and presented in accordance with the PRISMA declaration[Supplementary Table 1).

Inclusion and exclusion criteria

We included cohort studies comparing the long-term asthmatic sequelae of children with and without a history of viral LRTI in childhood. The PICOs in this study were: P, children and adults of all genders with a history of viral LRTI in childhood regardless of the virus responsible; I, LRTI at ≤ 2 years; C, children and adults of all genders with no history of viral LRTI in childhood; O, the main outcome was asthma as the long-term sequelae of LRTI in infancy. This study had no temporal, geographic, or linguistic limitations. We excluded irrelevant studies, case reports, cross-sectional studies, comments, reviews, and editorials, studies that did not report outcome of interest, articles that we did not have access to full text, studies without control groups, and studies including only high-risk subjects.

Case definition

The definitions of LRTI have been adapted as described by the authors of the primary studies. Asthma has been defined by three or more episodes of bronchial obstruction. We did not take into account the differentiation of atopic asthma. In this systematic review, several categories of asthma definitions were considered, including: (1) Current doctor-diagnosed asthma; (2) Current self-reported asthma; (3) Current asthma; (4) Asthma in the last 12 mo; and (5) Asthma ever. The warning signs of asthma were considered: (1) Cough; (2) Night cough; and (3) Prolonged cough. The use of anti-asthma treatment was also taken into account: (1) Current medication for asthma; (2) Use of bronchodilators; and (3) Use of inhaled steroid. When a study had multiple defined asthma phenotypes for the same participants, we selected the phenotype according to the order of priority of asthma diagnosed by a doctor, most recent asthma, treatment for asthma, and asthma symptoms.

Search strategy

We searched for relevant articles in PubMed and Global Index Medicus until October 24, 2021. The search keywords are described in Supplementary Table 2. We conducted an additional manual search using Reference Citation Analysis (https://www.referencecitationanalysis.com/) by reviewing the list of references for included articles and relevant reviews on the subject.

Study selection

We (JTEB and SK) have individually reviewed the titles and abstracts of the articles identified through the electronic search in the Rayyan website[66]. We evaluated the complete texts of the eligible articles after screening titles and abstracts. These two authors discussed disagreement about the inclusion or exclusion of an article to reach consent.

Data extraction

Two authors (JETB and SK) independently extracted all relevant data and entered into a standardized

questionnaire. The disagreements were resolved by discussion between the two investigators and consultation of a third author if an agreement could not be reached (AF). The standardized questionnaire included: (1) Title; (2) First author; (3) Year of publication; (4) Time of data collection; (5) Country; (6) Participants interview period; (7) LRTI type; (8) LRTI rank; (9) LRTI period; (10) Age at LRTI; (11) Type of infection associated with the LRTI; (12) Control age; (13) Control gender; (14) Total number of cases and controls; and (15) Numbers with asthma at follow-up and numbers of confounders in case and control groups.

Risk of bias assessment

We (JETB and SK) independently assessed the quality of publications using the Newcastle-Ottawa scale [67]. We assessed several potential sources of bias including patient selection in the study, comparability of groups, and outcome evaluation (Supplementary Table 3). We rated the studies as "low risk of bias" and "high risk of bias" for scores of 6-9 and 0-5, respectively.

Statistical analysis

Odds ratio (OR) was used as a measure of the association between bronchiolitis potential risk factors and bronchiolitis long-term respiratory sequelae. The heterogeneity was evaluated by visual inspection of the funnel diagram, the Q test, and the I^2 statistic[68,69]. Heterogeneity between studies was considered significant for values of $P < 0.1$ and $I^2 > 50\%$. The impact of the quality of the selected studies was evaluated by a sensitivity analysis omitting high risk of bias studies. Subgroup analysis was performed on the basis of the sampling approach, the countries, the age at LRTI development, the age at interview, the hospitalization status of the controls, the viruses responsible for LRTI, the type of LRTI, and the phenotype of asthma. Sensitivity analysis including only studies with the confounding factor proportions similar between cases and controls were carried out as described previously[70].

RESULTS

Overview of included studies

As shown in Figure 1, 875 articles were found in PubMed and Global Index Medicus. A total of 733 publications were excluded after selection according to titles and abstracts. Of the remaining 162 articles, 147 articles were eliminated for multiple reasons (no LRTI negative group, no data on asthma, wrong study design, not viral laboratory confirmed LRTI, and not LRTI, Supplementary Table 4). Based on the inclusion criteria, 15 comparative publications (18 unique studies) were finally selected for this systematic review[71-85].

Study characteristics

The characteristics and risk of bias of the 18 unique studies are summarized in Supplementary Tables 5-7. All studies were published from 1982 to 2018 and were conducted on children and adults between < 9 mo and 20 years of age. LRTIs were dominated by bronchiolitis (83.3%) and were recorded between 1967 and 2005. The authors of 61.1% of the studies reported that children had their first episode of LRTI and all children with LRTI were hospitalized. The majority of children recruited in the studies were < 2 years or < 1 year at the time of the LRTI in childhood (88.9%). Most studies presented a low risk of bias (77.8%) and were conducted in Europe (88.9%) with prospective follow-up (94.4%) of children included. All included articles were written in English and from high-income countries. The virus mainly reported in the studies was HRSV (83.3%).

Overall prevalence and sensitivity analysis of asthma in the LRTI group and controls

Compared to controls, most children in the LRTI group had subsequent asthma [OR = 5.0, 95%CI: 3.3-7.5], including doctor-diagnosed asthma (OR = 5.3, 95%CI: 3.3-8.6), current asthma (OR = 5.4, 95%CI: 2.7-10.6), and current medication for asthma (OR = 1.2, 95%CI: 0.7-3.9) (Figure 2). Sensitivity analyses including studies based on the first episode of LRTI (OR = 4.6, 95%CI: 2.6-8.1), doctor-diagnosed asthma (OR = 5.3, 95%CI: 3.3-8.6), and studies with low risk of bias (OR = 4.5, 95%CI: 2.9-7.2) showed conclusions consistent with overall analyses (Table 1). For the studies that reported confounding factors, we illustrated the definitions in Supplementary Tables 8 and 9. Qualitative confounders included gender, preterm birth, smoking exposure, crowding, family history of atopy, and family history of asthma. Quantitative confounders included age at LRTI development, age at interview, birth weight, gestational age, number of siblings, weight, and height. The association between LRTI and subsequent asthma was also maintained in all sensitivity analyses including more than two studies with confounding factor proportions similar between cases and controls, notably for male gender, weight, height, age, presence of pets in the home, family history of atopy, family history of asthma, and exposure to smoke.

Table 1 Asthma in children with and without viral lower respiratory tract infections in infancy and control without respiratory diseases

Asthma	OR (95%CI)	95% prediction interval	Studies, *n*	LRTI cases, *n*	Controls, *n*	H (95%CI)	I^2 (95%CI)	*P* value, heterogeneity	*P* value, Egger's test
Overall	5 (3.3-7.5)	(1.2-20.3)	18	906	9632	1.6 (1.2-2.0)	58.8 (30.6-75.5)	0.001	0.671
Sensitivity analyses									
First episode of LRTI	4.6 (2.6-8.1)	(0.8-27.1)	11	725	9199	1.7 (1.3-2.4)	67 (37.7-82.5)	0.001	0.974
Doctor-diagnosed asthma	5.3 (3.3-8.6)	(1.4-19.7)	10	571	9057	1.6 (1.1-2.2)	59.3 (18.4-79.7)	0.008	0.822
Low risk of bias	4.5 (2.9-7.2)	(1.1-18.2)	14	732	1441	1.5 (1.1-2.0)	54.5 (16.9-75.1)	0.007	0.873
Asthma in father	12.5 (4.9-31.9)	NA	2	55	60	1	0	0.741	NA
Asthma in mother	12.5 (4.9-31.9)	NA	2	55	60	1	0	0.741	NA
Asthma in parents	10.6 (5.4-20.9)	(2.4-47.1)	4	186	370	1 (1.0-2.6)	0 (0-84.7)	0.653	0.034
Asthma in siblings	12.5 (4.9-31.9)	NA	2	55	60	1	0	0.741	NA
Atopy in father	12.5 (4.9-31.9)	NA	2	55	60	1	0	0.741	NA
Atopy in mother	6.1 (4.1-8.9)	(0.5-72.6)	3	213	577	1.2 (1.0-3.7)	30.6 (0-92.8)	0.237	0.358
Atopy in parents	9.1 (4.7-17.5)	(3.1-26.4)	5	200	375	1.1 (1.0-2.3)	11.2 (0-81.5)	0.342	0.233
Atopy in siblings	14.9 (3.7-58.9)	NA	1	23	30	NA	NA	1	NA
Current allergy	2.3 (0.9-5.8)	NA	1	35	64	NA	NA	1	NA
Current eczema	2.3 (0.9-5.8)	NA	1	35	64	NA	NA	1	NA
Family history of asthma	14.9 (4.9-45.4)	NA	2	93	183	1	0	0.496	NA
Family history of atopy	14.9 (4.9-45.4)	NA	2	93	183	1	0	0.496	NA
Family smoking	14.6 (5.9-36.2)	(0-5178.5)	3	140	278	1 (1.0-3.1)	0 (0-89.6)	0.781	0.349
Father smoking	12.5 (4.9-31.9)	NA	2	55	60	1	0	0.741	NA
Father smoking, time of study	1.2 (0.4-3.9)	NA	1	130	111	NA	NA	1	NA
Heredity for asthma	13.9 (2.9-65.8)	NA	1	47	93	NA	NA	1	NA
Heredity for atopy	13.9 (2.9-65.8)	NA	1	47	93	NA	NA	1	NA
History of atopic dermatitis	1.2 (0.4-4.0)	NA	1	37	37	NA	NA	1	NA
Male gender	5.3 (3.9-7.2)	(3.6-7.8)	8	451	945	1.3 (1.0-2.0)	44.3 (0-75.3)	0.084	0.913
Mother smoking	12.5 (4.9-31.9)	NA	2	55	60	1	0	0.741	NA
Mother smoking, 10 yr before	1.2 (0.4-3.9)	NA	1	130	111	NA	NA	1	NA
Parental smoking	2.3 (0.9-	NA	1	35	64	NA	NA	1	NA

	5.8)								
Pets at home	6.5 (3.9-11.0)	(1.8-24.3)	7	482	965	1.4 (1.0-2.2)	50.8 (0-79.1)	0.058	0.934
Positive airway responsiveness	1.2 (0.4-4.0)	NA	1	37	37	NA	NA	1	NA
Positive skin prick test	1.2 (0.4-4.0)	NA	1	37	37	NA	NA	1	NA
Prematurity	10.8 (3.0-38.7)	NA	1	32	30	NA	NA	1	NA
Running water	3.9 (1.8-8.6)	NA	1	95	113	NA	NA	1	NA
Siblings in the house	2.3 (0.9-5.8)	NA	1	35	64	NA	NA	1	NA
Single heredity for asthma	28.1 (3.5-225.7)	NA	1	47	93	NA	NA	1	NA
Single heredity for atopy	28.1 (3.5-225.7)	NA	1	47	93	NA	NA	1	NA
Smoke exposure	5.1 (3.6-7.2)	(0.5-49.0)	3	299	722	1 (1.0-3.1)	0 (0-89.6)	0.665	0.801
Wheeze the first 5 yr of life	1.2 (0.4-4.0)	NA	1	37	37	NA	NA	1	NA
Age at interview (yr)	1.1 (0.1-13.8)	NA	1	14	5	NA	NA	1	NA
Age at recruitment (mo)	12.5 (4.9-31.9)	NA	2	55	60	1	0	0.741	NA
Gestational age (wk)	5.2 (3.4-8.0)	NA	1	158	517	NA	NA	1	NA
Height at age 6 (cm)	5.2 (3.4-8.0)	NA	1	158	517	NA	NA	1	NA
Height at interview (cm)	9.4 (4.6-19.3)	(0.1-1002.0)	3	139	277	1 (1.0-3.1)	0 (0-89.6)	0.711	0.194
Number of siblings	17.9 (5.1-62.2)	NA	2	94	186	1	0	0.596	NA
Weight at age 6 (kg)	5.2 (3.4-8.0)	NA	1	158	517	NA	NA	1	NA
Weight at interview (kg)	14.6 (5.9-36.2)	(0-5178.5)	3	140	278	1 (1.0-3.1)	0 (0-89.6)	0.781	0.349

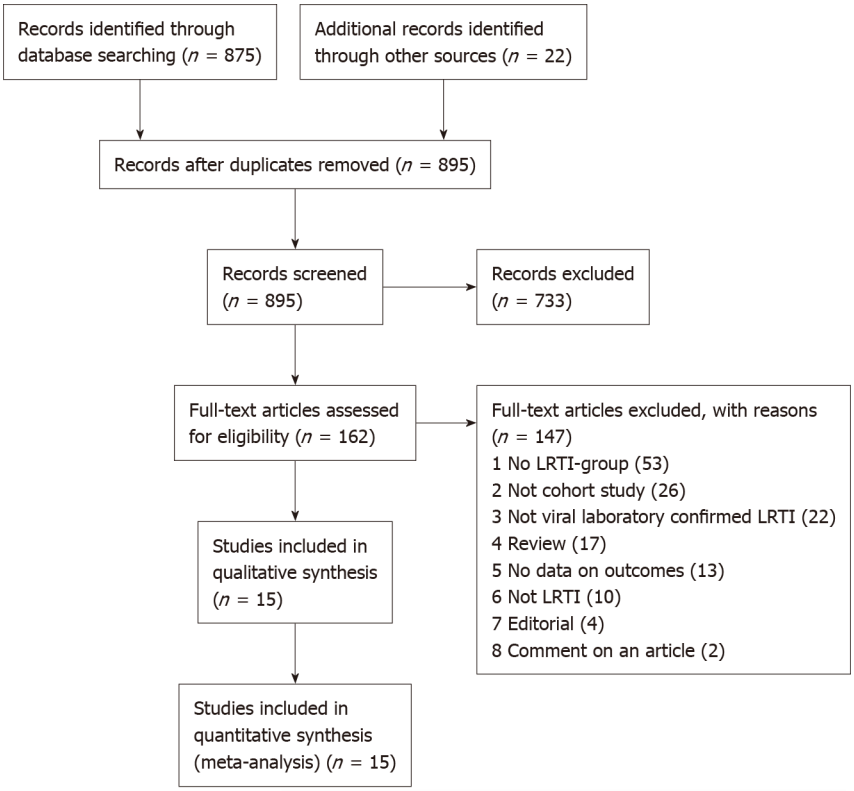
LRTI: Lower respiratory tract infection; OR: Odds ratio; NA: Not applicable.

Subgroup analysis

The subgroup analyses are displayed in Supplementary Table 10. The strength of the association between LRTI and asthma was significantly stronger for studies with probabilistic than non-probabilistic recruitment [OR = 4.5 (3.0-6.8) *vs* OR = 12.5 (4.9-31.9), P = 0.048]. The strength of association between LRTI and subsequent asthma also varied significantly among countries (P < 0.001). Age at follow-up was related to the strength of the association between LRTI in childhood and the development of asthma later (P = 0.005). The association of asthma with LRTI in childhood was higher in studies with hospitalized controls (OR = 14.2, 95%CI: 6.7-30.1) compared to studies with ambulatory controls (OR = 3.9, 95%CI: 2.3-6.6) and was statistically significant (P = 0.006). Other parameters including the age of LRTI development, the virus detected in children with LRTI, the type of LRTI, and the phenotype of asthma did not significantly influence the strength of the association between LRTI and subsequent asthma.

Heterogeneity and publication bias

Using visual inspection, the asymmetry distribution of the funnel graph was used to check for publication bias. We observed no publication bias by the funnel graph (Supplementary Figure 1). The P = 0.671 of the Egger regression test also indicated an absence of publication bias. We recorded a substantial heterogeneity [I^2 = 58.8 (30.6-75.5)] in the overall estimates (Table 1).



DOI: 10.5492/wjccm.v11.i4.298

Figure 1 Study selection. LRTI: Lower respiratory tract infection.

DISCUSSION

We have two main results in this meta-analysis: (1) By taking into account multiple confounding factors including gender, age at LRTI development, age at interview, gestational age, birth weight, weight, height, smoking exposure, overcrowding, and family history of atopy/asthma, this meta-analysis suggests that LRTI due to several viruses in children < 2 years is significantly associated with an increased risk of asthma up to 20 years later; and (2) This increased risk of developing asthma was present regardless of the virus detected in LRTI and the type of LRTI.

Our findings are correlated with similar systematic reviews previously conducted[44,86-89]. Kneyber *et al*[44] reported in a quantitative analysis in 2001 the increased risk of asthma in hospitalized children for bronchiolitis episodes due to HRSV at less than 1 year compared to controls. The systematic review by Pérez-Yarza *et al*[88] analyzed 8 published studies from 1985 to 2006 and found a positive association between HRSV respiratory infections at less than 3 years of age and the risk of subsequent physician-diagnosed asthma development. Régnier *et al*[89] in 2013 showed in a review of 15 studies published from 1977 to 2012 that hospitalizations with HRSV at less than 3 years were correlated significantly with a risk of developing a parent or physician-diagnosed asthma in the 12 mo preceding follow-up. Fauroux *et al*[86], in a systematic review without meta-analysis conducted in 2017 on studies published between 1995 and 2015 and conducted in Western countries, also reported increased risk of developing asthma following hospitalizations due to severe HRSV LRTI registered at less than 3 years. Liu *et al*[87] also reported in 2017 in a review of 15 studies published between 1988 and 2017 that wheezing due to RV predisposed children at high risk of asthma later[87]. In this study, the definitions of asthma were prioritized in order of decreasing priority: doctor-diagnosed asthma *vs* parent-diagnosed asthma and current asthma *vs* asthma during the previous year *vs* asthma at any time.

In a review published by Edmond *et al*[90] in 2012, no association was observed between childhood pneumonia and the development of subsequent asthma. Most studies on the association between viral LRTIs and the subsequent development of asthma have focused primarily on bronchiolitis such as LRTI. Early studies show that HRSV infections were associated with increased risk of asthma[44,86,88,89]. In this systematic review, regardless of the virus responsible for bronchiolitis in childhood, the association remained with asthma later. The risk was higher in non-HRSV viruses and more specifically in human metapneumovirus and RV, suggesting that the development of asthma after bronchiolitis in childhood is not different depending on the type of virus detected in the LRTI. This result is consistent with the meta-analysis of Liu *et al*[87], who had shown that childhood RV infections predisposed to the risk of developing asthma later. The systematic review by Fauroux *et al*[86] found that infections with non-HRSV respiratory viruses (influenza A, human bocavirus, human parainfluenza virus-3, human

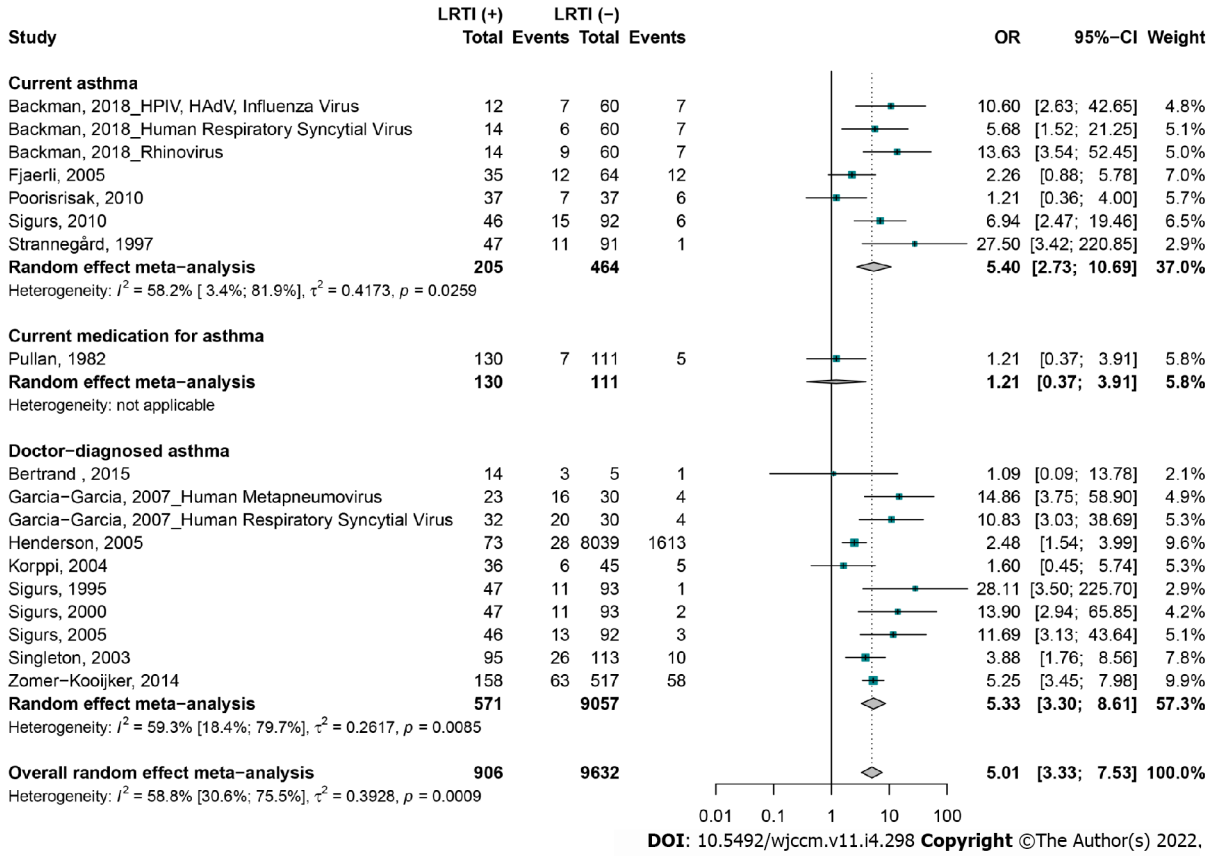


Figure 2 Forest plot of asthma in children with and without viral lower respiratory tract infections in infancy. LRTI: Lower respiratory tract infection; OR: Odds ratio.

adenovirus, human metapneumovirus, and unknown etiology) were associated with a higher risk of subsequent asthma than HRSV.

The attribution of the causal role of preschool or adult asthma to bronchiolitis remains a subject of debate[91]. Several other factors such as female sex, passive smoking, overweight, low weight at birth, premature birth, or family history of atopy have been proposed as factors associated with asthma at school age[24,92-97]. Breastfeeding was also reported as a protective factor against asthma as a result of bronchiolitis in childhood[58,98]. These multiple other risk factors could interact additively with bronchiolitis to promote the development of asthma[45]. This meta-analysis appropriately assessed for the first time the confounders of the relationship between bronchiolitis in childhood and asthma later. This meta-analysis revealed that bronchiolitis is independently associated with subsequent asthma.

In this systematic review, we followed a rigorous methodology according to the PRISMA guidelines and applied a very sensitive research strategy accompanied by a very intensive manual search. We carefully collected and shared the individual data from the included studies and gave the individual reasons for exclusion of all articles examined entirely. We have explored and explained almost all sources of heterogeneity. The multiple sensitivity analyses gave consistent results with the overall results.

However, some methodological weaknesses must be considered in interpreting the results of this study and in future research on the subject. First, some subgroup analyses were probably limited by the small number of studies, particularly the non-bronchiolitis and non-HRSV studies. Apart from these areas eligible for improvement, future work should focus on assessing the sequelae of non-bronchiolitis LRTI with non-HRSV etiology, particularly in low income countries (Africa and Southeast Asia) where the data suggested that asthma could be associated with a significant burden[99]. Another potential limitation of this review would be the absence of data in the included studies concerning the type of asthma observed, which could be allergic asthma or not.

CONCLUSION

In conclusion, the current meta-analysis has shown that viral LRTI at ≤ 2 years, independently of the detected virus, is a predictive factor of asthma sequelae up to the age of 20. Health care workers and parents should be aware of these findings when managing viral LRTI in childhood.

ARTICLE HIGHLIGHTS

Research background

We performed a literature search in PubMed and Global Index Medicus in December 2019 using keywords covering low respiratory tract infections AND common respiratory viruses AND asthma. The results of our research depicted in original articles, narrative reviews, and systematic reviews suggesting that human respiratory syncytial virus (HRSV) and rhinovirus (RV) bronchiolitis in childhood are associated with an increased risk of asthma later. This research also identified conflicting data on the influence of confounding factors on the high risk of developing asthma after bronchiolitis in childhood. It has also emerged from this research that the involvement of lower respiratory tract infections (LRTI) other than bronchiolitis and respiratory viruses other than HRSV and RV in the subsequent risk of asthma remains hypothetical to date.

Research motivation

Taking into account confounding factors, the influence of respiratory infections other than bronchiolitis in childhood and respiratory viruses other than HRSV and RV should be weighed against the risk of developing subsequent asthma.

Research objectives

This study was conducted to assess the influence of viral LRTI at < 2 years on the risk of subsequent asthma development.

Research methods

This meta-analysis included cohort studies with viral LRTI at < 2 years as exposure and asthma as outcome. R software version 4.1.0 was used to calculate the odds ratios and their 95%CI using a random-effects model.

Research results

This study included 15 articles and demonstrated the implications of childhood viral LRTI in the risk of subsequent asthma development up to the age of 20 (odds ratio = 5.0, 95%CI: 3.3-7.5). This risk of developing asthma was not influenced in sensitivity analyses including only confounding factors with similar proportions between exposed and unexposed. The estimates were not affected by publication bias, but there was significant heterogeneity.

Research conclusions

Childhood viral LRTIs, primarily HRSV bronchiolitis, are significantly associated with a risk of developing asthma later in life.

Research perspectives

To curb the heavy burden of asthma in patients of all ages, we hope that the results of this review will encourage the implementation of a sensitization program for this association of viral LRTI in childhood and the subsequent asthma risk. Interventional studies are needed to involve the causality relationship between neonatal viral LRTI and the subsequent risk of asthma.

FOOTNOTES

Author contributions: Kenmoe S, Ndip L, and Njouom R were responsible for conception and design of the study as well as project administration; Kenmoe S, Atenguena Okobalemba E, Takuissu GR, Ebogo-Belobo JT, Oyono MG, Magoudjou-Pekam JN, Kame-Ngasse GI, Taya-Fokou JB, Mbongue Mikangue CA, Kenfack-Momo R, Fall A, Mbaga DS, Bowo-Ngandji A, Kengne-Nde C, and Esemu SN were responsible for the data curation and interpretation of results; Kengne-Nde C and Kenmoe S were responsible for statistical analysis; Kenmoe S, Ndip L, and Njouom R were responsible for the project supervision; Kenmoe S wrote the original draft; All authors critically reviewed the first draft and approved the final version of the paper for submission and have read and approved the final manuscript.

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Country/Territory of origin: Cameroon

ORCID number: Sebastien Kenmoe 0000-0002-5536-080X; Etienne Atenguena Okobalemba 0000-0003-1556-4389; Guy Roussel Takuissu 0000-0002-7478-4165; Jean Thierry Ebogo-Belobo 0000-0002-4057-889X; Martin Gael Oyono 0000-0002-0990-4087; Jeannette Nina Magoudjou-Pekam 0000-0003-0176-6174; Ginette Irma Kame-Ngasse 0000-0003-1410-5156; Jean Bosco Taya-Fokou 0000-0003-1383-885X; Chris Andre Mbongue Mikangue 0000-0001-9131-6438; Raoul Kenfack-Momo 0000-0003-2827-628X; Donatien Serge Mbaga 0000-0002-9496-0445; Arnol Bowo-Ngandji 0000-0003-4463-1018; Cyprien Kengne-Ndé 0000-0002-8338-2221; Seraphine Nkie Esemu 0000-0003-2497-4689; Richard Njouom 0000-0003-3112-6370; Lucy Ndip 0000-0003-3511-6049.

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REFERENCES

1 **GBD 2015 Chronic Respiratory Disease Collaborators**. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 2017; **5**: 691-706 [PMID: 28822787 DOI: 10.1016/S2213-2600(17)30293-X]
2 **Domínguez-Ortega J**, Phillips-Anglés E, Barranco P, Quirce S. Cost-effectiveness of asthma therapy: a comprehensive review. *J Asthma* 2015; **52**: 529-537 [PMID: 25539023 DOI: 10.3109/02770903.2014.999283]
3 **Bartlett NW**, McLean GR, Chang YS, Johnston SL. Genetics and epidemiology: asthma and infection. *Curr Opin Allergy Clin Immunol* 2009; **9**: 395-400 [PMID: 19644362 DOI: 10.1097/ACI.0b013e32833066fa]
4 **Brunetti L**, Colazzo D, Francavilla R, Tesse R, De Sario V, Lorè M, Armenio L. The role of pulmonary infection in pediatric asthma. *Allergy Asthma Proc* 2007; **28**: 190-193 [PMID: 17479603 DOI: 10.2500/aap.2007.28.2964]
5 **Busse WW**, Lemanske RF Jr, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet* 2010; **376**: 826-834 [PMID: 20816549 DOI: 10.1016/S0140-6736(10)61380-3]
6 **Emuzyte R**, Firantiene R, Petraityte R, Sasnauskas K. Human rhinoviruses, allergy, and asthma: a clinical approach. *Medicina (Kaunas)* 2009; **45**: 839-847 [PMID: 20051716]
7 **Gavala ML**, Bertics PJ, Gern JE. Rhinoviruses, allergic inflammation, and asthma. *Immunol Rev* 2011; **242**: 69-90 [PMID: 21682739 DOI: 10.1111/j.1600-065X.2011.01031.x]
8 **Gern JE**. Rhinovirus and the initiation of asthma. *Curr Opin Allergy Clin Immunol* 2009; **9**: 73-78 [PMID: 19532096 DOI: 10.1097/ACI.0b013e32831f8f1b]
9 **Heymann PW**, Platts-Mills TA, Johnston SL. Role of viral infections, atopy and antiviral immunity in the etiology of wheezing exacerbations among children and young adults. *Pediatr Infect Dis J* 2005; **24**: S217-S222, discussion S220 [PMID: 16378049 DOI: 10.1097/01.inf.0000188164.33856.f9]
10 **Jackson DJ**. The role of rhinovirus infections in the development of early childhood asthma. *Curr Opin Allergy Clin Immunol* 2010; **10**: 133-138 [PMID: 19996738 DOI: 10.1097/ACI.0b013e3283352f7c]
11 **Kalina WV**, Gershwin LJ. Progress in defining the role of RSV in allergy and asthma: from clinical observations to animal models. *Clin Dev Immunol* 2004; **11**: 113-119 [PMID: 15330446 DOI: 10.1080/10446670410001722131]
12 **Kumar A**, Grayson MH. The role of viruses in the development and exacerbation of atopic disease. *Ann Allergy Asthma Immunol* 2009; **103**: 181-6; quiz 186 [PMID: 19788013 DOI: 10.1016/S1081-1206(10)60178-0]
13 **Garcia-Garcia ML**, Calvo Rey C, Del Rosal Rabes T. Pediatric Asthma and Viral Infection. *Arch Bronconeumol* 2016; **52**: 269-273 [PMID: 26766408 DOI: 10.1016/j.arbres.2015.11.008]
14 **Message SD**, Johnston SL. Viruses in asthma. *Br Med Bull* 2002; **61**: 29-43 [PMID: 11997297 DOI: 10.1093/bmb/61.1.29]
15 **Miller EK**, Mackay IM. From sneeze to wheeze: what we know about rhinovirus Cs. *J Clin Virol* 2013; **57**: 291-299 [PMID: 23714395 DOI: 10.1016/j.jcv.2013.04.015]
16 **Papadopoulos NG**, Kalobatsou A. Respiratory viruses in childhood asthma. *Curr Opin Allergy Clin Immunol* 2007; **7**: 91-95 [PMID: 17218817 DOI: 10.1097/ACI.0b013e328013d501]
17 **Piedimonte G**. Respiratory syncytial virus and asthma: speed-dating or long-term relationship? *Curr Opin Pediatr* 2013; **25**: 344-349 [PMID: 23657245 DOI: 10.1097/MOP.0b013e328360bd2e]
18 **Proud D**. Role of rhinovirus infections in asthma. *Asian Pac J Allergy Immunol* 2011; **29**: 201-208 [PMID: 22053589]
19 **Rossi GA**, Colin AA. Infantile respiratory syncytial virus and human rhinovirus infections: respective role in inception and persistence of wheezing. *Eur Respir J* 2015; **45**: 774-789 [PMID: 25359340 DOI: 10.1183/09031936.00062714]
20 **Singh AM**, Moore PE, Gern JE, Lemanske RF Jr, Hartert TV. Bronchiolitis to asthma: a review and call for studies of gene-virus interactions in asthma causation. *Am J Respir Crit Care Med* 2007; **175**: 108-119 [PMID: 17053206 DOI: 10.1164/rccm.200603-435PP]
21 **Song DJ**. Rhinovirus and childhood asthma: an update. *Korean J Pediatr* 2016; **59**: 432-439 [PMID: 27895690 DOI: 10.3345/kjp.2016.59.11.432]
22 **Tan WC**. Viruses in asthma exacerbations. *Curr Opin Pulm Med* 2005; **11**: 21-26 [PMID: 15591884 DOI: 10.1097/01.mcp.0000146781.11092.0d]

23 **Arruda LK**, Solé D, Baena-Cagnani CE, Naspitz CK. Risk factors for asthma and atopy. *Curr Opin Allergy Clin Immunol* 2005; **5**: 153-159 [PMID: 15764906 DOI: 10.1097/01.all.0000162308.89857.6c]

24 **Goksör E**, Amark M, Alm B, Gustafsson PM, Wennergren G. Asthma symptoms in early childhood--what happens then? *Acta Paediatr* 2006; **95**: 471-478 [PMID: 16720497 DOI: 10.1080/08035250500499440]

25 **Henry RL**, Hodges IG, Milner AD, Stokes GM. Respiratory problems 2 years after acute bronchiolitis in infancy. *Arch Dis Child* 1983; **58**: 713-716 [PMID: 6625633 DOI: 10.1136/adc.58.9.713]

26 **Hyvärinen M**, Piippo-Savolainen E, Korhonen K, Korppi M. Teenage asthma after severe infantile bronchiolitis or pneumonia. *Acta Paediatr* 2005; **94**: 1378-1383 [PMID: 16263629 DOI: 10.1080/08035250510046812]

27 **Hyvärinen MK**, Kotaniemi-Syrjänen A, Reijonen TM, Korhonen K, Korppi MO. Teenage asthma after severe early childhood wheezing: an 11-year prospective follow-up. *Pediatr Pulmonol* 2005; **40**: 316-323 [PMID: 16082689 DOI: 10.1002/ppul.20273]

28 **Jartti T**, Korppi M. Rhinovirus-induced bronchiolitis and asthma development. *Pediatr Allergy Immunol* 2011; **22**: 350-355 [PMID: 21535176 DOI: 10.1111/j.1399-3038.2011.01170.x]

29 **Koponen P**, Helminen M, Paassilta M, Luukkaala T, Korppi M. Preschool asthma after bronchiolitis in infancy. *Eur Respir J* 2012; **39**: 76-80 [PMID: 21700604 DOI: 10.1183/09031936.00040211]

30 **Korppi M**, Reijonen T, Pöysä L, Juntunen-Backman K. A 2- to 3-year outcome after bronchiolitis. *Am J Dis Child* 1993; **147**: 628-631 [PMID: 8506829 DOI: 10.1001/archpedi.1993.02160300034017]

31 **Kotaniemi-Syrjänen A**, Reijonen TM, Korhonen K, Korppi M. Wheezing requiring hospitalization in early childhood: predictive factors for asthma in a six-year follow-up. *Pediatr Allergy Immunol* 2002; **13**: 418-425 [PMID: 12485317 DOI: 10.1034/j.1399-3038.2002.02091.x]

32 **Lauhkonen E**, Koponen P, Nuolivirta K, Paassilta M, Toikka J, Korppi M. Lung function by impulse oscillometry at age 5-7 years after bronchiolitis at age 0-6 months. *Pediatr Pulmonol* 2015; **50**: 389-395 [PMID: 24668616 DOI: 10.1002/ppul.23039]

33 **Lemanske RF Jr**. The childhood origins of asthma (COAST) study. *Pediatr Allergy Immunol* 2002; **13**: 38-43 [PMID: 12688623 DOI: 10.1034/j.1399-3038.13.s.15.8.x]

34 **Piippo-Savolainen E**, Korppi M. Wheezy babies--wheezy adults? *Acta Paediatr* 2008; **97**: 5-11 [PMID: 18052998 DOI: 10.1111/j.1651-2227.2007.00558.x]

35 **Reijonen TM**, Korppi M, Kuikka L, Savolainen K, Kleemola M, Mononen I, Remes K. Serum eosinophil cationic protein as a predictor of wheezing after bronchiolitis. *Pediatr Pulmonol* 1997; **23**: 397-403 [PMID: 9220520 DOI: 10.1002/(sici)1099-0496(199706)23:6<397::aid-ppul1>3.0.co;2-g]

36 **Stern DA**, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. *Lancet* 2008; **372**: 1058-1064 [PMID: 18805334 DOI: 10.1016/S0140-6736(08)61447-6]

37 **Törmänen S**, Lauhkonen E, Saari A, Koponen P, Korppi M, Nuolivirta K. Excess weight in preschool children with a history of severe bronchiolitis is associated with asthma. *Pediatr Pulmonol* 2015; **50**: 424-430 [PMID: 24753502 DOI: 10.1002/ppul.23053]

38 **Valkonen H**, Waris M, Ruohola A, Ruuskanen O, Heikkinen T. Recurrent wheezing after respiratory syncytial virus or non-respiratory syncytial virus bronchiolitis in infancy: a 3-year follow-up. *Allergy* 2009; **64**: 1359-1365 [PMID: 19416146 DOI: 10.1111/j.1398-9995.2009.02022.x]

39 **Wennergren G**, Kristjánsson S. Relationship between respiratory syncytial virus bronchiolitis and future obstructive airway diseases. *Eur Respir J* 2001; **18**: 1044-1058 [PMID: 11829086 DOI: 10.1183/09031936.01.00254101]

40 **Almqvist C**, Worm M, Leynaert B; working group of GA2LEN WP 2. 5 Gender. Impact of gender on asthma in childhood and adolescence: a GA2LEN review. *Allergy* 2008; **63**: 47-57 [PMID: 17822448 DOI: 10.1111/j.1398-9995.2007.01524.x]

41 **Bont L**, Aalderen WM, Kimpen JL. Long-term consequences of respiratory syncytial virus (RSV) bronchiolitis. *Paediatr Respir Rev* 2000; **1**: 221-227 [PMID: 12531083 DOI: 10.1053/prrv.2000.0052]

42 **Everard ML**. The relationship between respiratory syncytial virus infections and the development of wheezing and asthma in children. *Curr Opin Allergy Clin Immunol* 2006; **6**: 56-61 [PMID: 16505613 DOI: 10.1097/01.all.0000200506.62048.06]

43 **Holt PG**, Strickland DH, Sly PD. Virus infection and allergy in the development of asthma: what is the connection? *Curr Opin Allergy Clin Immunol* 2012; **12**: 151-157 [PMID: 22356945 DOI: 10.1097/ACI.0b013e3283520166]

44 **Kneyber MCJ**, Steyerberg EW, de Groot R, Moll HA. Long-term effects of respiratory syncytial virus (RSV) bronchiolitis in infants and young children: a quantitative review. *Acta Paediatr* 2000; **89**: 654-660 [PMID: 10914957 DOI: 10.1080/080352500750043945]

45 **Kusel MM**, de Klerk NH, Kebadze T, Vohma V, Holt PG, Johnston SL, Sly PD. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol* 2007; **119**: 1105-1110 [PMID: 17353039 DOI: 10.1016/j.jaci.2006.12.669]

46 **Le Souëf PN**. Gene-environmental interaction in the development of atopic asthma: new developments. *Curr Opin Allergy Clin Immunol* 2009; **9**: 123-127 [PMID: 19295429 DOI: 10.1097/ACI.0b013e3283292283]

47 **Lemanske RF**. Viral infections and asthma inception. *J Allergy Clin Immunol* 2004; 114: 1023-1026 [PMID: 15536404 DOI: 10.1016/j.jaci.2004.08.031]

48 **Lemanske RF Jr**. Issues in understanding pediatric asthma: epidemiology and genetics. *J Allergy Clin Immunol* 2002; **109**: S521-S524 [PMID: 12063507 DOI: 10.1067/mai.2002.124564]

49 **Martinez FD**. Development of wheezing disorders and asthma in preschool children. *Pediatrics* 2002; **109**: 362-367 [PMID: 11826251]

50 **Puddu M**, Fanos V. Respiratory syncytial virus infection and recurrent wheezing: what next? *J Chemother* 2007; **19** Suppl 2: 8-11 [PMID: 18073170 DOI: 10.1080/1120009x.2007.11782434]

51 **Saglani S**. Viral infections and the development of asthma in children. *Ther Adv Infect Dis* 2013; **1**: 139-150 [PMID: 25165549 DOI: 10.1177/2049936113497202]

52 **Sly PD**, Kusel M, Holt PG. Do early-life viral infections cause asthma? *J Allergy Clin Immunol* 2010; **125**: 1202-1205 [PMID: 20304476 DOI: 10.1016/j.jaci.2010.01.024]

53 **Soto-Quiros M**, Avila L, Platts-Mills TA, Hunt JF, Erdman DD, Carper H, Murphy DD, Odio S, James HR, Patrie JT, Hunt W, O'Rourke AK, Davis MD, Steinke JW, Lu X, Kennedy J, Heymann PW. High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus. *J Allergy Clin Immunol* 2012; **129**: 1499-1505.e5 [PMID: 22560151 DOI: 10.1016/j.jaci.2012.03.040]

54 **Godfrey S**. Bronchiolitis and asthma in infancy and early childhood. *Thorax* 1996; **51** Suppl 2: S60-S64 [PMID: 8869355 DOI: 10.1136/thx.51.suppl_2.s60]

55 **Mikalsen IB**, Halvorsen T, Eide GE, Øymar K. Severe bronchiolitis in infancy: can asthma in adolescence be predicted? *Pediatr Pulmonol* 2013; **48**: 538-544 [PMID: 22976850 DOI: 10.1002/ppul.22675]

56 **Rhodes HL**, Thomas P, Sporik R, Holgate ST, Cogswell JJ. A birth cohort study of subjects at risk of atopy: twenty-two-year follow-up of wheeze and atopic status. *Am J Respir Crit Care Med* 2002; **165**: 176-180 [PMID: 11790650 DOI: 10.1164/ajrccm.165.2.2104032]

57 **Rhodes HL**, Sporik R, Thomas P, Holgate ST, Cogswell JJ. Early life risk factors for adult asthma: a birth cohort study of subjects at risk. *J Allergy Clin Immunol* 2001; **108**: 720-725 [PMID: 11692095 DOI: 10.1067/mai.2001.119151]

58 **Rylander E**, Eriksson M, Freyschuss U. Risk factors for occasional and recurrent wheezing after RSV infection in infancy. *Acta Paediatr Scand* 1988; **77**: 711-715 [PMID: 3201977 DOI: 10.1111/j.1651-2227.1988.tb10735.x]

59 **Wennergren G**, Amark M, Amark K, Oskarsdóttir S, Sten G, Redfors S. Wheezing bronchitis reinvestigated at the age of 10 years. *Acta Paediatr* 1997; **86**: 351-355 [PMID: 9174218 DOI: 10.1111/j.1651-2227.1997.tb09021.x]

60 **Walton RP**, Johnston SL. Role of respiratory viral infections in the development of atopic conditions. *Curr Opin Allergy Clin Immunol* 2008; **8**: 150-153 [PMID: 18317024 DOI: 10.1097/ACI.0b013e3282f889df]

61 **Simoes EA**, Groothuis JR, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick LM, Kimpen JL; Palivizumab Long-Term Respiratory Outcomes Study Group. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. *J Pediatr* 2007; **151**: 34-42, 42.e1 [PMID: 17586188 DOI: 10.1016/j.jpeds.2007.02.032]

62 **Yoshihara S**, Kusuda S, Mochizuki H, Okada K, Nishima S, Simões EA; C-CREW Investigators. Effect of palivizumab prophylaxis on subsequent recurrent wheezing in preterm infants. *Pediatrics* 2013; **132**: 811-818 [PMID: 24127479 DOI: 10.1542/peds.2013-0982]

63 **Edell D**, Khoshoo V, Ross G, Salter K. Early ribavarin treatment of bronchiolitis: effect on long-term respiratory morbidity. *Chest* 2002; **122**: 935-939 [PMID: 12226035 DOI: 10.1378/chest.122.3.935]

64 **Centers for Reviews and Dissemination**. CRD's guidance for undertaking reviews in 301 healthcare: centers for reviews and dissemination. England: York Associates

65 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097 [PMID: 19621072 DOI: 10.1371/journal.pmed.1000097]

66 **Ouzzani M**, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016; **5**: 210 [PMID: 27919275 DOI: 10.1186/s13643-016-0384-4]

67 **Hoy D**, Brooks P, Woolf A, Blyth F, March L, Bain C, Baker P, Smith E, Buchbinder R. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol* 2012; **65**: 934-939 [PMID: 22742910 DOI: 10.1016/j.jclinepi.2011.11.014]

68 **Higgins JP**, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539-1558 [PMID: 12111919 DOI: 10.1002/sim.1186]

69 **Cochran WG**. The Combination of Estimates from Different Experiments. *Biometrics* 1954; **10**: 101-129 [DOI: 10.2307/3001666]

70 **Kenmoe S**, Bowo-Ngandji A, Kengne-Nde C, Ebogo-Belobo JT, Mbaga DS, Mahamat G, Demeni Emoh CP, Njouom R. Association between early viral LRTI and subsequent wheezing development, a meta-analysis and sensitivity analyses for studies comparable for confounding factors. *PLoS One* 2021; **16**: e0249831 [PMID: 33857215 DOI: 10.1371/journal.pone.0249831]

71 **Backman K**, Ollikainen H, Piippo-Savolainen E, Nuolivirta K, Korppi M. Asthma and lung function in adulthood after a viral wheezing episode in early childhood. *Clin Exp Allergy* 2018; **48**: 138-146 [PMID: 29143374 DOI: 10.1111/cea.13062]

72 **Bertrand P**, Lay MK, Piedimonte G, Brockmann PE, Palavecino CE, Hernández J, León MA, Kalergis AM, Bueno SM. Elevated IL-3 and IL-12p40 levels in the lower airway of infants with RSV-induced bronchiolitis correlate with recurrent wheezing. *Cytokine* 2015; **76**: 417-423 [PMID: 26299549 DOI: 10.1016/j.cyto.2015.07.017]

73 **Fjaerli HO**, Farstad T, Rød G, Ufert GK, Gulbrandsen P, Nakstad B. Acute bronchiolitis in infancy as risk factor for wheezing and reduced pulmonary function by seven years in Akershus County, Norway. *BMC Pediatr* 2005; **5**: 31 [PMID: 16109158 DOI: 10.1186/1471-2431-5-31]

74 **García-García ML**, Calvo C, Casas I, Bracamonte T, Rellán A, Gozalo F, Tenorio T, Pérez-Breña P. Human metapneumovirus bronchiolitis in infancy is an important risk factor for asthma at age 5. *Pediatr Pulmonol* 2007; **42**: 458-464 [PMID: 17427899 DOI: 10.1002/ppul.20597]

75 **Henderson J**, Hilliard TN, Sherriff A, Stalker D, Al Shammari N, Thomas HM. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. *Pediatr Allergy Immunol* 2005; **16**: 386-392 [PMID: 16101930 DOI: 10.1111/j.1399-3038.2005.00298.x]

76 **Korppi M**, Piippo-Savolainen E, Korhonen K, Remes S. Respiratory morbidity 20 years after RSV infection in infancy. *Pediatr Pulmonol* 2004; **38**: 155-160 [PMID: 15211700 DOI: 10.1002/ppul.20058]

77 **Poorisrisak P**, Halkjaer LB, Thomsen SF, Stensballe LG, Kyvik KO, Skytthe A, Schioetz PO, Bisgaard H. Causal direction between respiratory syncytial virus bronchiolitis and asthma studied in monozygotic twins. *Chest* 2010; **138**: 338-344 [PMID: 20435661 DOI: 10.1378/chest.10-0365]

78 **Pullan CR**, Hey EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *Br Med J (Clin Res Ed)* 1982; **284**: 1665-1669 [PMID: 6805648 DOI: 10.1136/bmj.284.6330.1665]

79 **Sigurs N**, Bjarnason R, Sigurbergsson F, Kjellman B, Björkstén B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics* 1995; **95**: 500-505 [PMID: 7700748]

80 **Sigurs N**, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000; **161**: 1501-1507 [PMID: 10806145 DOI: 10.1164/ajrccm.161.5.9906076]

81 **Sigurs N**, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, Bjarnason R, Gustafsson PM. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax* 2010; **65**: 1045-1052 [PMID: 20581410 DOI: 10.1136/thx.2009.121582]

82 **Sigurs N**, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F, Kjellman B. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005; **171**: 137-141 [PMID: 15516534 DOI: 10.1164/rccm.200406-730OC]

83 **Singleton RJ**, Redding GJ, Lewis TC, Martinez P, Bulkow L, Morray B, Peters H, Gove J, Jones C, Stamey D, Talkington DF, DeMain J, Bernert JT, Butler JC. Sequelae of severe respiratory syncytial virus infection in infancy and early childhood among Alaska Native children. *Pediatrics* 2003; **112**: 285-290 [PMID: 12897275 DOI: 10.1542/peds.112.2.285]

84 **Strannegård O**, Cello J, Bjarnason R, Sigurbergsson F, Sigurs N. Association between pronounced IgA response in RSV bronchiolitis and development of allergic sensitization. *Pediatr Allergy Immunol* 1997; **8**: 1-6 [PMID: 9260211 DOI: 10.1111/j.1399-3038.1997.tb00134.x]

85 **Zomer-Kooijker K**, van der Ent CK, Ermers MJ, Uiterwaal CS, Rovers MM, Bont LJ; RSV Corticosteroid Study Group. Increased risk of wheeze and decreased lung function after respiratory syncytial virus infection. *PLoS One* 2014; **9**: e87162 [PMID: 24498037 DOI: 10.1371/journal.pone.0087162]

86 **Fauroux B**, Simões EAF, Checchia PA, Paes B, Figueras-Aloy J, Manzoni P, Bont L, Carbonell-Estrany X. The Burden and Long-term Respiratory Morbidity Associated with Respiratory Syncytial Virus Infection in Early Childhood. *Infect Dis Ther* 2017; **6**: 173-197 [PMID: 28357706 DOI: 10.1007/s40121-017-0151-4]

87 **Liu L**, Pan Y, Zhu Y, Song Y, Su X, Yang L, Li M. Association between rhinovirus wheezing illness and the development of childhood asthma: a meta-analysis. *BMJ Open* 2017; **7**: e013034 [PMID: 28373249 DOI: 10.1136/bmjopen-2016-013034]

88 **Pérez-Yarza EG**, Moreno A, Lázaro P, Mejías A, Ramilo O. The association between respiratory syncytial virus infection and the development of childhood asthma: a systematic review of the literature. *Pediatr Infect Dis J* 2007; **26**: 733-739 [PMID: 17848887 DOI: 10.1097/INF.0b013e3180618c42]

89 **Régnier SA**, Huels J. Association between respiratory syncytial virus hospitalizations in infants and respiratory sequelae: systematic review and meta-analysis. *Pediatr Infect Dis J* 2013; **32**: 820-826 [PMID: 23518824 DOI: 10.1097/INF.0b013e31829061e8]

90 **Edmond K**, Scott S, Korczak V, Ward C, Sanderson C, Theodoratou E, Clark A, Griffiths U, Rudan I, Campbell H. Long term sequelae from childhood pneumonia; systematic review and meta-analysis. *PLoS One* 2012; **7**: e31239 [PMID: 22384005 DOI: 10.1371/journal.pone.0031239]

91 **Kuehni CE**, Spycher BD, Silverman M. Causal links between RSV infection and asthma: no clear answers to an old question. *Am J Respir Crit Care Med* 2009; **179**: 1079-1080 [PMID: 19498062 DOI: 10.1164/rccm.200904-0567ED]

92 **Flaherman V**, Rutherford GW. A meta-analysis of the effect of high weight on asthma. *Arch Dis Child* 2006; **91**: 334-339 [PMID: 16428358 DOI: 10.1136/adc.2005.080390]

93 **Goksör E**, Amark M, Alm B, Gustafsson PM, Wennergren G. The impact of pre- and post-natal smoke exposure on future asthma and bronchial hyper-responsiveness. *Acta Paediatr* 2007; **96**: 1030-1035 [PMID: 17498194 DOI: 10.1111/j.1651-2227.2007.00296.x]

94 **Lin HW**, Lin SC. Environmental factors association between asthma and acute bronchiolitis in young children--a perspective cohort study. *Eur J Pediatr* 2012; **171**: 1645-1650 [PMID: 22777642 DOI: 10.1007/s00431-012-1788-3]

95 **Sears MR**, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, Cowan JO, Herbison GP, Silva PA, Poulton R. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003; **349**: 1414-1422 [PMID: 14534334 DOI: 10.1056/NEJMoa022363]

96 **Sears MR**, Holdaway MD, Flannery EM, Herbison GP, Silva PA. Parental and neonatal risk factors for atopy, airway hyper-responsiveness, and asthma. *Arch Dis Child* 1996; **75**: 392-398 [PMID: 8957951 DOI: 10.1136/adc.75.5.392]

97 **Sonnenschein-van der Voort AM**, Arends LR, de Jongste JC, Annesi-Maesano I, Arshad SH, Barros H, Basterrechea M, Bisgaard H, Chatzi L, Corpeleijn E, Correia S, Craig LC, Devereux G, Dogaru C, Dostal M, Duchen K, Eggesbø M, van der Ent CK, Fantini MP, Forastiere F, Frey U, Gehring U, Gori D, van der Gugten AC, Hanke W, Henderson AJ, Heude B, Iñiguez C, Inskip HM, Keil T, Kelleher CC, Kogevinas M, Kreiner-Møller E, Kuehni CE, Küpers LK, Lancz K, Larsen PS, Lau S, Ludvigsson J, Mommers M, Nybo Andersen AM, Palkovicova L, Pike KC, Pizzi C, Polanska K, Porta D, Richiardi L, Roberts G, Schmidt A, Sram RJ, Sunyer J, Thijs C, Torrent M, Viljoen K, Wijga AH, Vrijheid M, Jaddoe VW, Duijts L. Preterm birth, infant weight gain, and childhood asthma risk: a meta-analysis of 147,000 European children. *J Allergy Clin Immunol* 2014; **133**: 1317-1329 [PMID: 24529685 DOI: 10.1016/j.jaci.2013.12.1082]

98 **Oddy WH**, de Klerk NH, Sly PD, Holt PG. The effects of respiratory infections, atopy, and breastfeeding on childhood asthma. *Eur Respir J* 2002; **19**: 899-905 [PMID: 12030731 DOI: 10.1183/09031936.02.00103602]

99 **Østergaard MS**, Nantanda R, Tumwine JK, Aabenhus R. Childhood asthma in low income countries: an invisible killer? *Prim Care Respir J* 2012; **21**: 214-219 [PMID: 22623048 DOI: 10.4104/pcrj.2012.00038]

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Peer Reviewer of *World Journal of Critical Care Medicine*, Rakesh Garg, DNB, MD, Additional Professor, Department of Anaesthesiology, Critical Care, Pain and Palliative Medicine, All India Institute of Medical Sciences, Delhi 110029, India. drrgarg@hotmail.com

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EDITORIAL

Data science in the intensive care unit

Ming-Hao Luo, Dan-Lei Huang, Jing-Chao Luo, Ying Su, Jia-Kun Li, Guo-Wei Tu, Zhe Luo

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Ming-Hao Luo, Dan-Lei Huang, Shanghai Medical College, Fudan University, Shanghai 200032, China

Jing-Chao Luo, Ying Su, Jia-Kun Li, Guo-Wei Tu, Zhe Luo, Department of Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai 200032, China

Corresponding author: Zhe Luo, MD, PhD, Chief Doctor, Department of Critical Care Medicine, Zhongshan Hospital, Fudan University, No. 180 Fenglin Road, Shanghai 200032, China. luo.zhe@zs-hospital.sh.cn

Abstract

In this editorial, we comment on the current development and deployment of data science in intensive care units (ICUs). Data in ICUs can be classified into qualitative and quantitative data with different technologies needed to translate and interpret them. Data science, in the form of artificial intelligence (AI), should find the right interaction between physicians, data and algorithm. For individual patients and physicians, sepsis and mechanical ventilation have been two important aspects where AI has been extensively studied. However, major risks of bias, lack of generalizability and poor clinical values remain. AI deployment in the ICUs should be emphasized more to facilitate AI development. For ICU management, AI has a huge potential in transforming resource allocation. The coronavirus disease 2019 pandemic has given opportunities to establish such systems which should be investigated further. Ethical concerns must be addressed when designing such AI.

Key Words: Artificial intelligence; COVID-19; Data science; Intensive care units; Interaction

Core Tip: Data in intensive care units (ICUs) can be classified into qualitative and quantitative data with different technologies needed to translate and interpret them. Data science, in the form of artificial intelligence (AI), should find the right interaction between physicians, data and algorithm to maximize the utility. AI deployment in the ICUs should be emphasized more to facilitate AI development. Individual-level applications such as disease prediction, and ICU-level potentials such as resource allocation are both of paramount importance.

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INTRODUCTION

The intensive care unit (ICU) is a data-rich setting where the right decision can mean the difference between life and death. This gives the ICU the perfect opportunity to explore the impact of data science combined with artificial intelligence (AI) to maximize the utility and benefits. However, challenges remain because the interpretation of an incredibly huge amount of data is still a black hole with many questions unanswered. Although many models have been created, their clinical applications are limited. Attention is mostly paid to individual-level decision making such as diagnosing and predicting the prognosis of a specific disease, while potentials at a more macroscopic level such as ICU resource allocation, are largely omitted.

Generally speaking, data in the ICU can be classified into qualitative and quantitative data. Qualitative data include graphical data such as waves on the ventilation machine, and radiological data such as x-rays or computed tomography scans. Such data need to be translated first before being further calculated. Recently, we have seen a substantial number of researches focusing on such a translation process[1-4]. Quantitative data in the form of numbers such as physiological parameters, laboratory results, dosage of medication and ICU bed capacity, are common to intensivists. This kind of data has the advantage of being readily available for statistical analyses without the necessity for further processing into means that are more accessible.

The key to making full use of data in ICUs is to find the right interaction between three roles: physicians, data and algorithm (Figure 1). Physicians need to ask the right clinical question which points out the direction of the research and the data we should pay attention to. The data should be collected and interpreted in a way that can be processed by current software. The collection of data should follow certain statistical rules and avoid bias as much as possible. The algorithm can be built to find patterns based on a large quantity of data and these patterns should target clinical questions raised by physicians.

DECISION MAKING AND PREDICTIVE MODELS

Two examples where predictive models are supported by AI in decision making in ICUs are sepsis and mechanical ventilation. Sepsis is a leading cause of morbidity and mortality in critically ill patients. AI models have been studied in different stages such as the detection, prediction, risk stratification and management of sepsis. Goh *et al*[5] developed an algorithm with independent clinical notes and achieved high predictive accuracy 12 h before the onset of sepsis (Area under curve 0.94). It also has great potential for improving the early identification of patients who may benefit from the administration of antibiotics. Moreover, it can discover new phenotypes for sepsis potentially transforming sepsis treatment and offering a more tailored strategy for patients with sepsis[6], such as the use of glucocorticoids[7]. Clinicians hold a positive view in letting AI take a more active role when managing patients with sepsis[8].

Mechanical ventilation is another common situation in ICUs. Machine learning can predict the need for intubation in critically ill patients using commonly collected bedside clinical parameters and laboratory results[9]. AI has the potential to identify treatable phenotypes, optimize ventilation strategies and provide clinical decision support for patients who require mechanical ventilation[10]. Zhao *et al*[11] also created a model for predicting extubation failure in ICUs with an AUROC of 0.835 and 0.803, respectively, for internal and external validation.

Such an exciting trend should be viewed with caution. Current AI prediction models to diagnose sepsis are at a major risk of bias when the diagnostic criteria vary. The generalizability of these models is poor due to overfitting and the lack of standardized protocols. Similar conditions occur for mechanical ventilation. AI applied to mechanical ventilation has limited external validation and model calibration with a substantial risk of bias, significant gaps in reporting and poor code and data availability[10].

Mamdani and Slutsky summarized three themes in applied AI in medicine: (1) Enabling data; (2) AI development; and (3) AI deployment. We believe that AI development and AI deployment should be combined to revise current models and offer tangible benefits derived from current researches. A vast majority of developed ICU-AI models remain within the testing and prototyping environment and only a handful have been actually evaluated in clinical practice[12] which implies the lack of enough evidence to support the clinical values of published models. Focusing more on AI deployment in the form of

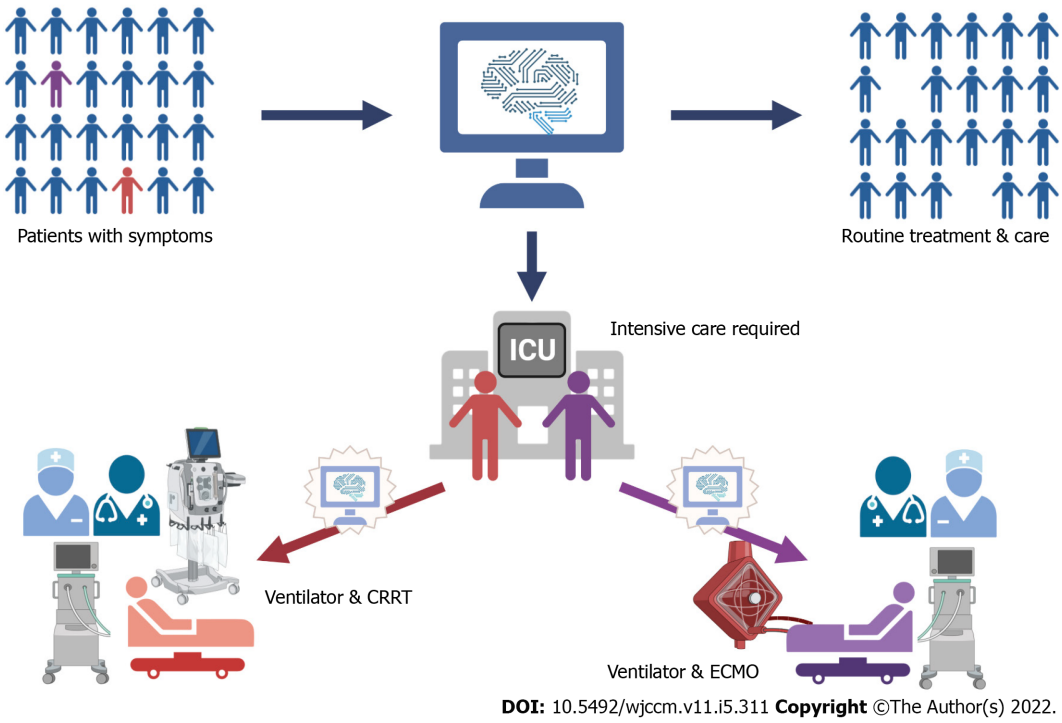

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Figure 1 Interaction between artificial intelligence development and artificial intelligence deployment. Artificial intelligence (AI) development and AI deployment should be combined to revise current models and offer tangible benefits derived from current researches. AI development should find the right interaction between three roles: physicians, data and algorithm. AI deployment in the form of prospective randomized controlled trials can facilitate published models to generate bedside merits and evaluate whether major biases exist. The results from deployment testing can, in turn, offer insights into the development and modify the substandard algorithm. CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation.

prospective randomized controlled trials would not only facilitate published models to generate bedside merits but also test and evaluate whether major biases exist and clinical needs can be met in a satisfactory way. The results from deployment testing can, in turn, offer insights into the development and modify the substandard algorithm (Figure 1).

RESOURCE ALLOCATION

Machine learning and algorithm have been widely used to manage resource allocation. Machine learning has been studied for predictive scheduling and resource allocation in large-scale manufacturing systems and resource allocation strategies in vehicular networks using machine learning have been extensively explored[13,14]. These settings are similar to ICUs in that both need to capture the value from big data processing and extract useful insights to optimize production and protect resources.

However, in the realm of critical care, where resource can be scarce due to factors such as bed capacity, the applications of machine learning has just shown a glimpse of light (Figure 2). Over the past 2 years, these applications in the context of the coronavirus disease 2019 (COVID-19) ICUs offered more chances to lay emphasis on resource allocation. Cheng *et al*[15] used machine learning to predict ICU transfer in hospitalized patients with COVID-19 and concluded that it could improve the management of hospital resources and patient-throughput planning. Similar principles were used to predict the use of ICU resources, such as mechanical ventilation, during the COVID-19 pandemic in Denmark[15]. At a healthcare system level, the National Health Service (NHS) in the United Kingdom started trials of a machine-learning system designed to help hospitals in England anticipate the demand on resources caused by COVID-19. COVID-19 Capacity Planning and Analysis System, a machine learning-based system for hospital resource planning, was subsequently developed that could be deployed at individual hospitals and across regions in the United Kingdom in coordination with NHS Digital[16].

Such models can take the application of AI in ICUs to another level. Although its insight into disease prediction, diagnosis and management is extremely important, it gives the chance to make the most use of resources, especially in ICUs where demand and supply frequently mismatch. Prediction in interventions such as mechanical ventilation would mean that the management groups can foresee changes and mobilize resource, such as equipment and staff, to cope with such demands in advance and this is a positive factor for patient outcomes.

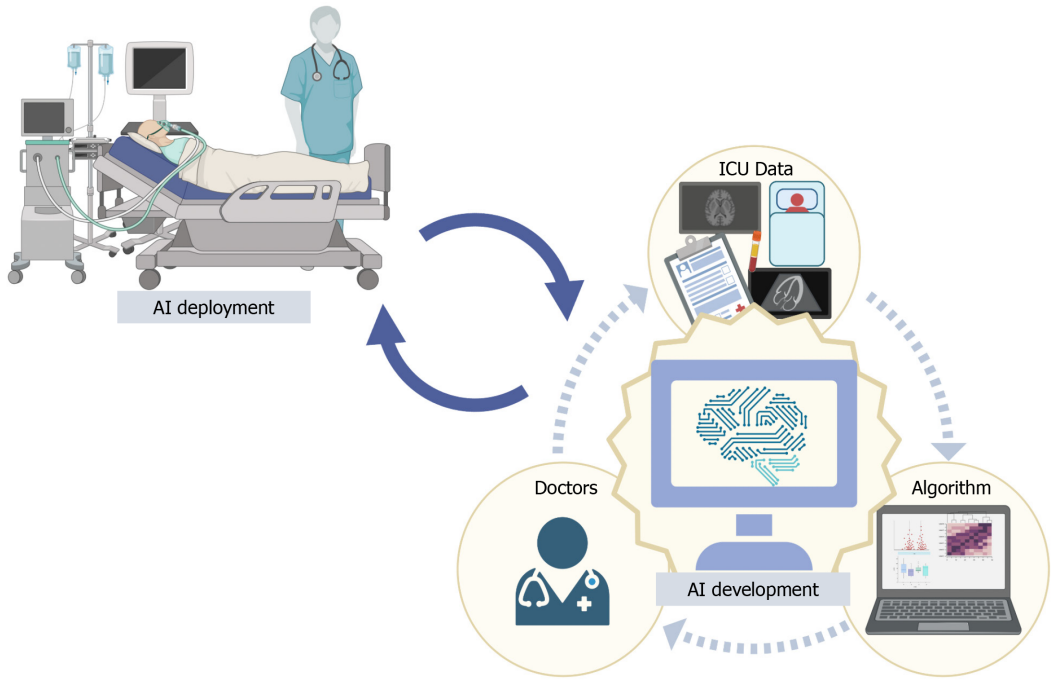

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Figure 2 Resource allocation in the intensive care units. The applications of machine learning can target patients in need of intensive care units (ICUs) and predict the use of ICU resources. Machine learning can predict ICU transfer in hospitalized patients and predict the use of ICU resources, such as mechanical ventilation. It gives the chance to make the most use of resources, especially in ICUs where demand and supply frequently mismatch. Prediction in interventions, such as mechanical ventilation, would mean that the management groups can foresee changes and mobilize resource, such as equipment and staff, to cope with such demands in advance which is a positive factor for patient outcomes. AI: Artificial intelligence.

Besides efficiency, another aspect that we must pay attention to is how to answer the ethical questions embodied in resource allocation to achieve a healthcare system that values equity and sustainability. This implies that ethical considerations must be included and certain ethical principles must be followed when designing the algorithm. Recently, a set of new studies focused on the ethics of healthcare resource allocation, drawing attentions to patient need, prognosis, equal treatment and cost-effectiveness[17]. Also, numerous comments were made during the COVID-19 pandemic that AI should stick to the ethical standards[18-20]. In a broader setting, the so-called algorithmic fairness highlights specific opportunities where machine learning and public and population health may synergize to achieve health equity[21]. Challenges remain as what ethical principles matter and what priority should be given to each ethical principle and coding them into an algorithm has not been intensively experimented.

CONCLUSION

AI has become more prevalent in the ICUs. Different kinds of data are collected constantly and should be interpreted in an accurate fashion. The key to maximizing AI in the ICU is to find the right balance between data, algorithms and physicians to ensure that the technical, computational and clinical needs are targeted.

For individuals, sepsis and mechanical ventilation have been two important aspects where AI has been extensively studied. However, major risks of bias, lack of generalizability and poor clinical values imply that AI is far from perfect. AI deployment in ICUs should be more emphasized to facilitate AI development.

More importantly, AI has huge potential in transforming resource allocation in ICUs. The COVID-19 pandemic has given some opportunities to establish such systems and more should be investigated. Ethical concerns must be addressed when designing such AI.

FOOTNOTES

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REFERENCES

1 **Homayounieh F**, Digumarthy S, Ebrahimian S, Rueckel J, Hoppe BF, Sabel BO, Conjeti S, Ridder K, Sistermanns M, Wang L, Preuhs A, Ghesu F, Mansoor A, Moghbel M, Botwin A, Singh R, Cartmell S, Patti J, Huemmer C, Fieselmann A, Joerger C, Mirshahzadeh N, Muse V, Kalra M. An Artificial Intelligence-Based Chest X-ray Model on Human Nodule Detection Accuracy From a Multicenter Study. *JAMA Netw Open* 2021; **4**: e2141096 [PMID: 34964851 DOI: 10.1001/jamanetworkopen.2021.41096]
2 **Siontis KC**, Noseworthy PA, Attia ZI, Friedman PA. Artificial intelligence-enhanced electrocardiography in cardiovascular disease management. *Nat Rev Cardiol* 2021; **18**: 465-478 [PMID: 33526938 DOI: 10.1038/s41569-020-00503-2]
3 **Xu Q**, Zhan X, Zhou Z, Li Y, Xie P, Zhang S, Li X, Yu Y, Zhou C, Zhang L, Gevaert O, Lu G. AI-based analysis of CT images for rapid triage of COVID-19 patients. *NPJ Digit Med* 2021; **4**: 75 [PMID: 33888856 DOI: 10.1038/s41746-021-00446-z]
4 **Su Y**, Qiu ZS, Chen J, Ju MJ, Ma GG, He JW, Yu SJ, Liu K, Lure FYM, Tu GW, Zhang YY, Luo Z. Usage of compromised lung volume in monitoring steroid therapy on severe COVID-19. *Respir Res* 2022; **23**: 105 [PMID: 35488261 DOI: 10.21203/rs.3.rs-698051/v1]
5 **Goh KH**, Wang L, Yeow AYK, Poh H, Li K, Yeow JJL, Tan GYH. Artificial intelligence in sepsis early prediction and diagnosis using unstructured data in healthcare. *Nat Commun* 2021; **12**: 711 [PMID: 33514699 DOI: 10.1038/s41467-021-20910-4]
6 **Seymour CW**, Kennedy JN, Wang S, Chang CH, Elliott CF, Xu Z, Berry S, Clermont G, Cooper G, Gomez H, Huang DT, Kellum JA, Mi Q, Opal SM, Talisa V, van der Poll T, Visweswaran S, Vodovotz Y, Weiss JC, Yealy DM, Yende S, Angus DC. Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis. *JAMA* 2019; **321**: 2003-2017 [PMID: 31104070 DOI: 10.1001/jama.2019.5791]
7 **Zhang Z**, Pan Q, Ge H, Xing L, Hong Y, Chen P. Deep learning-based clustering robustly identified two classes of sepsis with both prognostic and predictive values. *EBioMedicine* 2020; **62**: 103081 [PMID: 33181462 DOI: 10.1016/j.ebiom.2020.103081]
8 **Komorowski M**. Clinical management of sepsis can be improved by artificial intelligence: yes. *Intensive Care Med* 2020; **46**: 375-377 [PMID: 31834423 DOI: 10.1007/s00134-019-05898-2]
9 **Siu BMK**, Kwak GH, Ling L, Hui P. Predicting the need for intubation in the first 24 h after critical care admission using machine learning approaches. *Sci Rep* 2020; **10**: 20931 [PMID: 33262391 DOI: 10.1038/s41598-020-77893-3]
10 **Marshall DC**, Komorowski M. Is artificial intelligence ready to solve mechanical ventilation? *Br J Anaesth* 2022; **128**: 231-233 [PMID: 34903359 DOI: 10.1016/j.bja.2021.10.050]
11 **Zhao QY**, Wang H, Luo JC, Luo MH, Liu LP, Yu SJ, Liu K, Zhang YJ, Sun P, Tu GW, Luo Z. Development and Validation of a Machine-Learning Model for Prediction of Extubation Failure in Intensive Care Units. *Front Med (Lausanne)* 2021; **8**: 676343 [PMID: 34079812 DOI: 10.3389/fmed.2021.676343]
12 **van de Sande D**, van Genderen ME, Huiskens J, Gommers D, van Bommel J. Moving from bytes to bedside: a systematic review on the use of artificial intelligence in the intensive care unit. *Intensive Care Med* 2021; **47**: 750-760 [PMID: 34089064 DOI: 10.1007/s00134-021-06446-7]
13 **Morariu C**, Morariu O, Răileanu S, Borangiu T. Machine learning for predictive scheduling and resource allocation in large scale manufacturing systems. *Computers in Industry* 2020; **120**: 103244 [DOI: 10.1016/j.compind.2020.103244]
14 **Nurcahyani I**, Lee JW. Role of Machine Learning in Resource Allocation Strategy over Vehicular Networks: A Survey. *Sensors (Basel)* 2021; **21** [PMID: 34640858 DOI: 10.3390/s21196542]
15 **Cheng FY**, Joshi H, Tandon P, Freeman R, Reich DL, Mazumdar M, Kohli-Seth R, Levin M, Timsina P, Kia A. Using Machine Learning to Predict ICU Transfer in Hospitalized COVID-19 Patients. *J Clin Med* 2020; **9** [PMID: 32492874 DOI: 10.3390/jcm9061668]
16 **Qian Z**, Alaa AM, van der Schaar M. CPAS: the UK's national machine learning-based hospital capacity planning system for COVID-19. *Mach Learn* 2021; **110**: 15-35 [PMID: 33250568 DOI: 10.1007/s10994-020-05921-4]
17 **Munthe C**, Fumagalli D, Malmqvist E. Sustainability principle for the ethics of healthcare resource allocation. *J Med Ethics* 2021; **47**: 90-97 [PMID: 33154090 DOI: 10.1136/medethics-2020-106644]
18 **Cave S**, Whittlestone J, Nyrup R, O hEigeartaigh S, Calvo RA. Using AI ethically to tackle covid-19. *BMJ* 2021; **372**: n364 [PMID: 33722807 DOI: 10.1136/bmj.n364]

19 **Leslie D**, Mazumder A, Peppin A, Wolters MK, Hagerty A. Does "AI" stand for augmenting inequality in the era of covid-19 healthcare? *BMJ* 2021; **372**: n304 [PMID: 33722847 DOI: 10.1136/bmj.n304]
20 **Yu M**, Tang A, Brown K, Bouchakri R, St-Onge P, Wu S, Reeder J, Mullie L, Chassé M. Integrating artificial intelligence in bedside care for covid-19 and future pandemics. *BMJ* 2021; **375**: e068197 [PMID: 34972694 DOI: 10.1136/bmj-2021-068197]
21 **Mhasawade V**, Zhao Y, Chunara R. Machine learning and algorithmic fairness in public and population health. *Nature Machine Intelligence* 2021; **3**: 659-666 [DOI: 10.1038/s42256-021-00373-4]

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ORIGINAL ARTICLE

Retrospective Study

Prediction of hospital mortality in intensive care unit patients from clinical and laboratory data: A machine learning approach

Elena Caires Silveira, Soraya Mattos Pretti, Bruna Almeida Santos, Caio Fellipe Santos Corrêa, Leonardo Madureira Silva, Fabrício Freire de Melo

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Elena Caires Silveira, Soraya Mattos Pretti, Bruna Almeida Santos, Caio Fellipe Santos Corrêa, Leonardo Madureira Silva, Fabrício Freire de Melo, Multidisciplinary Institute of Health, Federal University of Bahia, Vitória da Conquista 45-029094, Brazil

Corresponding author: Fabrício Freire de Melo, PhD, Professor, Multidisciplinary Institute of Health, Federal University of Bahia, Rua Hormindo Barros, 58, Quadra 17, Lote 58, Candeias, Vitória da Conquista 45-029094, Brazil. freiremeloufba@gmail.com

Abstract

BACKGROUND

Intensive care unit (ICU) patients demand continuous monitoring of several clinical and laboratory parameters that directly influence their medical progress and the staff's decision-making. Those data are vital in the assistance of these patients, being already used by several scoring systems. In this context, machine learning approaches have been used for medical predictions based on clinical data, which includes patient outcomes.

AIM

To develop a binary classifier for the outcome of death in ICU patients based on clinical and laboratory parameters, a set formed by 1087 instances and 50 variables from ICU patients admitted to the emergency department was obtained in the "WiDS (Women in Data Science) Datathon 2020: ICU Mortality Prediction" dataset.

METHODS

For categorical variables, frequencies and risk ratios were calculated. Numerical variables were computed as means and standard deviations and Mann-Whitney *U* tests were performed. We then divided the data into a training (80%) and test (20%) set. The training set was used to train a predictive model based on the Random Forest algorithm and the test set was used to evaluate the predictive effectiveness of the model.

RESULTS

A statistically significant association was identified between need for intubation, as well predominant systemic cardiovascular involvement, and hospital death. A number of the numerical variables analyzed (for instance Glasgow Coma Score

punctuations, mean arterial pressure, temperature, pH, and lactate, creatinine, albumin and bilirubin values) were also significantly associated with death outcome. The proposed binary Random Forest classifier obtained on the test set (n = 218) had an accuracy of 80.28%, sensitivity of 81.82%, specificity of 79.43%, positive predictive value of 73.26%, negative predictive value of 84.85%, F1 score of 0.74, and area under the curve score of 0.85. The predictive variables of the greatest importance were the maximum and minimum lactate values, adding up to a predictive importance of 15.54%.

CONCLUSION

We demonstrated the efficacy of a Random Forest machine learning algorithm for handling clinical and laboratory data from patients under intensive monitoring. Therefore, we endorse the emerging notion that machine learning has great potential to provide us support to critically question existing methodologies, allowing improvements that reduce mortality.

Key Words: Hospital mortality; Machine learning; Patient outcome assessment; Routinely collected health data; Intensive care units; Critical care outcomes

Core Tip: Considering the critical nature of patients admitted to intensive care units (ICUs), this study seeks to analyze clinical and laboratory data using a machine learning model based on a Random Forest algorithm. Consequently, we developed a binary classifier that forecasts death outcome, achieving a relevant area under the curve value of 0.85 and identifying the variables that contributed the most to the prediction. With this, we aim to contribute to the improvement and methodological advancement in the development of clinically relevant machine learning tools, seeking to make medical practice decisions more accurate and reduce mortality in ICU patients.

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INTRODUCTION

The intensive care unit (ICU) is the section of the hospital responsible for monitoring acute patients, and it relies on specialized multidisciplinary staff and high-technology equipment to ensure the best support for these patients, who are usually unstable and at high risk of death. These patients demand continuous monitoring of the most diverse clinical and laboratory parameters that directly influence their medical progress and the staff's decision-making. Lactate levels obtained from arterial blood samples, for example, may indicate the levels and severity of tissue hypoxia[1]. The elevation in serum lactate levels (hyperlactatemia) is associated with increased mortality[2,3]. Another important parameter in critically ill patients is the prothrombin time expressed in international normalized ratio (INR), which reveals abnormalities in the coagulation status[4]. This parameter is also associated with an increased mortality when at altered levels. Besides these, many other laboratory and clinical data like temperature, oxygen and carbon dioxide pressure, systolic and diastolic pressure, motor, ocular, and verbal responses, among others, require team supervision since they are all related in some way to the severity of these ill patients[5].

These data are so vital in the assistance of these patients that they are already used by several scoring systems, including the Acute Physiology and Chronic Health Evaluation (APACHE) and the Simplified Acute Physiology Score (SAPS), which are designed to assess and predict the patient's prognosis and allow for appropriate interventions[6]. The APACHE score, for example, which has been widely used since its creation in the 1980s and has been undergoing updates ever since, relies on the use of parameters evaluated in three major groups: Demographic characteristics, comorbidities, and physiological measures. From these data, numerical weights are assigned to each one and then summed to assign a severity classification and predict outcomes[7].

Machine learning may be understood as a scientific discipline by which a computer system is enabled to cross-reference numerous data in order to build statistical prediction models through pattern recognition[8]. To reach this pattern perception capability, it is essential during the use of the supervised

machine learning approach to separate the data subsets for training and for testing. The training data are presented to the algorithm in order to create the model, and then the test data is also presented after the creation of the model in order to simulate this model's prediction and evaluate its performance. The machine learning approach is already used for medical predictions based on clinical data, which includes patient outcome. Heo *et al*[9] used it to predict the long-term outcome of patients who suffered an ischemic stroke. In another study, Lynch *et al*[10] sought a survival prediction of lung cancer patients using machine learning by providing a series of patient data such as age, tumor size, type of intervention, and more.

The use of machine learning has been consolidated as an alternative for the development of predictive models of mortality in the critical care setting. An example is the retrospective study by Liu *et al*[11], who developed a logistic model of the death risk grade in patients with pulmonary tuberculosis using data from patients admitted to ICUs in three hospitals. In this multivariate analysis study, where the sensitivity was 83.3% and specificity was 73.1%, the Apache II score, C-reactive protein levels, albumin levels, and pressure of oxygen in arterial blood (PaO_2) were considered the main factors influencing the outcome. However, a registered limitation was the small dataset utilized.

The limiting matter caused by the database used in machine learning predictive models was also observed in the study by Hou *et al*[12], who developed a model regarding 30-d mortality in patients who fit the Third International Consensus Definitions for Sepsis (Sepsis-3). This paper used a public database Medical Information Mart for Intensive Care III (MIMIC III) from a single-center critical care database. Another study that also relates the development of a predictive machine learning model in the context of patients with sepsis is the one proposed by Nemati *et al*[13] that, in addition to using the aforementioned MIMIC III, also relied on ICU admission data from two hospital centers. In this study, as well as in the two previously mentioned, the potentialuses of this tool in the early identification of severity of cases and the possibility of making fundamental decisions to the positive outcome for patients was observed.

In addition, more recently, in light of the advent of the severe acute respiratory syndrome coronavirus 2 pandemic, the application of these predictive models using machine learning technology have been employed on various grounds, such as for risk of critical coronavirus disease 2019 (COVID-19)[14], need for ICU transfer, and the prognosis of intensive care COVID-19 patients[15,16]. The latter one was associated with eight main component factors, namely: Lymphocyte percentage, prothrombin time, lactate dehydrogenase, total bilirubin, eosinophil percentage, creatinine, and neutrophil percentage. And although it also emphasized the difficulties of small databases, they pointed out the significance of this approach in critical patients with a panel of such complicated parameters.

Understanding a clinical setting as complex and full of variables as the ICU, identifying existing patterns, and enabling outcome prediction is a valuable tool for the improvement of health assistance to these patients. Therefore, the aim of the current paper is to develop a predictive model for the outcome of death in ICU patients based on clinical and laboratory parameters using a binary classifier, with predicted outcome consisting of in-hospital death and discharge.

MATERIALS AND METHODS

Data acquisition

We used anonymized retrospective data from ICU patients admitted to the emergency department to build a predictive model geared towards predicting death outcomes in these patients. For this purpose, a dataset used in the study was created from the larger "WiDS (Women in Data Science) Datathon 2020: ICU Mortality Prediction" dataset[17], which presents clinical and laboratory data pertaining to the first 24 h of ICU patient admission. The criteria for inclusion of instances (*i.e.*, patients) in the study dataset were: (1) ICU admission and emergency department admission; and (2) Completeness (*i.e.*, absence of missing data) with respect to the variables of interest. Since all the data were obtained from a public and anonymized dataset[16], it was not necessary to submit this study to the ethics committee, being in accordance with all the established precepts by the Committee on Publication Ethics.

Data preprocessing and exploratory data analysis

Aligned with the goal of building an interpretable predictive model from clinical and laboratory data, variables related to the clinical status of patients (such as vital signs, clinical score scores, blood counts, and biochemical test results) were prioritized in the definition of variables of interest - with exclusion of variables of this type only when redundant or when they represented the application of formulas instead of measured or scored values - to the detriment of anthropometric and demographic variables, with age being the only representative of this group of variables included. Additionally, factors referring to logistical aspects of hospitalization (such as source and type of admission and readmission status) were also not included among the variables of interest.

This way, a set formed by 1087 instances and 50 variables was obtained, of which 49 were assumed as predictive variables and 1 as predicted variable (outcome variable). The predictive numerical variables were: (1) Age; (2) Disease score; (3) Eye opening score on the Glasgow coma scale (GCS); (4) Heart rate;

(5) Hematocrit; (6) Mean arterial pressure; (7) Maximum albumin; (8) Maximum bilirubin; (9) Maximum blood urea nitrogen; (10) Maximum calcium; (11) Maximum creatinine; (12) Maximum diastolic blood pressure; (13) Maximum glucose; (14) Maximum HCO_3; (15) Maximum hemoglobin; (16) Maximum INR; (17) Maximum lactate; (18) Maximum platelets; (19) Maximum potassium; (20) Maximum sodium; (21) Minimum systolic blood pressure; (22) Maximum saturation of peripheral oxygen (SpO_2); (23) Maximum white blood cells (WBC); (24) Minimum albumin; (25) Minimum bilirubin; (26) Maximum blood urea nitrogen; (27) Minimum calcium; (28) Minimum creatinine; (29) Minimum diastolic blood pressure; (30) Minimum glucose; (31) Minimum HCO_3; (32) Minimum hemoglobin; (33) Minimum INR; (34) Minimum lactate; (35) Minimum platelets; (36) Minimum potassium; (37) Minimum sodium; (38) Minimum systolic blood pressure; (39) Minimum SpO_2; (40) Minimum WBC; (41) Motor response on the GCS; (42) Partial PaO_2; (43) Partial pressure of carbonic gas in arterial blood ($PaCO_2$); (44) pH; (45) Respiratory rate; (46) Temperature; and (47) Verbal response on the GCS. The predictive categorical variables were: (1) Need for intubation or not; and (2) Predominant systemic involvement. The outcome variable was the evolution or not with hospital death.

The disease score corresponded to the number of diseases present among the following conditions: (1) Acquired immunodeficiency syndrome; (2) Cirrhosis; (3) Diabetes; (4) Hepatic failure; (5) Immunosuppression; (6) Leukemia; (7) Lymphoma; and (8) Solid tumor. The categories of predominant systemic involvement considered were: (1) Cardiovascular involvement; (2) Gastrointestinal involvement; (3) Genitourinary involvement; (4) Hematological involvement; (5) Metabolic involvement; (6) Musculoskeletal/skin involvement; (7) Neurological involvement; (8) Respiratory involvement; (9) Sepsis; and (10) Trauma.

Initially, a descriptive and comparative analysis of the data was performed. The data were categorized according to the outcome variable. After that, the occurrence frequencies of each category for of categorical predictive variables and the means and standard deviations for all numerical predictive variables in both groups were computed. Finally, the differences for each variable between the groups were analyzed using the χ^2 test for risk ratios (for categorical variables) and the Mann-Whitney U test (for numerical variables). Since a decision tree ensemble algorithm was chosen to constitute our predictive model, it was not necessary to normalize or standardize the data, since tree partitioning algorithms are insensitive to scaling.

Machine learning algorithm selection

To perform our predictive analysis, we chose to build a Random Forest algorithm, a model consisting of an ensemble of randomized decision trees. As an extension of bootstrap aggregation (bagging) of decision trees, in Random Forest algorithms each individual model in the ensemble is employed to generate a prediction for a new sample, and these individual model predictions are averaged to give the forest's prediction, resulting in better performance than any single tree. By combining individual models, the ensemble model tends to be more flexible and efficient. Accordingly, random forests have been incredibly successful in a variety of classification and regression problems with clinical applications. Furthermore, the algorithm does not require any feature scaling since decision trees predictions are partitioning-based instead of distance-based.

Model training and evaluation

We then proceeded to the development of the predictive model for the outcome variable. The data were divided into a training set (80%) and a test set (20%). The training set was used to train a predictive model based on the Random Forest algorithm[18], implemented here through the Scikit-learn open source library[19]. The test set was used to evaluate the predictive effectiveness of the model. The metrics used for such evaluation were accuracy, sensitivity, specificity, area under the curve (AUC) score, positive predictive value, and negative predictive value. The adopted methodology is schematically summarized in Figure 1. Besides the predictive performance, the feature importance attributed by the model to each variable was also considered, which not only adds explainability to the model, but also potentially provides insights regarding the evaluation of critically ill patients and the factors associated with higher mortality in this clinical setting. All steps of statistical analysis and development of the predictive model were performed in Python (version 3.6.9) using SciPy and Scikit-learn libraries.

RESULTS

Data from 1087 ICU patients were analyzed and used in the construction of the predictive model, of which 388 evolved with hospital death, while the remaining 699 did not. With regard to the predictive variables categories - need or not of intubation and predominantly affected body system -, among the 388 patients who evolved with hospital death: 275 were intubated and 63 were not; 106 had sepsis as predominant systemic involvement, 18 respiratory involvement, 4 metabolic involvement, 154 cardiovascular involvement, 11 trauma, 16 neurological involvement, 25 gastrointestinal involvement, 2 genitourinary involvement, 1 musculoskeletal/skin involvement, and 1 hematological involvement. Among the 699 patients who did not progress to hospital death: 534 were intubated and 215 were not;

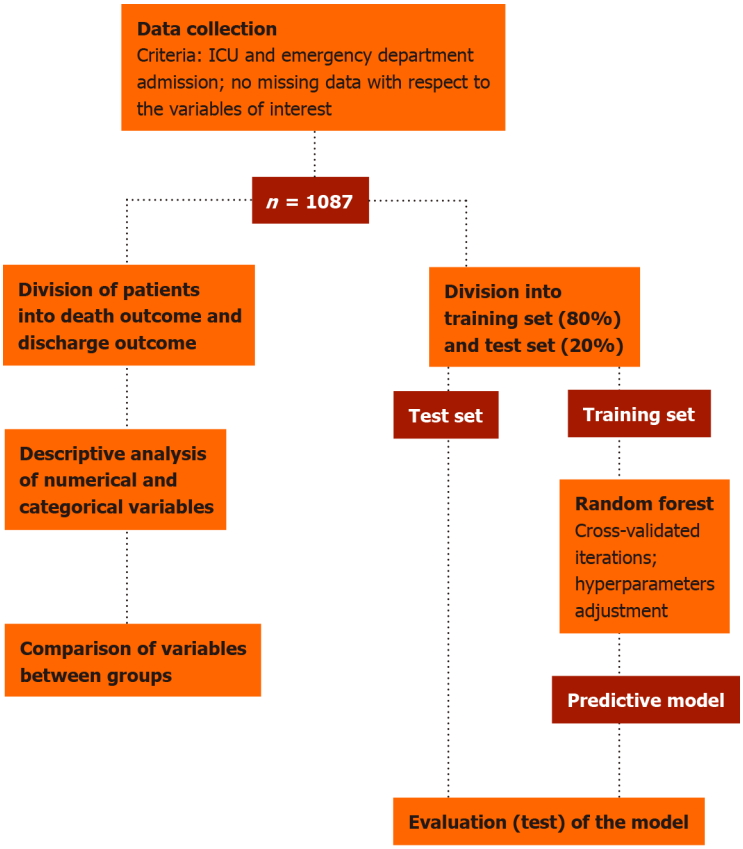

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Figure 1 Methodological design of the study. The proposed workflow encompasses selective collection of clinical, laboratorial and outcome data, splitting and pre-processing of the data, iterative training of the classificatory model, and finally evaluation of its performance. ICU: Intensive care unit.

206 had sepsis as predominant systemic involvement, 107 respiratory involvement, 79 metabolic involvement, 167 cardiovascular involvement, 38 trauma, 49 neurological involvement, 74 gastro-intestinalintestinal involvement, 17 genitourinary involvement, 9 musculoskeletal/skin involvement, and 3 hematological involvement. A statistically significant association was identified between need for intubation and hospital death (risk ratio = 1.5, $\chi^2 = 11.87$, $P < 0.001$), as well as between the predominant systemic cardiovascular involvement and hospital death compared to the musculoskeletal system/skin, which related to lower rate of hospital death (risk ratio = 4.80, $\chi^2 = 4.20$, $P = 0.04$). With regards to numerical predictive variables, their mean ± SD, and the respective comparison between both outcome groups (performed using the Mann-Whitney *U* test) are shown in Table 1.

The search for the best hyperparameters in our Random Forest model training was done using randomized search. In this way, 100 random combinations of hyperparameters were tested. Each combination was iterated 6 times, as a 6-fold validation scheme was adopted. In this scheme, the training set ($n = 869$) was split into 6 parts, and in each iteration a different part was used for validation. Ultimately, during training we performed 600 fits, obtaining the following hyperparameters: (1) Number of estimators = 213; (2) Maximum depth = 23; (3) Maximum leaf nodes = 24; (4) Minimum samples split = 5; (5) Class weights = 3.9; and (6) Bootstrap = true.

The model obtained accuracy of 80.28%, sensitivity of 81.82%, specificity of 79.43%, positive predictive value of 73.26%, negative predictive value of 84.85%, F1 score of 0.74, and AUC score of 0.85 on the test set ($n = 218$). The confusion matrix for the model is shown in Figure 2, and its receiver operating characteristic (ROC) curve is shown in Figure 3. The predictive variables with the greatest importance were the maximum and minimum lactate values, adding up to a predictive importance of 15.54%, followed by temperature (6.47%), motor punctuation in GCS (5.25%), maximum blood urea nitrogen (4.35%), and minimum WBC (3.31%). The percentage importance of the other variables in the prediction are listed in Table 2.

DISCUSSION

The presented predictive model, a Random Forest binary classifier, was able to predict in the test set the occurrence or not of hospital death with an accuracy of 80.28%, sensitivity of 81.82%, and specificity of

Table 1 Descriptive and univariate comparative analyses for numerical predictive variables according to outcome

Variable	mean ± SD		*U* value	*P* value
	Death outcome, *n* = 338	Survival outcome, *n* = 749		
Age	63.4 ± 15.7	60.1 ± 16.1	111072	< 0.001
Disease score	1.3 ± 0.8	1.2 ± 0.7	121505.5	0.110
Eye opening (GCS)	2.0 ± 1.2	2.5 ± 1.2	97325.0	< 0.001
Heart rate	114.3 ± 34.9	111.1 ± 31.1	117672.0	0.031
Hematocrit	31.7 ± 8.3	32.8 ± 7.3	116749.0	0.02
MAP	84.7 ± 53.9	87.4 ± 48.7	108432.0	< 0.001
Max albumin	2.7 ± 0.7	2.8 ± 0.6	109136.0	< 0.001
Max bilirubin	2.2 ± 3.8	1.2 ± 1.8	98589.5	< 0.001
Max BUN	40.0 ± 25.2	33.8 ± 24.5	102300.0	< 0.001
Max calcium	8.0 ± 0.9	8.1 ± 0.8	117155.0	0.024
Max creatinine	2.6 ± 2.0	2.0 ± 1.9	96278.5	< 0.001
Max DBP	92.0 ± 23.1	94.8 ± 21.5	116162.0	0.015
Max glucose	231.4 ± 113.0	210.1 ± 105.2	11090.0	< 0.001
Max HCO_3	21.0 ± 5.1	23.3 ± 4.8	94750.0	< 0.001
Max hemoglobin	11.7 ± 2.5	11.7 ± 2.3	124619.0	0.341
Max INR	2.1 ± 1.3	1.6 ± 0.8	83944.0	< 0.001
Max lactate	7.3 ± 5.5	3.2 ± 2.8	62255.5	< 0.001
Max platelets	189446.7 ± 98687.9	198186.9 ± 96842.7	120773.5	0.113
Max potassium	4.7 ± 0.9	4.5 ± 0.8	106603.0	< 0.001
Max sodium	142.1 ± 6.7	140.9 ± 5.4	113894.0	0.004
Max SBP	147.5 ± 29.3	151.1 ± 26.2	113747.5	0.004
Max SpO_2	99.6 ± 1.5	99.8 ± 0.6	119714.5	0.005
Max WBC	17442.9 ± 10269.3	15302 ± 8516	111218.5	0.001
Min albumin	2.5 ± 0.7	2.7 ± 0.6	101997.5	< 0.001
Min bilirubin	1.9 ± 3.3	1.1 ± 1.7	101177.5	< 0.001
Min BUN	34.2 ± 22.9	29.0 ± 21.0	106584.5	< 0.001
Min calcium	7.4 ± 0.9	7.7 ± 0.9	98668.5	< 0.001
Min creatinine	2.08 ± 1.7	1.6 ± 1.3	99935.0	< 0.001
Min glucose	104.6 ± 47.0	110.7 ± 38.1	111941.5	0.001
Min HCO_3	17.0 ± 5.5	20.6 ± 5.5	79747.5	< 0.001
Min hemoglobin	10.3 ± 2.7	10.8 ± 2.4	111370.0	0.001
Min INR	1.8 ± 0.9	1.5 ± 0.6	89909.5	< 0.001
Min lactate	4.7 ± 4.0	2.1 ± 1.58	69894.5	< 0.001
Min platelets	157252 ± 94655.6	177120.8 ± 90595.7	110075.0	< 0.001
Min potassium	3.8 ± 0.8	3.8 ± 0.7	125962.0	< 0.001
Min SBP	75.4 ± 20.3	84.9 ± 19.6	92919.0	< 0.001
Min sodium	137.9 ± 6.1	138.2 ± 5.5	121722.5	0.155
Min WBC	13247.1 ± 8505.4	12.7 ± 6.9	122208.5	0.181
Min DBP	38.7 ± 14.9	44.9 ± 12.7	93559.5	< 0.001
Min SpO_2	81.3 ± 19.0	88.0 ± 12.0	94624.5	< 0.001

Motor response (GCS)	2.9 ± 2.2	4.3 ± 2.0	83488.5	< 0.001
$PaCO_2$	40.0 ± 13.9	39.5 ± 11.6	124352.0	0.321
PaO_2	137.4 ± 102.3	130.9 ± 82.4	121043.0	0.124
pH	7.3 ± 0.1	7.3 ± 0.1	109784.0	< 0.001
Respiratory rate	31.2 ± 15.1	27.5 ± 14.9	107284.5	< 0.001
Temperature	35.2 ± 1.9	36.2 ± 1.4	80674.5	< 0.001
Verbal response (GCS)	1.9 ± 1.5	2.3 ± 1.7	109666.5	< 0.001

BUN: Blood urea nitrogen; DBP: Diastolic blood pressure; GCS: Glasgow coma scale; INR: International normalized ratio; MAP: Medium Arterial Pressure; $PaCO_2$: Partial pressure of carbonic gas in arterial blood; PaO_2: Partial pressure of oxygen in arterial blood; SBP: Systolic blood pressure; SpO_2: Saturation of peripheral oxygen; WBC: White blood cells.

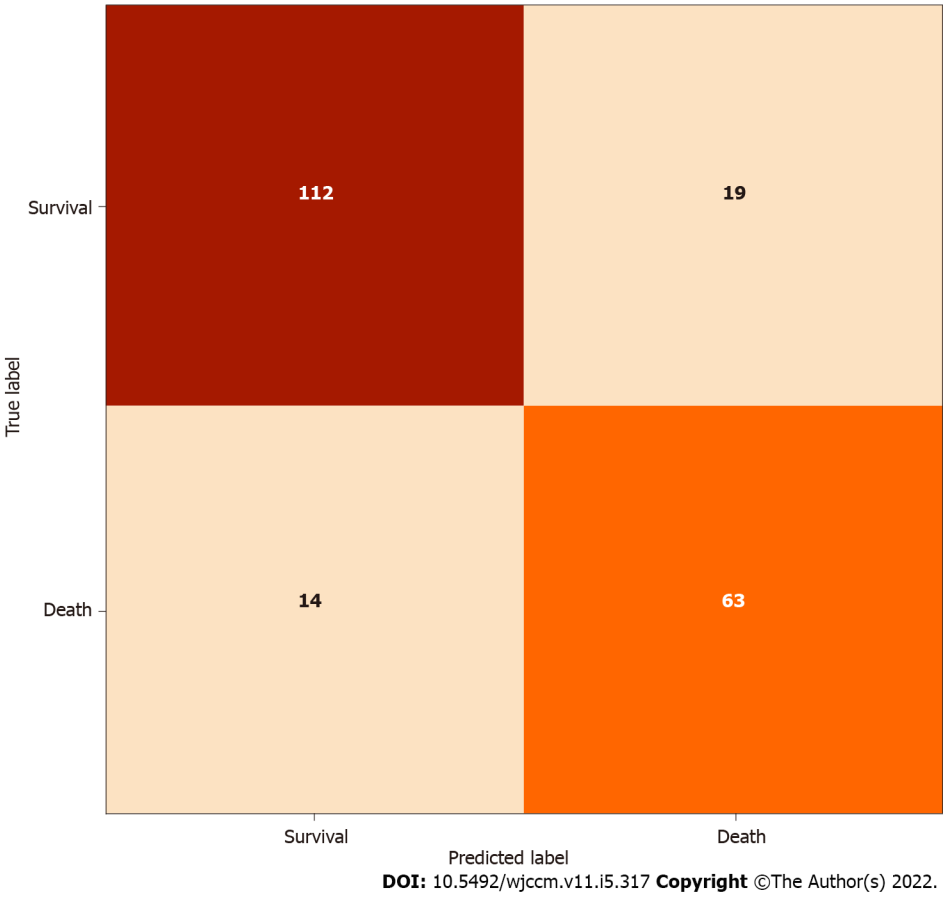

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Figure 2 Model confusion matrix. As illustrated, the model was able to accurately predict occurrence of death outcome for 63 of 77 patients and non-occurrence for 112 of 131 patients, with true positive and true negative rates of 76.8% and 88.9%, respectively.

79.43%. It is well established in the literature that this type of classifier is generally well suited for high-dimensional problems with highly correlated features (a frequent situation when it comes to medical data)[20]. Our results are consistent with that, as they demonstrate the potential for using random forests to handle clinical and laboratory data from patients under intensive monitoring.

The ICU mortality is high, and the patients require interventions that are cost-effective in order to avoid mortality without inputting unnecessary costs or demand to the medical team. Mortality prediction models work with the objective to assess the severity of the patients so that, based on its findings, the treatment needed can be directed. The analysis presented in this study works in the same way; if we identify those patients that have major mortality rates, faster and better care can be provided in order to prevent the worse outcome[21]. For this purpose, a variety of assessment scores already exist, like APACHE, SAPS or Mortality Probability Model (MPM). The ROC value of our model (0.85) was comparable with some of these highly used models, like 0.836 for APACHE II, or 0.826 for SAPS II[22], which showcase the good results obtained.

Table 2 Percentual importance of variables in the outcome prediction

Variable	Predictive importance, %
Maximum lactate	9.05
Minimum lactate	6.49
Temperature	6.47
Motor GCS	5.25
Maximum BUN	4.35
Minimum WBC	3.31
Minimum creatinine	3.22
Maximum INR	3.15
Minimum HCO_3	2.84
Maximum glucose	2.69
Minimum SpO_2	2.45
pH	2.18
Age	2.09
Minimum INR	1.95
Platelets	1.9
Maximum HCO_3	1.83
Minimum SBP	1.82
Minimum DBP	1.82
Maximum creatinine	1.79
Minimum albumin	1.67
Minimum sodium	1.66
Predominant systemic involvement	1.64
Maximum bilirubin	1.63
Maximum WBC	1.63
PaO_2	1.62
Minimum hemoglobin	1.6
Maximum SBP	1.6
Maximum albumin	1.5
MAP	1.5
Eyes opening GCS	1.46
Respiratory rate	1.41
Minimum calcium	1.4
Maximum hemoglobin	1.39
Minimum platelets	1.35
Minimum BUN	1.28
Hematocrit	1.22
Minimum bilirubin	1.2
$PaCO_2$	1.19
Maximum sodium	1.13
Maximum DBP	1.12
Maximum calcium	0.93

Minimum glucose	0.92
Minimum potassium	0.92
Maximum potassium	0.82
Heart rate	0.72
Verbal GCS	0.42
Intubated	0.15
Disease score	0.14
Maximum SpO_2	0.13

BUN: Blood urea nitrogen; DBP: Diastolic blood pressure; GCS: Glasgow coma scale; INR: International normalized ratio; MAP: Medium Arterial Pressure; $PaCO_2$: Partial pressure of carbonic gas in arterial blood; PaO_2: Partial pressure of oxygen in arterial blood; SBP: Systolic blood pressure; SpO_2: Saturation of peripheral oxygen; WBC: White blood cells.

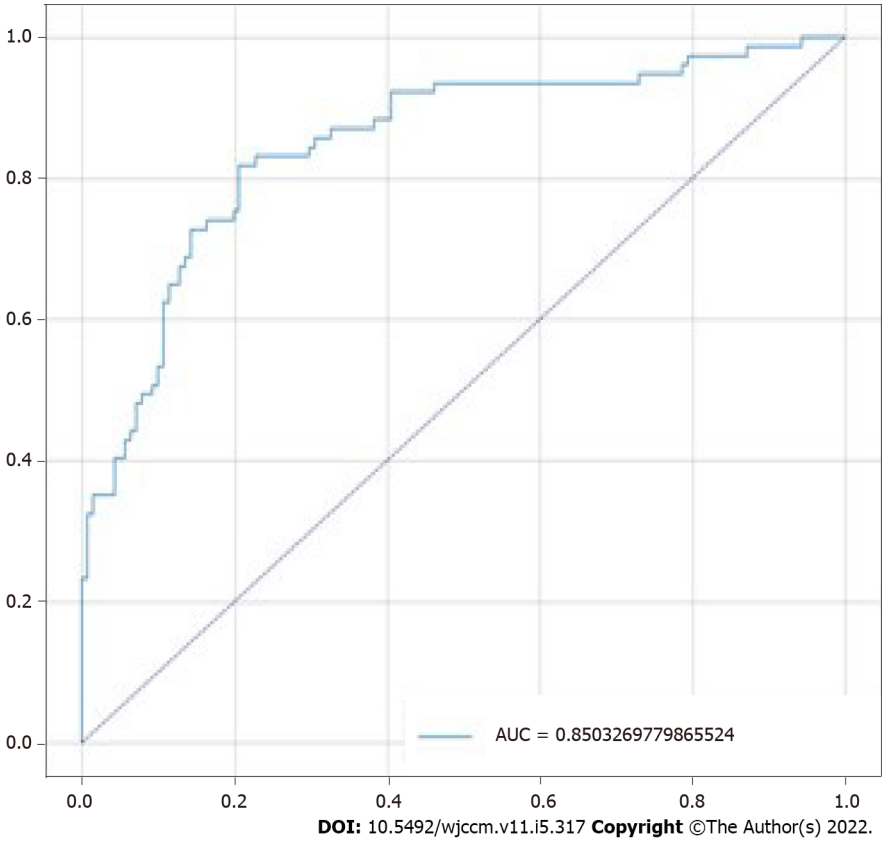

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Figure 3 Model receiver operating characteristic curve. The graph demonstrates the relationship between true and false positive rates, which led to an area under the curve of 85%. AUC: Area under the curve.

Furthermore, the machine learning approach to predict mortality in ICU patients has been documented. For example, Veith and Steele[23] developed a LazyKStar model to predict mortality in ICU patients at the time of hospital admission, obtaining a 10-fold validation AUC value of 0.75.A recurrent neural network inputted with 44 clinical and laboratory features from the first 24 h of ICU patient admission proposed by Thorsen-Meyer *et al*[24] achieved an AUC of 0.82. The extreme gradient boosted trees classifier developed by Chia *et al*[25] reached an AUC of 0.83 using 42 predictive variables. The formats and results of these last two studies are comparable to ours, since we reached an AUC of 0.85 using a random forest fed by 50 features.

Due to the COVID-19 pandemic, there was a great growth of publications focused on machine learning models for predicting ICU mortality in a disease-specific manner, such as those by Pan *et al* [16], Lichtner *et al*[26], and Subudhi *et al*[27]. Meanwhile, many of the previous studies in this field also focus on predicting ICU outcomes for specific diseases or morbid conditions, like sepsis or death from pulmonary tuberculosis[11,13,28], which lead to an assessment of parameters specific for the disease studied, somewhat restricting the research. Many of the renowned models and scales for ICU mortality

prediction demand a series of measurements to make their use possible, but not always all the data required are available. In this sense, it is important to understand what the main variables involved related to the outcome of interest (and its prediction) are, so that they can be closely monitored. In our study, lactate level proved to be the most influential one, which is in accordance with its physiological role that indicates poor oxygenation, anaerobic metabolism, acidosis and muscle fatigue, involved in a systemic response of the organ is mand corroborates the findings by Bou Chebl *et al*[29], Villar *et al*[30] and Vincent *et al*[2]. Despite its predictive importance found in our study (15.54%), lactate is not a variable of most scores used, and is not included in APACHE, SAPS or MPM.

Temperature, which is part of APACHE and SAPS, was the second variable that influenced the most the outcome prediction; its variation (hyper or hypothermia) is related with a loss of control of body homeostasis, and the mean valor for death outcome was 35.2 ± 1.9. While we have an increase of nearly 1 point in the mean value for the survival outcome, these data could represent that an increase of the temperature or even fever could be a positive body response, indicating an immune system attempt to fight the pathology[31,32].

The third variable of major impact is the motor GCS punctuation, which is part of GCS, a widely known scale for neurologic damage used in hospital admissions as well as assessment models[33].This motor element has a specific field only in APACHE IV. Lower punctuations in GCS are related with greater neurologic damage, with 3 and 1 as its bottom punctuation for the global and motor scale respectively, the mean of 2.9 ± 2.2 for the death outcome in contrast with the value of 4.3 ± 2.0 for the survival mean demonstrate a considerable difference between those patients since the greatest value possible for the motor component is 6. The stratification of the data based on its predictive value is a great contribution since the variables above discussed account for approximately 27% of the result, while the other 45 for the remaining 73%, indicating that continuous monitoring of them may be of great value. Considering their importance, a detailed survey with either a dataset with per hour measurement of parameters or the data separated by ICU type could lead to more specific approaches for the medical staff.

Despite the good results found, this study faces as its main limitation the incompleteness of the original dataset for many instances regarding important clinical and laboratory variables, which lead to the use of a relatively small quantity of instances to train the predictive model. Since machine learning algorithms are essentially data-driven, a larger amount of data could lead to greater accuracy and a wider generalizability of the model, thus being useful for additional testing and refinement. Another potential limitation is related to the clinically broad nature of the variables analyzed, since the purpose was to study the possible parameters available in the ICU, which contrasts with research focused on the outcomes for a specific disease and, therefore, fed with more specific variables with regards to the considered pathophysiological process.

Although the use of a wide range of clinical and laboratory parameters was critical for our purpose of assessing the predictive significance of the variables in the context of building a model that is not only explainable but also clinically interpretable, this factor may restrict the possibilities of potential datasets to be used to ascertain the reproducibility of the findings, since some parameters may be unavailable. However, since these are variables commonly evaluated in critically ill patients in the ICU, for whom the prognostic evaluation of mortality is more important (in view of their higher mortality rates), we believe that this should not be a limiting factor to the clinical applicability of the proposed model.

CONCLUSION

In the study, it was possible to develop a reliable model for predicting mortality in the ICU, in which the influence of lactate level stands out as the main variable involved in the outcome prediction, followed by temperature and motor GCS. What can be perceived through the research is that machine learning comes to contribute and to make medical practice more efficient, as it allows faster analysis that otherwise would be complex and time-consuming. More than that, it also allows us to critically question existing parameters and methodologies through the results it provides in order to allow improvements that reduce the mortality of patients and are time and cost-effective. This study also highlights the importance of complete and organized registers of ICU patient data in order to enable the development of predictive models towards prevention and prediction of in-hospital bad outcomes.

ARTICLE HIGHLIGHTS

Research background

The monitoring of clinical and laboratory parameters of patients in the intensive care unit (ICU) is an extremely important part of the routine of intensive care staff. Additionally, several scores already utilize these parameters to guide the assistance of these patients. In the meantime, the advance of technological resources, such as the machine learning approach, allows the development of predictive

models capable of being applied to medical practice.

Research motivation

Mortality in the ICU is something that worries and drives the search for alternatives that can help the team in directing treatment to avoid this negative outcome. Therefore, a predictive model that uses the patient's parameters can precisely influence this treatment guidance, improving the cost-effectiveness quickly and safely.

Research objectives

The objective of our study is the development of a binary classifier predictive model between the outcomes of death and non-death in ICU patients. This paper demonstrates the potency of emerging technological realities within the medical field and how it is possible to harness them to improve healthcare practices.

Research methods

Initially, we obtained a set of 1087 instances and 50 variables related to patients admitted to an ICU by using a public database. We calculated frequency and risk rate for categorical variables and means, standard deviations, and the Mann-Whitney *U* test for numerical variables. Afterwards, we divided the data for the application in training of the predictive model based on the Random Forest algorithm and then to test the effectiveness of the model.

Research results

Among the 50 variables associated with death outcome, the maximum and minimum lactate values were the most important predictors (15.54%) followed by temperature (6.47%), and motor Glasgow coma scale punctuation (5.25%). The Random Forest binary classifier predictive model (death and no death) showed accuracy of 80.28%, sensitivity of 81.82%, specificity of 79.43%, positive predictive value of 73.26%, negative predictive value of 84.85%, F1 score of 0.74, and area under the curve score of 0.85.

Research conclusions

This study demonstrated the development of a predictive model with high accuracy, sensitivity, and specificity for ICU patients by applying a machine learning approach, the Random Forest algorithm, to clinical and laboratory data.

Research perspectives

The proper registration of patient parameters, as well as the availability of more and larger databases and even further development of digital tools, can enhance machine learning approaches, enabling the refinement of predictive models and patient care.

FOOTNOTES

Author contributions: Caires Silveira E collected and entered the data, performed the data analysis/statistics and interpretation, and participated in preparation and review of manuscript; Mattos Pretti S and Santos BA participated in the preparation of manuscript and wrote the literature analysis/search; Santos Corrêa CF and Madureira Silva L participated in review of manuscript; Freire de Melo F designed the research and participated in review of manuscript.

Institutional review board statement: For this study, there was no need for an appraisal by an ethics committee, since only publicly available anonymized data were used.

Informed consent statement: This manuscript does not involve "Signed Informed Consent Form", as it was produced from previously anonymized, publicly available and free of charge data, obeying the norms of medical bioethics. Thus, there was no direct or even indirect contact between researchers and patients, with no necessity for "Signed Informed Consent Form" to carry out our study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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ORCID number: Elena Caires Silveira 0000-0003-3470-9205; Soraya Mattos Pretti 0000-0002-9835-7635; Bruna Almeida Santos 0000-0002-4543-3163; Caio Fellipe Santos Corrêa 0000-0002-5271-6911; Leonardo Madureira Silva 0000-0002-6444-8264; Fabrício Freire de Melo 0000-0002-5680-2753.

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REFERENCES

1 **Fuller BM**, Dellinger RP. Lactate as a hemodynamic marker in the critically ill. *Curr Opin Crit Care* 2012; **18**: 267-272 [PMID: 22517402 DOI: 10.1097/MCC.0b013e3283532b8a]
2 **Vincent JL**, Quintairos E Silva A, Couto L Jr, Taccone FS. The value of blood lactate kinetics in critically ill patients: a systematic review. *Crit Care* 2016; **20**: 257 [PMID: 27520452 DOI: 10.1186/s13054-016-1403-5]
3 **Nichol AD**, Egi M, Pettila V, Bellomo R, French C, Hart G, Davies A, Stachowski E, Reade MC, Bailey M, Cooper DJ. Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. *Crit Care* 2010; **14**: R25 [PMID: 20181242 DOI: 10.1186/cc8888]
4 **Levi M**, Opal SM. Coagulation abnormalities in critically ill patients. *Crit Care* 2006; **10**: 222 [PMID: 16879728 DOI: 10.1186/cc4975]
5 **Hunt BJ**. Bleeding and coagulopathies in critical care. *N Engl J Med* 2014; **370**: 847-859 [PMID: 24571757 DOI: 10.1056/NEJMra1208626]
6 **Ko M**, Shim M, Lee SM, Kim Y, Yoon S. Performance of APACHE IV in Medical Intensive Care Unit Patients: Comparisons with APACHE II, SAPS 3, and MPM_0 III. *Acute Crit Care* 2018; **33**: 216-221 [PMID: 31723888 DOI: 10.4266/acc.2018.00178]
7 **Ihnsook J**, Myunghee K, Jungsoon K. Predictive accuracy of severity scoring system: a prospective cohort study using APACHE III in a Korean intensive care unit. *Int J Nurs Stud* 2003; **40**: 219-226 [PMID: 12605944 DOI: 10.1016/s0020-7489(02)00062-7]
8 **Deo RC**. Machine Learning in Medicine. *Circulation* 2015; **132**: 1920-1930 [PMID: 26572668 DOI: 10.1161/CIRCULATIONAHA.115.001593]
9 **Heo J**, Yoon JG, Park H, Kim YD, Nam HS, Heo JH. Machine Learning-Based Model for Prediction of Outcomes in Acute Stroke. *Stroke* 2019; **50**: 1263-1265 [PMID: 30890116 DOI: 10.1161/STROKEAHA.118.024293]
10 **Lynch CM**, Abdollahi B, Fuqua JD, de Carlo AR, Bartholomai JA, Balgemann RN, van Berkel VH, Frieboes HB. Prediction of lung cancer patient survival *via* supervised machine learning classification techniques. *Int J Med Inform* 2017; **108**: 1-8 [PMID: 29132615 DOI: 10.1016/j.ijmedinf.2017.09.013]
11 **Liu Q**, Gao J, Luo B, Liu J, Zhang L, Kang W, Han F. Prediction model for death in patients with pulmonary tuberculosis accompanied by respiratory failure in ICU: retrospective study. *Ann Palliat Med* 2020; **9**: 2731-2740 [PMID: 32787360 DOI: 10.21037/apm-20-182]
12 **Hou N**, Li M, He L, Xie B, Wang L, Zhang R, Yu Y, Sun X, Pan Z, Wang K. Predicting 30-days mortality for MIMIC-III patients with sepsis-3: a machine learning approach using XGboost. *J Transl Med* 2020; **18**: 462 [PMID: 33287854 DOI: 10.1186/s12967-020-02620-5]
13 **Nemati S**, Holder A, Razmi F, Stanley MD, Clifford GD, Buchman TG. An Interpretable Machine Learning Model for Accurate Prediction of Sepsis in the ICU. *Crit Care Med* 2018; **46**: 547-553 [PMID: 29286945 DOI: 10.1097/CCM.0000000000002936]
14 **Assaf D**, Gutman Y, Neuman Y, Segal G, Amit S, Gefen-Halevi S, Shilo N, Epstein A, Mor-Cohen R, Biber A, Rahav G, Levy I, Tirosh A. Utilization of machine-learning models to accurately predict the risk for critical COVID-19. *Intern Emerg Med* 2020; **15**: 1435-1443 [PMID: 32812204 DOI: 10.1007/s11739-020-02475-0]
15 **Cheng FY**, Joshi H, Tandon P, Freeman R, Reich DL, Mazumdar M, Kohli-Seth R, Levin M, Timsina P, Kia A. Using Machine Learning to Predict ICU Transfer in Hospitalized COVID-19 Patients. *J Clin Med* 2020; **9** [PMID: 32492874 DOI: 10.3390/jcm9061668]
16 **Pan P**, Li Y, Xiao Y, Han B, Su L, Su M, Zhang S, Jiang D, Chen X, Zhou F, Ma L, Bao P, Xie L. Prognostic Assessment of COVID-19 in the Intensive Care Unit by Machine Learning Methods: Model Development and Validation. *J Med Internet Res* 2020; **22**: e23128 [PMID: 33035175 DOI: 10.2196/23128]
17 **Lee M**, Raffa J, Ghassemi M, Pollard T, Kalanidhi S, Badawi O, Matthys K, Celi LA. WiDS (Women in Data Science) Datathon 2020: ICU Mortality Prediction (version 1.0.0). *PhysioNet* 2020 [DOI: 10.13026/vc0e-th79]
18 **Breiman L**. Random Forests. *Mach Learn* 2001; **45**: 5-32 [DOI: 10.1023/A:1010933404324]
19 **Pedregosa F**, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O, Blondel M, Louppe G, Prettenhofer P, Weiss R, Weiss RJ, Vanderplas J, Passos A, Cournapeau D, Brucher M, Perrot M, Duchesnay E. Scikit-learn: Machine Learning in Python. *J MachLearn Res* 2011; **12**: 2825-2830
20 **Yang F**, Wang HZ, Mi H, Lin CD, Cai WW. Using random forest for reliable classification and cost-sensitive learning for medical diagnosis. *BMC Bioinformatics* 2009; **10** Suppl 1: S22 [PMID: 19208122 DOI: 10.1186/1471-2105-10-S1-S22]
21 **Awad A**, Bader-El-Den M, McNicholas J, Briggs J, El-Sonbaty Y. Predicting hospital mortality for intensive care unit patients: Time-series analysis. *Health Informatics J* 2020; **26**: 1043-1059 [PMID: 31347428 DOI: 10.1177/1460458219850323]
22 **Fuchs PA**, Czech IJ, Krzych ŁJ. The Pros and Cons of the Prediction Game: The Never-ending Debate of Mortality in the

Intensive Care Unit. *Int J Environ Res Public Health* 2019; **16** [PMID: 31540201 DOI: 10.3390/ijerph16183394]

23 **Veith N**, Steele R. Machine Learning-based Prediction of ICU Patient Mortality at Time of Admission. Proceedings of the 2nd International Conference on Information System and Data Mining; 2018 Mar; Lakeland, USA. New York: Association for Computing Machinery, 2018: 34-38 [DOI: 10.1145/3206098.3206116]

24 **Thorsen-Meyer HC**, Nielsen AB, Nielsen AP, Kaas-Hansen BS, Toft P, Schierbeck J, Strøm T, Chmura PJ, Heimann M, Dybdahl L, Spangsege L, Hulsen P, Belling K, Brunak S, Perner A. Dynamic and explainable machine learning prediction of mortality in patients in the intensive care unit: a retrospective study of high-frequency data in electronic patient records. *Lancet Digit Health* 2020; **2**: e179-e191 [PMID: 33328078 DOI: 10.1016/S2589-7500(20)30018-2]

25 **Chia A**, Khoo M, Lim A, Ong K, Sun Y, Nguyen B, Chua M, Pang J. Explainable machine learning prediction of ICU mortality. *Inform Med Unlocked* 2021; **25**: 100674 [DOI: 10.1016/j.imu.2021.100674]

26 **Lichtner G**, Balzer F, Haufe S, Giesa N, Schiefenhövel F, Schmieding M, Jurth C, Kopp W, Akalin A, Schaller SJ, Weber-Carstens S, Spies C, von Dincklage F. Predicting lethal courses in critically ill COVID-19 patients using a machine learning model trained on patients with non-COVID-19 viral pneumonia. *Sci Rep* 2021; **11**: 13205 [PMID: 34168198 DOI: 10.1038/s41598-021-92475-7]

27 **Subudhi S**, Verma A, Patel AB, Hardin CC, Khandekar MJ, Lee H, McEvoy D, Stylianopoulos T, Munn LL, Dutta S, Jain RK. Comparing machine learning algorithms for predicting ICU admission and mortality in COVID-19. *NPJ Digit Med* 2021; **4**: 87 [PMID: 34021235 DOI: 10.1038/s41746-021-00456-x]

28 **Su L**, Xu Z, Chang F, Ma Y, Liu S, Jiang H, Wang H, Li D, Chen H, Zhou X, Hong N, Zhu W, Long Y. Early Prediction of Mortality, Severity, and Length of Stay in the Intensive Care Unit of Sepsis Patients Based on Sepsis 3.0 by Machine Learning Models. *Front Med (Lausanne)* 2021; **8**: 664966 [PMID: 34291058 DOI: 10.3389/fmed.2021.664966]

29 **Bou Chebl R**, El Khuri C, Shami A, Rajha E, Faris N, Bachir R, Abou Dagher G. Serum lactate is an independent predictor of hospital mortality in critically ill patients in the emergency department: a retrospective study. *Scand J Trauma Resusc Emerg Med* 2017; **25**: 69 [PMID: 28705203 DOI: 10.1186/s13049-017-0415-8]

30 **Villar J**, Short JH, Lighthall G. Lactate Predicts Both Short- and Long-Term Mortality in Patients With and Without Sepsis. *Infect Dis (Auckl)* 2019; **12**: 1178633719862776 [PMID: 31431799 DOI: 10.1177/1178633719862776]

31 **Young PJ**, Saxena M, Beasley R, Bellomo R, Bailey M, Pilcher D, Finfer S, Harrison D, Myburgh J, Rowan K. Early peak temperature and mortality in critically ill patients with or without infection. *Intensive Care Med* 2012 [PMID: 22290072 DOI: 10.1007/s00134-012-2478-3]

32 **Rehman T**, deBoisblanc BP. Persistent fever in the ICU. *Chest* 2014; **145**: 158-165 [PMID: 24394828 DOI: 10.1378/chest.12-2843]

33 **Jain S**, Iverson LM. Glasgow Coma Scale. 2021 Jun 20. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan– [PMID: 30020670]

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CASE REPORT

Acute kidney injury associated with consumption of starfruit juice: A case report

Thajudeen Mohammed Zuhary, R Ponampalam

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Thajudeen Mohammed Zuhary, R Ponampalam, Department of Emergency Medicine, Singapore General Hospital, Singapore 169608, Singapore

Corresponding author: Thajudeen Mohammed Zuhary, MBBS, Doctor, Department of Emergency Medicine, Singapore General Hospital, Outram Road, Singapore 169608, Singapore. thajudeen.mohd.zuhary@sgh.com.sg

Abstract

BACKGROUND

This study aims to highlight the potential serious complications of acute kidney injury (AKI) resulting from the consumption of excessive amounts of starfruit, a common traditional remedy.

CASE SUMMARY

A 78-year-old male with a past medical history of hypertension, diabetes mellitus and hyperlipidemia without prior nephropathy presented to the emergency department (ED) with hiccups, nausea, vomiting and generalized weakness. In the preceding 1 wk, he had consumed 3 bottles of concentrated juice self-prepared from 1 kg of small sour starfruits. His serum creatinine was noted to be 1101 μmol/L from baseline normal prior to his ED visit. He was diagnosed with AKI secondary to excessive starfruit consumption.

CONCLUSION

Consumption of starfruit can cause acute renal failure, with a good outcome when promptly identified and treated.

Key Words: Acute kidney injury; Acute renal failure; Starfruit; Hemodialysis; Case report

Core Tip: Physicians should have a high index of suspicion on possible interactions and toxicities that may occur with the use of traditional medications in combination with prescription drugs in susceptible patients. This report highlights the toxicity of starfruit when consumed as a traditional remedy for diabetes mellitus resulting in acute kidney injury.

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INTRODUCTION

The starfruit (Averrhoa carambola) is a popular fruit in tropical countries due to its nutritional and medicinal benefits[1], and is used to treat various ailments such as diabetes mellitus, rheumatism, and cough. The starfruit is used as a traditional remedy in Asian countries such as Malaysia and Indonesia to treat diabetes mellitus due to its hypoglycemic properties[2]. Despite its frequent consumption, many people are unaware of the dangers of overindulging in starfruit. When consumed in large quantities, the fruit contains high levels of oxalic acid, which can be nephrotoxic. Starfruit-induced neurotoxicity and nephrotoxicity, which manifests as acute kidney injury (AKI) in individuals with underlying renal dysfunction, is well documented[3,4]. AKI in individuals with normal renal function is rare. We present a case report of AKI following the consumption of starfruit.

CASE PRESENTATION

Chief complaints

A 78-year-old male presented to the emergency department (ED) with hiccups, nausea, vomiting and generalized weakness.

History of present illness

In the preceding week, he had consumed 3 bottles of concentrated juice which were self-prepared from 1 kg of starfruits. Following ingestion of the third bottle of the fruit juice, he developed bouts of severe nausea and vomiting without abdominal pain or diarrhea.

History of past illness

He had a past medical history of hypertension, diabetes mellitus and hyperlipidemia.

Personal and family history

No significant family history.

Physical examination

On arrival at the ED, his vital signs were stable (temperature was 36.8°C, pulse rate 60 bpm, respiratory rate 18 breaths/min, and blood pressure 161/78 mmHg) and there was no pitting edema. Examinations of his cardiovascular, respiratory, abdominal and neurological systems were normal.

Laboratory examinations

Laboratory examination results are shown in Figure 1 and Table 1.

Imaging examinations

No imaging was undertaken.

MULTIDISCIPLINARY EXPERT CONSULTATION

The patient was initially seen in the ED and admitted under renal medicine for specialized care.

FINAL DIAGNOSIS

Acute kidney injury.

Table 1 Trend in patient's blood investigations

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Day 13	Day 17	Day 24	Day 60	Day 135
Renal function											
Serum creatinine (μmol/L)	1101		680	659	495	340	328	208	177	127	99
Serum urea (mmol/L)	38.1		23.1	27.1	22.0	14.5	25.2	17.4	10.6	12.4	6.2
Electrolytes											
Sodium (mmol/L)	134		142	146	147	137	135	136	138	140	144
Potassium (mmol/L)	4.4		3.5	3.5	3.1	4.0	4.3	4.0	4.1	3.8	3.9
Chloride (mmol/L)	101		105	102	100	98	101	102	105	108	110
Bicarbonate (mmol/L)	15.9		22.8	26.8	31.1	24.6	28.3	23.7	24.6	23.5	24.9
Magnesium (mmol/L)	0.91										
Liver function											
Total protein (g/L)	60										76
Serum albumin (g/L)	32										41
Total bilirubin (mmol/L)	07										09
Alkaline phosphatase (U/L)	58										65
Alkaline transaminase (U/L)	57										17
Routine tests											
White blood cells (× 10^9/L)	9.33					10.25					9.89
Neutrophil (%)	78.8					74.6					74.1
Lymphocytes (%)	11.1					11.6					15.9
Hemoglobin (g/dL)	12.3					13.8					14.1
Platelet count (× 10^9/L)	208					307					281
Coagulation											
APTT (secs)	27.0					28.5					
Prothrombin time (secs)	11.2					11.4					
Other indicators											
Creatine kinase (U/L)	7224			4755	2863	754		84			84
PTH (pg/mL)	11.0										
Urine creatinine (μmol/L)			5233					3862	7747		8035

APTT: Activated partial thromboplastin time; PTH: Parathyroid hormone.

TREATMENT

The patient was treated with 4 sessions of hemodialysis and supportive care such as intravenous fluid. After each session of hemodialysis, blood tests to determine renal function were repeated. Progressive improvement in renal function was noted with each session of hemodialysis.

OUTCOME AND FOLLOW-UP

The patient's renal function returned to normal.

DISCUSSION

Starfruit has several toxins including caromboxin, an excitatory central nervous system stimulant and

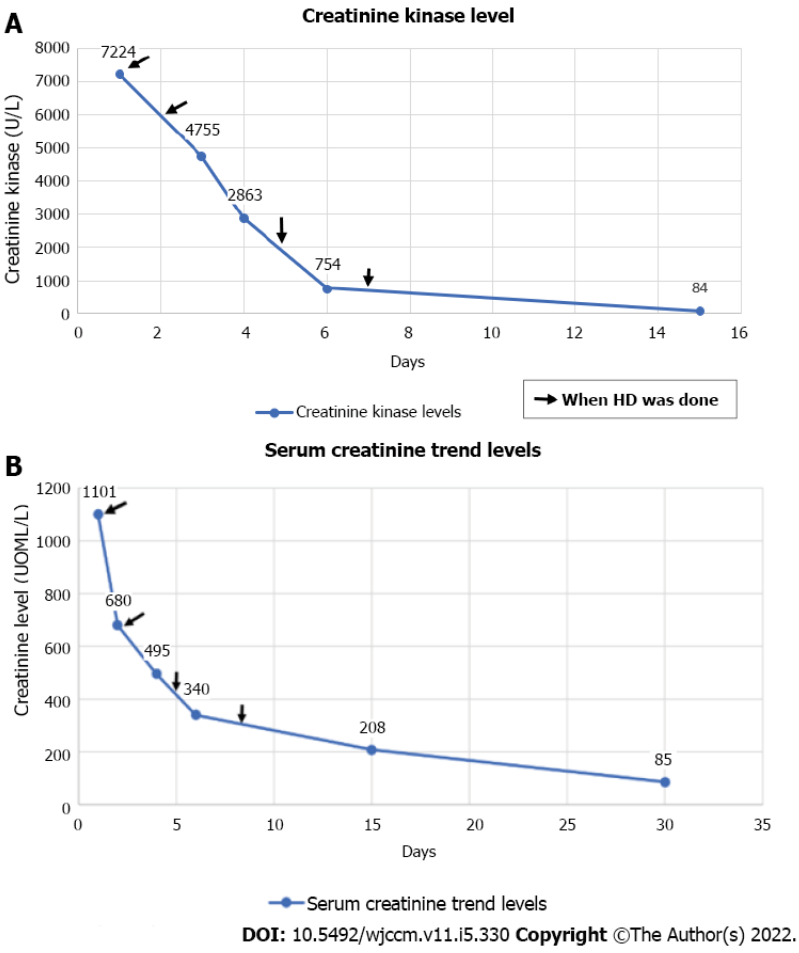

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Figure 1 Laboratory examination results. A: Trend in creatinine kinase following hemodialysis; B: Trend in serum creatinine.

oxalate a nephrotoxic agent[5-7]. The sour type of starfruit has higher levels of oxalate than the sweet type. Homemade and medicinal supplements often have high levels of oxalate. When consumed in large amounts, especially when fasting or dehydrated, deposits of calcium oxalate crystals in the renal tubules lead to kidney damage[6]. Chronic kidney disease has been identified as a major risk factor for starfruit-induced kidney toxicity. Starfruit juice volume of approximately 25 mL is known to cause nephrotoxicity in patients with chronic kidney disease. Other known risk factors include dehydration, the amount of starfruit ingested, and consumption on an empty stomach. Patients with starfruit toxicity show gastrointestinal symptoms such as nausea, vomiting, and abdominal discomfort immediately after ingestion. These symptoms are believed to be due to the direct corrosive effects of dietary oxalates rather than systemic effects[8]. This may be followed by a decrease in urinary output, which can lead to renal dysfunction and acute renal failure. Typical histological findings are the intraluminal and intraepithelial deposition of colorless oxalate crystals. There is no specific treatment for acute kidney damage from starfruit. In patients requiring renal replacement therapy, hemodialysis and hemoperfusion are preferred[9].

Our patient had no evidence of pre-existing renal failure or other contributory factors predisposing to AKI such as sepsis, dehydration, nephrotoxic drugs or obstructive urological causes based on clinical evaluation and tests done. In addition, over the course of four sessions of hemodialysis, he had gradual restoration of his renal function. The temporal relationship between the ingestion of large amount of fruit juice and the onset of symptoms in this case strongly suggests starfruit intoxication as the transient and reversible etiology likely due to resolving oxalate nephropathy.

CONCLUSION

In Asian countries where starfruit is commonly consumed as a traditional remedy, it is imperative for emergency physicians to be aware of starfruit toxicity in patients with unexplained AKI. This will help identify and treat these patients promptly to prevent starfruit-induced nephrotoxicity. Patient history is the key to reaching an early diagnosis. It is essential to prevent starfruit nephrotoxicity by educating the public and especially diabetics on the risks of consuming excess starfruit. Consumption of starfruit as a

traditional remedy to control blood sugar levels in diabetics should be discouraged by educating the public.

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Country/Territory of origin: Singapore

ORCID number: Thajudeen Mohammed Zuhary 0000-0003-1196-2670; R Ponampalam 0000-0002-5813-2044.

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REFERENCES

1 **Muthu N**, Lee SY, Phua KK, Bhore SJ. Nutritional, Medicinal and Toxicological Attributes of Star-Fruits (Averrhoa carambola L.): A Review. *Bioinformation* 2016; **12**: 420-424 [PMID: 28405126 DOI: 10.6026/97320630012420]
2 **Gunasekara LCA**, Fernando PHP, Sivakanesan R. A Preliminary Study on the Hypoglycaemic Effect of Averrhoa carambola (Star Fruit) in Rats. Sri Lanka: Proceedings of the Peradeniya University Research Sessions; 2011; 83 [DOI: 10.18006/2015.3(5).423.429]
3 **Neto MM**, Silva GE, Costa RS, Vieira Neto OM, Garcia-Cairasco N, Lopes NP, Haendchen PF, Silveira C, Mendes AR, Filho RR, Dantas M. Star fruit: simultaneous neurotoxic and nephrotoxic effects in people with previously normal renal function. *NDT Plus* 2009; **2**: 485-488 [PMID: 25949386 DOI: 10.1093/ndtplus/sfp108]
4 **Chang JM**, Hwang SJ, Kuo HT, Tsai JC, Guh JY, Chen HC, Tsai JH, Lai YH. Fatal Outcome after Ingestion of Star Fruit (AverrhoaCarambola) in Uremic Patients. *Am J Kidney Dis* 2000; **35**: 189-193 [DOI: 10.1016/S0272-6386(00)70325-8]
5 **Fang HC**, Lee PT, Lu PJ, Chen CL, Chang TY, Hsu CY, Chung HM, Chou KJ. Mechanisms of star fruit-induced acute renal failure. *Food Chem Toxicol* 2008; **46**: 1744-1752 [PMID: 18294746 DOI: 10.1016/j.fct.2008.01.016]
6 **Chen CL**, Fang HC, Chou KJ, Wang JS, Chung HM. Acute oxalate nephropathy after ingestion of star fruit. *Am J Kidney Dis* 2001; **37**: 418-422 [PMID: 11157385 DOI: 10.1053/ajkd.2001.21333]
7 **Su YJ**, Lee CH, Huang SC, Chuang FR. Quiz page April 2011. A woman with oliguria. Acute oxalate nephropathy caused by excess intake of pure carambola juice. *Am J Kidney Dis* 2011; **57**: A23-A25 [PMID: 21421133 DOI: 10.1053/j.ajkd.2010.11.023]
8 **Konta T**, Yamaoka M, Tanida H, Matsunaga T, Tomoike H. Acute renal failure due to oxalate ingestion. *Intern Med* 1998; **37**: 762-765 [PMID: 9804084 DOI: 10.2169/internalmedicine.37.762]
9 **Chen LL**, Fang JT, Lin JL. Chronic renal disease patients with severe star fruit poisoning: hemoperfusion may be an effective alternative therapy. *Clin Toxicol (Phila)* 2005; **43**: 197-199 [PMID: 15902795 DOI: 10.1081/CLT-57872]

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CASE REPORT

Cardiac arrest due to massive aspiration from a broncho-esophageal fistula: A case report

Gustavo Lagrotta, Mina Ayad, Ifrah Butt, Mauricio Danckers

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Gustavo Lagrotta, Graduate Medical Education, Pulmonary Disease, Aventura Hospital and Medical Center, Aventura, FL 33180, United States

Mina Ayad, Department of Internal Medicine, Aventura Hospital and Medical Center, Aventura, FL 33180, United States

Ifrah Butt, Department of Gastroenterology, Aventura Hospital and Medical Center, Aventura, FL 33180, United States

Mauricio Danckers, Division of Pulmonary and Critical Care Medicine, Aventura Hospital and Medical Center, Aventura, FL 331380, United States

Corresponding author: Gustavo Lagrotta, DO, Doctor, Graduate Medical Education, Pulmonary Disease, Aventura Hospital and Medical Center, 20900 Biscayne Blvd., Aventura, FL 33180, United States. gustavo.lagrottasaavedra@hcahealthcare.com

Abstract

BACKGROUND

Tracheo and broncho esophageal fistulas and their potential complications in adults are seldom encountered in clinical practice but carries a significant morbidity and mortality.

CASE SUMMARY

We present a case of a 39-year-old otherwise healthy man who presented to our hospital after ingestion of drain cleaner substance during a suicidal attempt. He unexpectedly suffered from cardiac arrest during his stay in the intensive care unit. The patient had developed extensive segmental trachea-broncho-esophageal fistulous tracks that led to a sudden and significant aspiration event of gastric and duodenal contents with subsequent cardiopulmonary arrest. Endoscopic evaluation of extension of fistulous track proved a slow and delayed progression of disease despite initial management with esophageal stenting for his caustic injury.

CONCLUSION

The aim of this case presentation is to share with the reader the dire natural history of trachea-broncho-esophageal fistulas and its delayed progression. We aim to illustrate pitfalls in the endoscopic examination and provide further aware-ness on critical care monitoring and management strategies to reduce its morbidity and mortality.

Key Words: Tracheoesophageal fistula; Broncho esophageal fistula; Caustic ingestion; Cardiopulmonary arrest; Critical care; Case report

Core Tip: Trachea-esophageal and broncho-esophageal in the setting of caustic ingestion is an unusual complication associated with high morbidity and mortality. Close monitoring of the gastrointestinal tract patency and motility is critical to avoid gastric distention and large aspiration events with detrimental consequences. Although there is no general consensus on the initial approach to patients with fistula formation, our case proposes serial esophagogastroduodenoscopy and flexible bronchoscopy for at least 6 mo as well as a low threshold for surgical referral when progression of disease or new findings are encountered.

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INTRODUCTION

Injuries from caustic substance ingestion are associated with varying grades of damage to the gastrointestinal and respiratory tract including esophagitis, mucosal burns, necrosis and perforation, stenosis, and rarely, trachea-esophageal (TEF), and broncho-esophageal (BEF) fistulas. Suicidal caustic ingestion strongly correlates with severity of injury and carries high morbidity and mortality[1]. We present the case of a young man after suicidal caustic ingestion of drain cleaner fluid who developed a sudden massive gastric and duodenal content aspiration into his airway through acquired large TEF and BEF fistulas leading to cardiopulmonary arrest.

CASE PRESENTATION

Chief complaints

A 39-year-old man arrived at our emergency department from another institution where he had been endotracheally intubated for airway protection.

History of present illness

The patient had sought medical attention five hours after a suicidal attempt where he ingested an unknown amount of drain cleaner liquid that contained sodium hydroxide, potassium hydroxide, and carbonyl diamide.

History of past illness

The patient had a free previous medical history.

Physical examination

Upon arrival to our facility, his vital signs were stable. His physical exam revealed edematous oral mucosa and chemical injuries to the face.

Laboratory examinations

His initial laboratory data was remarkable for a white blood cell count of 12.9 × 10^3/μL and a D-dimer > 5250 ng/mL DDU.

Imaging examinations

Chest computer tomography (CT) with contrast revealed thickening and submucosal edema of the esophageal and gastric wall, along with trace para-esophageal and peri-gastric stranding and fluid. No free air was reported.

FINAL DIAGNOSIS

Tracheo and broncho esophageal fistulas leading to massive aspiration and cardiac arrest.

TREATMENT

He was started on a proton pump inhibitor, intravenous fluids, and prophylactic antibiotics. A tracheostomy and jejunostomy tube were placed on hospital day 13. He was noted to have bouts of coughing during routine sedation-awakening trials and with reduction in sedatives. On hospital day 18, he became acutely hypoxic, and his oxygen saturation decreased to 50% followed by pulseless electrical arrest. Advanced cardiopulmonary resuscitation was initiated with recovery of spontaneous circulation after two 5-min rounds of cardiopulmonary resuscitation. Copious amounts of frothy, yellow-tinted secretions were noted from the tracheostomy in-line suction setup. No oral secretions were noted during oral cavity suction. A nasogastric tube was placed for gastric cavity decompression and approximately 400-500 mL of fluid were suctioned. Figure 1 demonstrates chest imaging obtained prior and post cardiopulmonary arrest highlighting the patient's acute clinical change. On day 22, the patient underwent successful placement of a 1.8 cm in outer diameter and 12.3 cm in length fully covered esophageal stent.

The patient's hospital course was complicated by acute respiratory distress syndrome and recurrent septic shock secondary to aspiration pneumonia. He was eventually liberated from mechanical ventilation and transitioned to a tracheostomy collar. He continued on enteral nutrition through a jejunostomy feeding tube. He left the intensive care unit on day 40 and was discharged home with home-health on day 114.

OUTCOME AND FOLLOW-UP

His endoscopy surveillance revealed progression and further extend of disease. Bronchoscopies performed on day 1 and day 8 as noted in Figure 2 demonstrate the progression of the insult. Bronchoscopy performed after 17 wk revealed new tracheoesophageal fistula with esophageal lumen opening at midway through posterior wall of the trachea (Figure 3A and B). His prior bronchoscopy at 7 wk had shown protrusion of esophageal stent through the left main broncho-esophageal fistula without any additional fistulous tracts (Figure 3C). Esophagoduodenoscopy (EGD) performed 7 mo after initial presentation visualized tracheostomy tube through a combined lumen formed by the esophagus and trachea (Figure 3D). Distal to the tracheostomy tube, a double lumen is identified with the esophagus opening at the proximal end of the stent (Figure 3E) as well as a complete obliteration of the stent in his distal end due to in-growth tissues (Figure 3F). The patient has been referred for cardiothoracic surgical evaluation where he will complete nutritional optimization prior to potential surgical intervention. Chron-ology of events is listed in Table 1.

DISCUSSION

Caustic ingestion remains a rare but potentially catastrophic mechanism for injury leading to significant morbidity and mortality. Specific management guidelines have yet to be defined[2]. Injury severity is determined by multiple factors including type of agent, its concentration, amount consumed, and time of contact with gastrointestinal mucosa. Agents can be either acidic or alkali. Our patient ingested drain cleaner liquid, predominantly an alkali substance.

TEF is a delayed and unusual complication that occurs approximately in 3% of patients with caustic ingestion[2]. BEF are not extensively described in the literature and their true incidence unknown. The rarity of BEFs is likely due to the anatomical relationship between the left mainstem bronchus and the esophagus. The thoracic esophagus extends caudally towards the diaphragmatic hiatus, passing posteriorly to the trachea, the tracheal bifurcation, and the left main stem bronchus[3]. The area of contact of the posterior wall of the left main bronchus with the anterior wall of the esophagus, in contrast to that of the trachea, is significantly smaller, making left main BEFs less likely to develop than TEF.

Hemorrhage, thrombosis, and inflammation with edema occur within the first 24 h. If caustic ingestion is severe enough, transmural necrosis leads to perforation and regional fistulous tract formation. TEFs and BEFs can lead to sepsis, aspiration pneumonia, acute respiratory distress syndrome, strictures, malignancy among other systemic complications[2]. In our patient, the fistulous tract was significant enough to allow for large amounts of gastric and duodenal content to reach the airway causing hypoxemia and cardiopulmonary arrest.

Medical literature on the incidence of cardiopulmonary arrest due to aspiration through a BEF is lacking, and its incidence is not defined. We infer that our patient's aspiration leading to his arrest was

Table 1 Timeline of major events in chronological order

Event	Time
Admission to hospital/ICU	Day 0
EGD #1	Day 0
Bronchoscopy #1	Day 1
Bronchoscopy #2	Day 8
Cardiac arrest	Day 18
Esophageal stent placement with EGD #2	Day 22
Bronchoscopy #3	7 wk
Hospital discharge	16 wk
Bronchoscopy #4	17 wk
EGD #3	28 wk

ICU: Intensive care unit; EGD: Esophagoduodenoscopy.

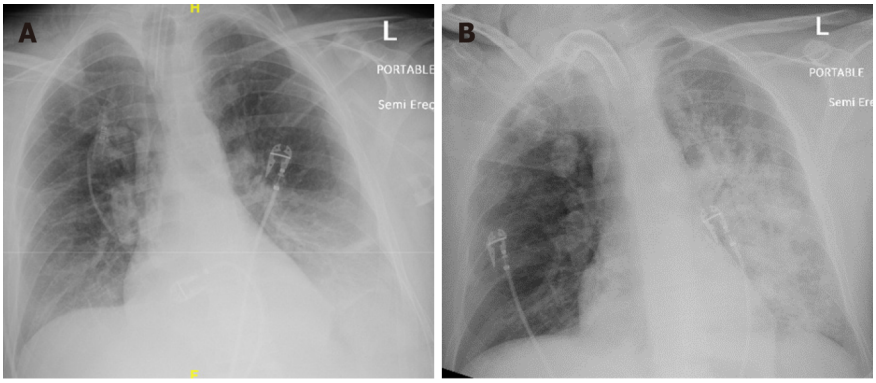

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Figure 1 Chest X-ray. A: Chest X-ray on the left was obtained one day prior to cardiac arrest which shows bibasilar atelectasis; B: Chest X-ray on the right obtained following episode of cardiopulmonary arrest showing significant patchy airspace opacities occupying most of left hemithorax.

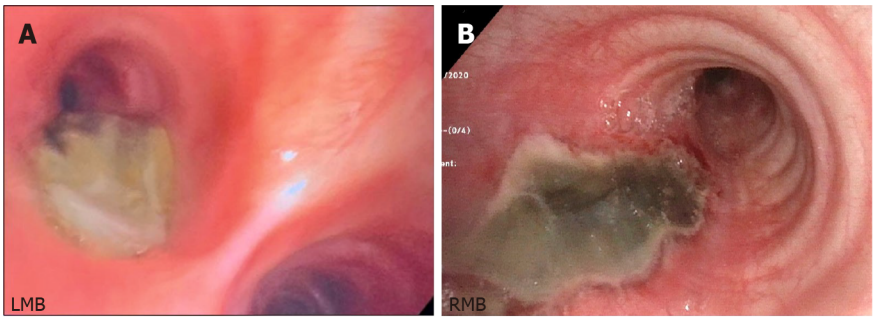

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Figure 2 Flexible bronchoscopy. A: Day 1: Two-centimeter bronchoesophageal fistula (asterisk) with adjacent yellow tinged devitalized mucosa on the posterior wall of left main bronchi; B: Day 8: Further delineation of fistulous track (asterisk) with necrotic mucosa and well-defined borders. LMB: Left main bronchi; RMB: Right main bronchi.

due to increased output through a persistently large fistulous track in the setting of transient duodenal outlet stenosis from mucosal damage and impaired gastrointestinal motility. Our patient exhibited large amounts of bile-colored tracheal secretions in the peri-arrest period confirming a high output fistulous passage of duodenal content. Although in our case the volume we aspirated through naso-gastric suctioning was 400-500 mL, the exact volume of gastric content aspirated is unknown. However, it was large enough to infiltrate the lingula and left lower lobe.

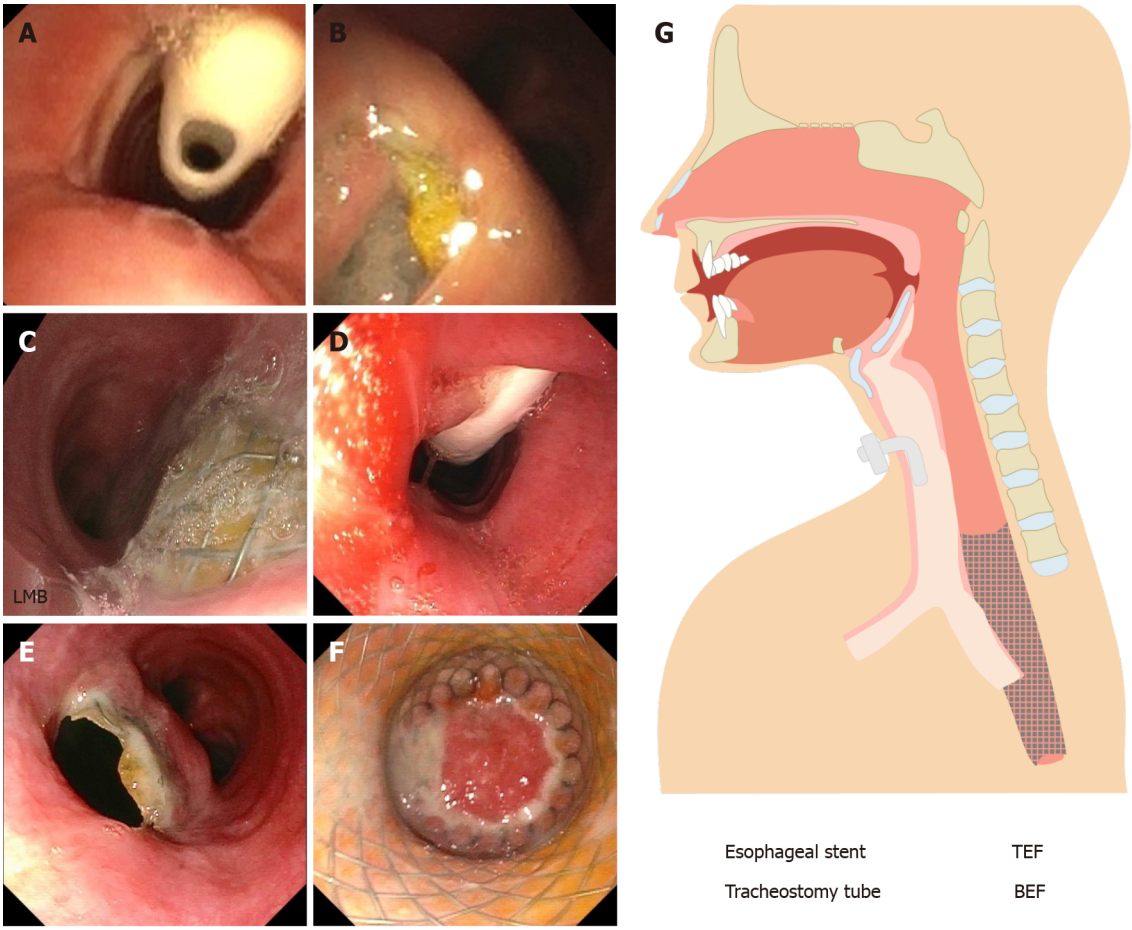

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Figure 3 Flexible bronchoscopy at 17 wk. A: Visualization of tracheostomy tube (asterisk) shortly after bronchoscope is advanced through vocal cords; B: Esophageal lumen visualized at the level of mid-trachea confirming TEF. Flexible Bronchoscopy at 7 wk; C: Protruding esophageal stent through left main bronchi BEF. Esophagoduodenoscopy at 28 wk; D: Visualization of tracheostomy tube (asterisk) through a combined lumen of the esophagus and trachea at 14 cm; E: Proximal end of the esophageal stent located below the end of the tracheotomy at 23cm with a double lumen track, esophagus at 8 o'clock and trachea at 2 o'clock; F: Complete obliteration of esophageal stent due to in-growth of tissue at 35 cm (asterisk); G: Schematic diagram. LMB: Left main bronchi; TEF: Tracheoesophageal fistula; BEF: Bronchoesophageal fistula.

The incidence of aspiration pneumonia related to corrosive ingestion has been estimated in up to 4.2% of cases with a mortality up to 60%[4]. Due to high risk of aspiration, enteral nutrition is often restricted[4]. In addition, caloric restriction and malnutrition further lead to recurrent pulmonary infections, bronchopneumonia, and sepsis[5]. Alternative means of enteral nutrition through the insertion of a jejunostomy tube were sought in our patient to enhance nutritional state as well as to promote fistula healing. A high index of suspicion should be maintained for functional or anatomic gastrointestinal tract obstruction as a consequence of caustic injury and should be considered when addressing nutritional support to select the most suitable nutritional route.

Risk stratification is needed during the initial approach. Symptoms such as dysphagia, hematemesis, stridor, cough, respiratory distress, drooling, and abdominal pain have been described. A sudden bout of uncontrolled paroxysmal cough, a reported symptom associated with BEF[6], was witnessed in our patient while mechanically ventilated during daily sedation awakening trials suggesting aspiration events and persistent fistula.

There is no consensus within the medical community of the initial and emergent management of TEF/BEF after caustic ingestion. In 2015, the World Society of Emergency Surgery recommended a management algorithm which includes both endoscopy and CT imaging as part of the initial assessment [7]. Our patient underwent both, esophagogastroduodenoscopy and non-contrast CT scan within the first twenty-four hours of ingestion. Figure 4 demonstrates initial esophagoduodenoscopy findings. In order to quantify the severity of the injury, we utilized the Zargar classification system which placed him in the IIIB category[8]. This grading is useful for predicting systemic complications, respiratory failure, nutritional autonomy, and survival. In general, the degree of esophageal injury at endoscopy is a predictor of systemic complication and death with a 9-fold increase in morbidity and mortality for every increased injury grade[9] which aligns with our case study. An important tool for the clinician about risk rather than timing.

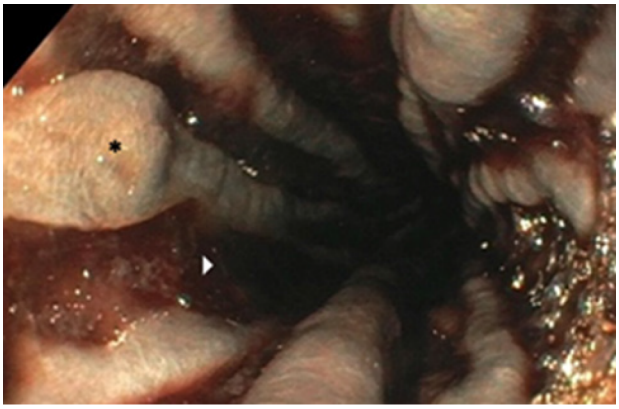

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Figure 4 Esophagoduodenoscopy. Extensive esophageal esophagitis with devitalized mucosa (asterisk) and deep brownish black ulcers (arrowhead).

However, risk stratification cannot accurately predict the depth of necrosis which could lead to inappropriate non-operative management and/or unnecessary surgical resection[2]. In order to properly evaluate the extent of necrosis, we propose that there is a benefit for surveillance endoscopic examination through EGD and flexible bronchoscopies for early fistula detection and therapeutic interventions. This would also serve for the monitoring of long term sequelae such as airway stenosis, or such in our case, further development of fistulous tracks. The interval of bronchoscopies would be dictated by endoscopic findings. In our case, evidence of a large newly detected TEF occurred 4 mo after the initial event. Prior biweekly and monthly bronchoscopies only reported the known BEF. It is reasonable to suggest monthly endoscopic surveillance in patients with high Zargar Score for at least 4-6 mo following the initial ingestion. In patients who are able to be discharged from the hospital, surgical referral should be sought if endoscopic examination does not show a favorable course, new fistulous tracks are detected, or if the patient's symptoms severely impair quality of life.

The treatment of TEFs and BEFs is based on previous case reports, reviews, and case series, along with experts' opinions. In our case, a multidisciplinary team agreed on the placement of an 18 mm × 123 mm fully covered esophageal wall stent. According to the World Journal of Emergency Surgery, endoscopic treatment is the gold standard for closing large esophageal defects such suspected in our patient for the exam of injury during initial endoscopic examination. Self-expandable stents have showed to have a higher success rate and lower mortality rate when compared to surgical approach [10]. Our patient underwent self-expandable sent placement due to the clinical complexity and added surgical risk in the setting of a recent cardiac arrest. This case illustrates both the prolonged hospital course of a cardiac arrest survival due to delayed complications of a BEF associated with functional impairment and also the protracted progression of the disease more than 6 mo later.

CONCLUSION

In conclusion, TEF and BEF in the setting of caustic ingestion is an unusual complication associated with high morbidity and mortality. Early and frequent endoscopic evaluation of the upper gastrointestinal tract and bronchial tree, as well as maintaining a high index of clinical suspicion, are necessary for its prompt recognition. This will lead to early detection of delayed complications including new fistulous tracks, and timely institution of therapeutic interventions. We remind the reader of the importance of close monitoring of the gastrointestinal tract patency and motility to avoid gastric distention and large aspiration events with detrimental consequences. Although there is no general consensus on the initial approach to patients with fistula formation, our case proposes serial EGDs and flexible bronchoscopy for at least 6 mo as well as a low threshold for surgical referral when progression of disease or new findings are encountered.

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ORCID number: Gustavo Lagrotta 0000-0003-1800-5654; Mina Ayad 0000-0002-6505-5390; Ifrah Butt 0000-0002-1593-6894; Mauricio Danckers 0000-0002-6387-1060.

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REFERENCES

1 **Ertekin C**, Yanar H, Taviloglu K, Guloglu R, Alimoglu O. Can endoscopic injection of epinephrine prevent surgery in gastroduodenal ulcer bleeding? *J Laparoendosc Adv Surg Tech A* 2004; **14**: 147-152 [PMID: 15245666 DOI: 10.1089/1092642041255513]
2 **Mircea C**, Bonavina L, Kelly MD, Sarfati E, Cattan P. Caustic ingestion. *Lancet* 2017; **389**: 2041-2052 [DOI: 10.1016/s0140-6736(16)30313-0]
3 **Braden K**, Urma D. Esophagus-anatomy and development. *GI Motility* 2006 [DOI: 10.1007/978-1-4614-3794-9_19]
4 **Tseng YL**, Wu MH, Lin MY, Lai WW. Outcome of acid ingestion related aspiration pneumonia. *Eur J Cardiothorac Surg* 2002; **21**: 638-643 [DOI: 10.1016/s1010-7940(02)00045-3]
5 **Argüder E**, Aykun G, Karalezli A, Hasanoğlu HC. Bronchoesophageal fistula. *J Bronchology Interv Pulmonol* 2012; **19**: 47-49 [PMID: 23207263 DOI: 10.1097/LBR.0b013e31823fc99e]
6 **Aggarwal D**, Mohapatra PR, Malhotra B. Acquired bronchoesophageal fistula. *Lung India* 2009; **26**: 24-25 [PMID: 20165591 DOI: 10.4103/0970-2113.45201]
7 **Bonavina L**, Chirica M, Skrobic O, Kluger Y, Andreollo NA, Contini S, Simic A, Ansaloni L, Catena F, Fraga GP, Locatelli C, Chiara O, Kashuk J, Coccolini F, Macchitella Y, Mutignani M, Cutrone C, Poli MD, Valetti T, Asti E, Kelly M, Pesko P. Foregut caustic injuries: results of the world society of emergency surgery consensus conference. *World J Emerg Surg* 2015; **10**: 44 [PMID: 26413146 DOI: 10.1186/s13017-015-0039-0]
8 **Cheng HT**, Cheng CL, Lin CH, Tang JH, Chu YY, Liu NJ, Chen PC. Caustic ingestion in adults: the role of endoscopic classification in predicting outcome. *BMC Gastroenterol* 2008; **8**: 31 [PMID: 18655708 DOI: 10.1186/1471-230X-8-31]
9 **Zargar SA**, Kochhar R, Mehta S, Mehta SK. The role of fiberoptic endoscopy in the management of corrosive ingestion and modified endoscopic classification of burns. *Gastrointest Endosc* 1991; **37**: 165-169 [PMID: 2032601 DOI: 10.1016/s0016-5107(91)70678-0]
10 **Chirica M**, Kelly MD, Siboni S, Aiolfi A, Riva CG, Asti E, Ferrari D, Leppäniemi A, Ten Broek RPG, Brichon PY, Kluger Y, Fraga GP, Frey G, Andreollo NA, Coccolini F, Frattini C, Moore EE, Chiara O, Di Saverio S, Sartelli M, Weber D, Ansaloni L, Biffl W, Corte H, Wani I, Baiocchi G, Cattan P, Catena F, Bonavina L. Esophageal emergencies: WSES guidelines. *World J Emerg Surg* 2019; **14**: 26 [PMID: 31164915 DOI: 10.1186/s13017-019-0245-2]

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Peer Reviewer of *World Journal of Critical Care Medicine*, Yin Ping Wong, FIAC, MD, Assistant Professor, Department of Pathology, Universiti Kebangsaan Malaysia, Cheras 56000, Kuala Lumpur, Malaysia. ypwong@ppukm.ukm.edu.my

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MINIREVIEWS

Rationale for integration of palliative care in the medical intensive care: A narrative literature review

Nishkarsh Gupta, Raghav Gupta, Anju Gupta

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Nishkarsh Gupta, Department of Anesthesiology, All India Institute of Medical Sciences, Delhi 110029, India

Raghav Gupta, Department of Onco-Anesthesiology and Palliative Medicine, All India Institute of Medical Sciences, Delhi 110029, India

Anju Gupta, Department of Anesthesiology, Pain Medicine and Critical Care, All India Institute of Medical Sciences, Delhi 110029, India

Corresponding author: Anju Gupta, MBBS, MD, DNB, Assistant Professor, Department of Anesthesiology, Pain Medicine and Critical Care, All India Institute of Medical Sciences, Ansari Nagar, Delhi 110029, India. dranjugupta2009@rediffmail.com

Abstract

Despite the remarkable technological advancement in the arena of critical care expertise, the mortality of critically ill patients remains high. When the organ functions de-teriorate, goals of care are not fulfilled and life-sustaining treatment becomes a burden on the patient and caregivers, then it is the responsibility of the physician to provide a dignified end to life, control the symptoms of the patient and provide psychological support to the family members. Palliative care is the best way forward for these patients. It is a multidimensional specialty which emphasizes patient and family-based care and aims to improve the quality of life of patients and their caregivers. Although intensive care and palliative care may seem to be at two opposite ends of the spectrum, it is necessary to amalgamate the postulates of palliative care in intensive care units to provide holistic care and best benefit patients admitted to intensive care units. This review aims to highlight the need for an alliance of palliative care with intensive care in the present era, the barriers to it, and models proposed for their integration and various ethical issues.

Key Words: Intensive care; Palliative care; Support; Barriers; Holistic care; End of life

Core Tip: Critical care and palliative care may seem to be mutually exclusive, but the amalgamation of the two provides the best combination of care to the patients needing intensive care. Palliative care has several beneficial roles in intensive care, such as symptom control, end-of-life discussions, and providing psychological support to patients' caregivers. However, there are several barriers to its implementation. These can be overcome by education and awareness improvement, capacity building, and developing a national-level framework policy for incorporating palliative care with intensive care.

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INTRODUCTION

The aim of admitting patients to the intensive care unit (ICU) is to maintain the homeostasis of the body and to reduce overall morbidity and mortality. Despite the technological advancement and critical care expertise available, the death rate in ICU is still as high as 18.1%[1]. When the organ functions deteriorate, goals of care are not fulfilled and life-sustaining treatment becomes a burden on both the patient and caregivers, then it is the responsibility of the physician to provide a dignified end to life, control the symptoms of the patient and provide psychological support to the family members. Also, it has been observed that patients who survive the ICU stay suffer from 'post-intensive care syndrome' in which they face anxiety, stress and depression for a long period even after discharge. The same syndrome has also been identified in caregivers[2]. The possible solution to this conundrum is palliative care. It is a multidimensional specialty which emphasizes patient and family-based care. It has been defined by International Association for Hospice & Palliative Care (IAHPC) in 2018 as "The active holistic care of individuals across all ages with serious health-related suffering due to severe illness, and especially of those near the end of life. It aims to improve the quality of life of patients and their caregivers"[3]. It states that dying is a natural process and the aim is neither to quicken the death nor delay the inevitable.

Although intensive care and palliative care may seem to be at two opposite ends of the spectrum, it is necessary to amalgamate the postulates of palliative care in ICU to provide holistic care and best benefit ICU patients. This review aims to highlight the need for a coalition of palliative care with intensive care.

MATERIALS AND METHODS

Literature search strategy

Search strategy and selection criteria were developed to identify relevant articles, and key questions were formulated to construct an analytic framework. Using PubMed, Embase, and Google Scholar and a systematic review method, a comprehensive literature search was conducted with the inclusion criteria related to the role of palliative care in intensive care management, specifically studies and reports on the present status, applications, benefits, roadblocks, various models to provide palliative care in critical care setup and ethical issues related to this topic. Studies published prior to 2012 were excluded. Keywords searched included "palliative care," "intensive care," "critical care," "intensive therapy unit," "intensive care unit", "integration", "application", "barriers", "models", "benefits", "ethical issues", "pain assessment" and "capacity building initiative". The various keywords were joined using Boolean operators "And" "Or" and "Not" in various combinations to obtain the relevant articles, which were then carefully screened for eligibility for inclusion in the review. The references of relevant articles were further hand searched. This information was extracted and organized in text and tabular form. The search mainly focused on identifying studies on palliative care in relation to critical care and was then narrowed to relevant literature.

Inclusion criteria

Studies that were included had to meet the following criteria: (1) Having a publication date of on or after 2012 and in the English language; (2) studies related to palliative care and intensive care; (3) all ages, genders and ethnicities; and (4) study designs being case-control studies, case studies, case reviews, guidelines, systematic reviews, and meta-analysis.

Exclusion criteria

Studies that were published prior to 2012; articles in languages other than English; literature that did not

have a full text available; and articles reporting on interventions without evidence of integration or insufficient information to support their approach, were excluded from the review.

Data analysis

This literature review is presented as a qualitative non-meta-analysis narrative review. The data extracted is established on the grounds of previously reviewed articles. The first step in extracting the data was to decide which type of study designs were to be included in this review. Then any publication prior to 2012 was excluded. The next step was to focus on extracting those articles that were related to and supported the core concept of this review while minimizing bias and maintaining the reliability and validity of the data.

DISCUSSION

Key components of palliative care in ICU

Identifying patients who are terminally ill. Inviting patients and caregivers in the decision-making process through effective communication. Inviting a primary physician in the combined decision-making process. Ensuring appropriate ICU admission which benefits the patient. Implementing effective symptom control and management. Providing psychological support to caregivers. Using a step-down approach from ICU to ward after family meeting[4]. Providing bereavement care.

Indications for palliative care in ICU

In case of an acute catastrophic event, patients need to be admitted to ICU for intensive monitoring and better symptom control; and for conducting end-of-life care discussions with the family[5].

Indications for palliative care referral in ICU

Indications for palliative care referral in ICU included: Age > 80 years, chronic critical illness with ICU stay > 14 d; patients with multiple comorbid conditions (e.g., advanced malignancy, chronic liver/kidney disease, *etc*.); advanced medical directive from the patient requesting for minimal interventions; and conditions where life-sustaining treatments are deemed medically futile by primary physicians[6-9]. These indications for the requirement of palliative care in ICU are present in 14%-20% of admitted patients[10]. Identification of triggering factors will lead to better and effective mobilization of ICU resources and help in identifying patients' unmet palliative care needs[11]. Also, according to the recently conducted 'Cross Country Comparison of Expert Assessments of the Quality of Death and Dying' which attempted to assess the standard of end-of-life care given by various countries - India ranked 59th out of 80 countries[12]. This highlights the fact that awareness in India regarding end-of-life care is poor especially due to the reluctance to discuss openly death. Dying in ICU is considered to be impersonal and invasive. A good death is a peaceful end occurring in the presence of loved ones[13]. Thus it is imperative to provide dignified death to a terminally sick patient based on the principle of right attitude, appropriate behavior, compassion and honest communication[14].

Barriers to providing palliative care in ICU

Barriers are at two levels: (1) The level of patient and caregivers. There is an inability to accept the poor outcome, and an inability to accept that there is an endpoint to life-sustaining treatment. There are differences in opinion among caregivers. In many cases, patients are not in a physical condition to make a decision for themselves; (2) the level of the physician[15,16]. There is a misconception that palliative care is only for patients who are actively dying, a concept that if palliative care is provided, it would accelerate the death of the patient, misunderstanding that palliative care is totally different from critical care, rather than being two aspects of the holistic treatment process, challenge to assess and screen the patients for whom palliative care referral should be administered, lack of knowledge and awareness at the level of patients and the physicians are the biggest hurdle. Also, there is a lack of training at the undergraduate level which leads to this lack of knowledge related to palliative care among physicians. There are a few factors at various levels which preclude the integration of palliative care in ICU[17].

Other barriers involve the followings. There is a lack of management resources, training and knowledge among the healthcare workers to provide palliative care in ICU. Also, there is a lack of uniform guidelines and policies.

There is an absence of appropriate infrastructure to facilitate the involvement of family members in providing palliative care. Also, healthcare workers have to face a lot of moral and emotional distress while providing palliative care in ICU.

In many cases, there is disagreement among the family members regarding providing palliative care. Also, patients are unable to participate in the decision-making process during terminal illness.

Lack of communication and interaction among the members of the multidisciplinary team impedes the integration of palliative care in the ICU.

Benefits of integrating palliative care in ICU

The benefits include increased patient and caregiver satisfaction; better patient assessment and symptomatic management; decreased length of ICU and hospital stay; decreased duration of ventilation; decreased anxiety and depression among family members.

Models to provide palliative care in critical care setup

There can be various models: (1) Integration model - Palliative care principles are understood and implemented by ICU physicians without involving any palliative care specialist. The emphasis is to improve the internal system and enhance the skills and knowledge of ICU physicians in providing appropriate palliative care where required. To enhance their knowledge and skills, critical care specialists can attend various programs, *e.g.*, End of Life Nursing Education Consortium (ELNEC)–Critical Care training program and Critical Care Communication skills program ("C-3"); (2) Consultation model - The ICU clinicians request Palliative consultations from Palliative care specialists. This model is superior as it improves overall outcomes. It caters to patients with a higher risk of poor outcomes rather than all the cases in the ICU. Initially, the consultations may be for a specific group of patients, but after the benefits are shown the number of referrals will increase for other patients in ICU as well. Sometimes psychologists, social workers and spiritual workers can also be involved to provide holistic care. This model has a disadvantage in that patients and relatives may feel that there are too many physicians involved and there is no single point of contact for them. Also, ICU clinicians may not develop the interest to enhance their skills pertaining to palliative care if they feel that they already have specialists available; and (3) Mixed model - The primary physician manages basic palliative care problems themselves and consultation with a palliative care specialist is required if they feel that they are unable to resolve the problem. The need for consultation from a palliative care specialist is identified by the factors, *e.g.*, pre-existing functional dependence, age > 80 years, advanced malignancy, multi-organ dysfunction, severe traumatic brain injury and extreme prematurity in pediatric patients. This model incorporates advantages from both the integrative and consultation model (Table 1)[18,19].

Ethical issues in providing palliative care in ICU

End-of-life care discussions: These discussions are always a challenge for both caregivers and physicians in ICU. The acceptance takes time and the cycle of discussion often begins with denial, where a 'cafeteria approach' should be followed. Caregivers must be explained the advantages and disadvantages of aggressive ICU treatment. Caregivers must always be given an assurance that comfort and symptom management of their patients will always be ensured in all circumstances. If the patient has given advanced directive regarding what they would want for themselves if they are critically ill, then it becomes easy for both the physician and caregivers as it reduces the burden on family members to take that difficult decision[20,21]. However, in many countries, the concept of an advanced directive is still in a nascent phase. In Europe, end-of-life care discussions are being carried out by intensive care physicians rather than palliative care specialists[22].

Assessment of the decision capacity of the patient and caregivers: It is important to assess the decision capacity of patients which may be difficult sometimes in the critically ill because of their poor general condition, age, and cognitive and hearing impairment. In such cases, the decision capacity of caregivers should be assessed. But in many cases, there are many family members involved. Thus, it becomes imperative to identify who are the family members available and who among them will take a concrete decision for their patient.

The decision to withhold or withdraw the treatment: This is a very sensitive decision and discussions should be done along with family members and the primary physician before coming to any conclusion. The futility of any further treatment should be established, the consensus among all the decision makers should be reached and the process should be documented before withholding or withdrawing further active treatment measures.

Pain assessment in ICU patients

Pain is the fifth vital sign and is often overlooked in the hospital setting. Pain assessment and management in critically ill patients in ICU is an integral component of providing holistic palliative care [23,24]. Assessment of pain becomes even more difficult in patients who are intubated and unable to communicate. Thus, we must know about various assessment scales.

Scales to assess pain in patients who can communicate: Visual analog scale: The patient marks their pain level on a 10 cm line; Numeric rating scale: patients rate their pain level, zero means no pain and 10 means the worst possible pain they are bearing; Verbal rating scale: Patients can choose a word like mild, moderate and severe which describes their pain level intensity[25].

Scales to assess pain in patients who cannot communicate: Behavioral Pain Scale (BPS): it computes the pain based upon facial expressions, compliance with the mechanical ventilator and upper limb movements. Critical Care Pain Observation Tool (CPOT): Apart from three parameters involved in behavioural pain score, muscle tension should also be considered[26].

Table 1 Steps to choose an appropriate model to provide palliative care in critical care setup

Assess the capacity of staff, availability of resources and level of skills and knowledge among the clinicians
Assess the understanding of ICU clinicians regarding the need for palliative care in ICU and their receptivity to the same
Assess the interest level of ICU clinicians to strengthen their knowledge and skills related to palliative care
Form a multidisciplinary committee including a critical care specialist, palliative care physician, hospital administrator, nursing staff, psychologist and a social worker to decide upon the best model for providing palliative care in the ICU of their institute.
Try to use the 'mixed model' for providing palliative care in ICU as it incorporates advantages of both the integration and consultation model

ICU: Intensive care unit.

Palliative sedation in ICU

Another key component of palliative care is to provide palliative sedation to relieve the patient from unbearable symptoms at the end of life. This is done most commonly with the help of sedatives like opioids and benzodiazepines. The drugs chosen should be easily available and must have good efficacy with minimal side effects. Before initiating palliative sedation, one must ensure that alternative methods to provide relief were not effective or led to major side effects. Palliative sedation should not be considered the same as euthanasia, as it only intends to relieve a patient's suffering and not hasten the process of death[27]. It is based upon the principle of informed consent and autonomy[28].

Capacity building initiative of developing palliative care in ICU

Adding MD and Ph.D. programs in palliative medicine: Palliative care should be included in the academic curricula of all medical colleges. Increasing public awareness and organizing camps with help of non-governmental organizations: Developing national level framework policy for developing palliative care in ICU. Initiating the workshops in which trainers are trained themselves first, which will help in developing local expertise. Teleconsultation should be utilized to gain knowledge from experts. Keyholders from different areas - like ICU care physicians, hospital administrators and palliative care physicians should come together and form a team to implement palliative care in the ICU. Leaders from ICU, palliative care consultation service and hospital administration: conducting a needs assessment and evaluating the resources. There should be a sufficient number of trained personnel. Educational resources such as libraries should be available for physicians to strengthen their knowledge related to palliative care. Legal documents should be there for surrogate decision-making. An alternate place to provide care to the patient should be decided on who no longer needs ICU care. Developing an action plan: According to the availability of resources, goals of care to address the unmet need should be established. Targets should be set that are easy and plausible. Changes that are required in the system should be identified to achieve the set target. The documentation process should be valid. Regular audits should be conducted to evaluate the changes and progress made[29,30].

CONCLUSION

The role of palliative care in critically ill patients admitted to ICU is important and the principles of palliative care should be integrated at the earliest. Integration of palliative care in the ICU improves the overall quality of life and decreases the hospital and ICU stay without affecting the overall mortality. Ensuring a dignified end to life is an art that every physician should learn. ICU doctors should be given palliative care training and they must consult palliative care specialists when required. Training and education starting from the undergraduate level is the way to ensure that all patients who are admitted to ICU along with their caregivers get access to palliative care services.

FOOTNOTES

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ORCID number: Nishkarsh Gupta 0000-0002-8444-2564; Anju Gupta 0000-0003-1726-1488.

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REFERENCES

1 **Divatia JV**, Amin PR, Ramakrishnan N, Kapadia FN, Todi S, Sahu S, Govil D, Chawla R, Kulkarni AP, Samavedam S, Jani CK, Rungta N, Samaddar DP, Mehta S, Venkataraman R, Hegde A, Bande BD, Dhanuka S, Singh V, Tewari R, Zirpe K, Sathe P; INDICAPS Study Investigators. Intensive Care in India: The Indian Intensive Care Case Mix and Practice Patterns Study. *Indian J Crit Care Med* 2016; **20**: 216-225 [PMID: 27186054 DOI: 10.4103/0972-5229.180042]

2 **Needham DM**, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, Zawistowski C, Bemis-Dougherty A, Berney SC, Bienvenu OJ, Brady SL, Brodsky MB, Denehy L, Elliott D, Flatley C, Harabin AL, Jones C, Louis D, Meltzer W, Muldoon SR, Palmer JB, Perme C, Robinson M, Schmidt DM, Scruth E, Spill GR, Storey CP, Render M, Votto J, Harvey MA. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med* 2012; **40**: 502-509 [PMID: 21946660 DOI: 10.1097/CCM.0b013e318232da75]

3 **IAHPC**. Global Consensus based palliative care definition. Houston, TX: The International Association for Hospice and Palliative Care. 2018. Available from: https://hospicecare.com/what-we-do/projects/consensus-based-definition-of-palliative-care/definition/

4 **Cox S**, Handy JM, Blay A. Palliative Care in the ICU. *J Intensive Care Soc* 2012; **13**: 320-326 [DOI: 10.1177/175114371201300411]

5 **Melville A**, Kolt G, Anderson D, Mitropoulos J, Pilcher D. Admission to Intensive Care for Palliative Care or Potential Organ Donation. *Crit Care Med* 2017; **45**

6 **Mosenthal AC**, Weissman DE, Curtis JR, Hays RM, Lustbader DR, Mulkerin C, Puntillo KA, Ray DE, Bassett R, Boss RD, Brasel KJ, Campbell M, Nelson JE. Integrating palliative care in the surgical and trauma intensive care unit: a report from the Improving Palliative Care in the Intensive Care Unit (IPAL-ICU) Project Advisory Board and the Center to Advance Palliative Care. *Crit Care Med* 2012; **40**: 1199-1206 [PMID: 22080644 DOI: 10.1097/CCM.0b013e31823bc8e7]

7 **Nelson JE**, Curtis JR, Mulkerin C, Campbell M, Lustbader DR, Mosenthal AC, Puntillo K, Ray DE, Bassett R, Boss RD, Brasel KJ, Frontera JA, Hays RM, Weissman DE; Improving Palliative Care in the ICU (IPAL-ICU) Project Advisory Board. Choosing and using screening criteria for palliative care consultation in the ICU: a report from the Improving Palliative Care in the ICU (IPAL-ICU) Advisory Board. *Crit Care Med* 2013; **41**: 2318-2327 [PMID: 23939349 DOI: 10.1097/CCM.0b013e31828cf12c]

8 **Cox CE**, Curtis JR. Using Technology to Create a More Humanistic Approach to Integrating Palliative Care into the Intensive Care Unit. *Am J Respir Crit Care Med* 2016; **193**: 242-250 [PMID: 26599829 DOI: 10.1164/rccm.201508-1628CP]

9 **Bradley CT**, Brasel KJ. Developing guidelines that identify patients who would benefit from palliative care services in the surgical intensive care unit. *Crit Care Med* 2009; **37**: 946-950 [PMID: 19237901 DOI: 10.1097/CCM.0b013e3181968f68]

10 **Hua MS**, Li G, Blinderman CD, Wunsch H. Estimates of the need for palliative care consultation across united states intensive care units using a trigger-based model. *Am J Respir Crit Care Med* 2014; **189**: 428-436 [PMID: 24261961 DOI: 10.1164/rccm.201307-1229OC]

11 **Adler K**, Schlieper D, Kindgen-Milles D, Meier S, Schwartz J, van Caster P, Schaefer MS, Neukirchen M. [Integration of palliative care into intensive care : Systematic review]. *Anaesthesist* 2017; **66**: 660-666 [PMID: 28589374 DOI: 10.1007/s00101-017-0326-0]

12 **Finkelstein EA**, Bhadelia A, Goh C, Baid D, Singh R, Bhatnagar S, Connor SR. Cross Country Comparison of Expert Assessments of the Quality of Death and Dying 2021. *J Pain Symptom Manage* 2022; **63**: e419-e429 [PMID: 34952169 DOI: 10.1016/j.jpainsymman.2021.12.015]

13 **Meier EA**, Gallegos JV, Thomas LP, Depp CA, Irwin SA, Jeste DV. Defining a Good Death (Successful Dying): Literature Review and a Call for Research and Public Dialogue. *Am J Geriatr Psychiatry* 2016; **24**: 261-271 [PMID: 26976293 DOI: 10.1016/j.jagp.2016.01.135]

14 **Cook D**, Rocker G. Dying with dignity in the intensive care unit. *N Engl J Med* 2014; **370**: 2506-2514 [PMID: 24963569 DOI: 10.1056/NEJMra1208795]

15 **Scheunemann LP**, McDevitt M, Carson SS, Hanson LC. Randomized, controlled trials of interventions to improve communication in intensive care: a systematic review. *Chest* 2011; **139**: 543-554 [PMID: 21106660 DOI: 10.1378/chest.10-0595]

16 **Kennedy R**, Abdullah N, Bhadra R, Bonsu NO, Fayezizadeh M, Ickes H. Barriers to Effective use of Palliative Care Services in the Acute Care Setting with Emphasis on Terminal Noncancer Diseases. *Indian J Palliat Care* 2019; **25**: 203-209 [PMID: 31114104 DOI: 10.4103/IJPC.IJPC_201_18]

17 **Hamdan Alshehri H**, Olausson S, Öhlén J, Wolf A. Factors influencing the integration of a palliative approach in intensive care units: a systematic mixed-methods review. *BMC Palliat Care* 2020; **19**: 113 [PMID: 32698809 DOI: 10.1186/s12904-020-00616-y]

18 **Mercadante S**, Gregoretti C, Cortegiani A. Palliative care in intensive care units: why, where, what, who, when, how. *BMC Anesthesiol* 2018; **18**: 106 [PMID: 30111299 DOI: 10.1186/s12871-018-0574-9]

19 **Hua M**, Wunsch H. Integrating palliative care in the ICU. *Curr Opin Crit Care* 2014; **20**: 673-680 [PMID: 25233330 DOI: 10.1097/MCC.0000000000000149]

20 **Quill TE**, Holloway R. Time-limited trials near the end of life. *JAMA* 2011; **306**: 1483-1484 [PMID: 21972312 DOI: 10.1001/jama.2011.1413]

21 **Chow GV**, Czarny MJ, Hughes MT, Carrese JA. CURVES: a mnemonic for determining medical decision-making capacity and providing emergency treatment in the acute setting. *Chest* 2010; **137**: 421-427 [PMID: 20133288 DOI: 10.1378/chest.09-1133]

22 **Metaxa V**, Anagnostou D, Vlachos S, Arulkumaran N, van Dusseldorp I, Bensemmane S, Aslakson R, Davidson JE, Gerritsen R, Hartog C, Curtis R. Palliative care interventions in intensive care unit patients - a systematic review protocol. *Syst Rev* 2019; **8**: 148 [PMID: 31228954 DOI: 10.1186/s13643-019-1064-y]

23 **Payen JF**, Bosson JL, Chanques G, Mantz J, Labarere J; DOLOREA Investigators. Pain assessment is associated with decreased duration of mechanical ventilation in the intensive care unit: a post Hoc analysis of the DOLOREA study. *Anesthesiology* 2009; **111**: 1308-1316 [PMID: 19934877 DOI: 10.1097/ALN.0b013e3181c0d4f0]

24 **Devlin JW**, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, Watson PL, Weinhouse GL, Nunnally ME, Rochwerg B, Balas MC, van den Boogaard M, Bosma KJ, Brummel NE, Chanques G, Denehy L, Drouot X, Fraser GL, Harris JE, Joffe AM, Kho ME, Kress JP, Lanphere JA, McKinley S, Neufeld KJ, Pisani MA, Payen JF, Pun BT, Puntillo KA, Riker RR, Robinson BRH, Shehabi Y, Szumita PM, Winkelman C, Centofanti JE, Price C, Nikayin S, Misak CJ, Flood PD, Kiedrowski K, Alhazzani W. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med* 2018; **46**: e825-e873 [PMID: 30113379 DOI: 10.1097/CCM.0000000000003299]

25 **Karcioglu O**, Topacoglu H, Dikme O. A systematic review of the pain scales in adults: Which to use? *Am J Emerg Med* 2018; **36**: 707-714 [PMID: 29321111 DOI: 10.1016/j.ajem.2018.01.008]

26 **Severgnini P**, Pelosi P, Contino E, Serafinelli E, Novario R, Chiaranda M. Accuracy of Critical Care Pain Observation Tool and Behavioral Pain Scale to assess pain in critically ill conscious and unconscious patients: prospective, observational study. *J Intensive Care* 2016; **4**: 68 [PMID: 27833752 DOI: 10.1186/s40560-016-0192-x]

27 **Cherny NI**, Portenoy RK. Sedation in the management of refractory symptoms: guidelines for evaluation and treatment. *J Palliat Care* 1994; **10**: 31-38 [PMID: 8089815]

28 **Boyle J**. Medical ethics and double effect: the case of terminal sedation. *Theor Med Bioeth* 2004; **25**: 51-60 [PMID: 15180095 DOI: 10.1023/b:meta.0000025096.25317.22]

29 **Aslakson RA**, Curtis JR, Nelson JE. The changing role of palliative care in the ICU. *Crit Care Med* 2014; **42**: 2418-2428 [PMID: 25167087 DOI: 10.1097/CCM.0000000000000573]

30 **Jazieh AR**. Capacity Building in Palliative Care. *J Palliative Care Med* 2013; **3**: 138 [DOI: 10.4172/2165-7386.1000138]

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MINIREVIEWS

Current role of high dose vitamin C in sepsis management: A concise review

Deven Juneja, Prashant Nasa, Ravi Jain

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Deven Juneja, Institute of Critical Care Medicine, Max Super Speciality Hospital, New Delhi 110017, India

Prashant Nasa, Department of Critical Care Medicine, NMC Specialty Hospital, Dubai 7832, United Arab Emirates

Ravi Jain, Department of Critical Care Medicine, Mahatma Gandhi Medical College and Hospital, Jaipur 302022, Rajasthan, India

Corresponding author: Deven Juneja, DNB, FCCP, MBBS, Director, Institute of Critical Care Medicine, Max Super Speciality Hospital, No. 1 Press Enclave Road, Saket, New Delhi 110017, India. devenjuneja@gmail.com

Abstract

Sepsis and septic shock are common diagnoses for patients requiring intensive care unit admission and associated with high morbidity and mortality. In addition to aggressive fluid resuscitation and antibiotic therapy, several other drugs have been tried as adjuvant therapies to reduce the inflammatory response and improve outcomes. Vitamin C has been shown to have several biological actions, including anti-inflammatory and immunomodulatory effects, which may prove beneficial in sepsis management. Initial trials showed improved patient outcomes when high dose vitamin C was used in combination with thiamine and hydrocortisone. These results, along with relative safety of high-dose (supra-physiological) vitamin C, encouraged physicians across the globe to add vitamin C as an adjuvant therapy in the management of sepsis. However, subsequent large-scale randomised control trials could not replicate these results, leaving the world divided regarding the role of vitamin C in sepsis management. Here, we discuss the rationale, safety profile, and the current clinical evidence for the use of high-dose vitamin C in the management of sepsis and septic shock.

Key Words: Ascorbic acid; Critical care; Infection; Sepsis; Septic shock; Vitamin C

Core Tip: High-dose vitamin C is increasingly used in varied clinical conditions including sepsis and septic shock. Even though a few initial studies showed remarkable improvements in outcomes, later studies failed to replicate these effects. Through this article, we wish to review the rationale and current clinical evidence for use of vitamin C in the management of patients with sepsis and septic shock.

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INTRODUCTION

Vitamin C, or ascorbic acid, is a water-soluble vitamin that acts as an anti-oxidant and as a co-factor for multiple enzymes. For a long time, vitamin C deficiency has been associated with the occurrence of Scurvy disease. However, in recent years, vitamin C has been established to have different biochemical effects and has been increasingly used in varied clinical conditions that include severe acute pancreatitis, sepsis, and cancer[1-3]. Being a water-soluble vitamin, vitamin C is generally considered to be safe even at high dosages. Although no clear guidelines or recommendations exist for the administration of vitamin C, it is still being used to manage these diseases, even in critically-ill patients. Mortality associated with sepsis and septic shock remains high though the disease, its prognosis, and management procedures are well established earlier. Intravenous fluid resuscitation and hemodynamic support, early administration of appropriate antibiotics, source control, and organ support form the mainstay of therapy[4]. Over the years, various therapeutic methods that include activated protein C, ulinastatin, and vitamin C have been tested as adjuvant therapies to improve the outcomes[2,5,6]. However, these therapies failed to achieve any significant and meaningful outcome and their role in sepsis management remains ambiguous[4]. In this background, the aim of the current review is to discuss the scientific rationale behind the usage of high-dose vitamin C (HDVC) in patients with sepsis and septic shock and evaluate its clinical evidence.

RATIONALE

In general, normal serum contains more than 50 μmol/L vitamin C[7]. However, acutely-ill patients exhibit a rapid reduction in their vitamin C levels, while critically-ill patients, especially those with sepsis, show extremely low vitamin C levels (below 11 μmol/L), in spite of the recommended enteral and parenteral nutritional intakes[8]. Moreover, commonly-employed organ-support intensive care unit (ICU) interventions like continuous renal replacement therapy (CRRT) also reduce the levels of water-soluble vitamins like vitamin C[9].

Vitamin C exhibits several biochemical effects that may potentially benefit the management of patients with sepsis and septic shock (Table 1)[10,11]. Sepsis results in the release of several reactive oxygen species (ROS) which are capable of causing severe injury to lipids, proteins, and nucleic acid that in turn results in endothelial and mitochondrial dysfunction, cell death, and ultimately multiple organ dysfunction syndrome (MODS). Vitamin C exerts its anti-oxidant effects by scavenging these ROS. Further, it also helps in recycling other anti-oxidants like vitamin E and tetrahydrobioptrin (BH4). Thus, it plays a major role in preventing oxidative damage and cell death[12,13].

Sepsis tends to reduce the functions of adenosine triphosphate (ATP) and causes bioenergetic failure of mitochondria, secondary to oxidative damage caused by mitochondrial ROS and alterations in fatty acid metabolism[14]. Vitamin C exhibits anti-oxidant effect and prevents the oxidative damage, and it also helps in carnitine production that improves fatty acid metabolism in mitochondria[15]. These actions may be helpful in the prevention of cell death, leading to septic cardiomyopathy and MODS.

Sepsis causes microvascular dysfunction which reduces the arteriolar reactivity to vasoconstrictors. This phenomenon results in vasodilation and shock. Vitamin C acts as a co-factor for the enzymes that are required for the synthesis of catecholamines and vasopressors. Thus, it enhances the synthesis of these enzymes and improves arteriolar sensitivity to vasopressors by inhibiting endothelial expression of inducible nitric oxide synthase (iNOS). In addition, vitamin C also has several immuno-modulatory and anti-inflammatory effects that help in abating cytokine storm associated with sepsis-induced MODS [10,11,16].

Table 1 Biological effects of vitamin C

Biological effects of vitamin C	Mechanisms of action
Antioxidant properties	Reduced production of reactive oxygen species; Reduced production of endothelial nitric oxide
Prevention of mitochondrial dysfunction	Reduction of oxidation injury; Reduces apoptosis
Prevention of septic cardiomyopathy	Reduction of oxidation injury; Increased carnitine synthesis; Reduces apoptosis
Prevention of micro and macro vascular dysfunction	Acts as a co-factor for synthesis of catecholamines (epinephrine, norepinephrine) and vasopressin; Inhibition of iNOS expression
Anti-inflammatory effects	Supresses activation of nuclear factor kappa-B (NF-κB); Inhibits tumor necrosis factor-α; Reduces pro-inflammatory cytokines like high mobility group box-1; Lowers histamine levels
Immune enhancing effects	T-cell maturation and modulation; Improves neutrophil chemotaxis and phagocytosis; Enhances oxidative killing; Promotes proliferation of lymphocytes; Stimulates interferon production; Increased antibody production

CLINICAL STUDIES

Several randomised controlled trials (RCTs) have been conducted in recent years to explore the plausibility of clinical benefits, achieved from the antioxidative effect of vitamin C, in reducing sepsis-induced tissue injury (Table 2). The authors conducted a systematic search using keywords such as 'Vitamin C' OR 'Ascorbic acid' AND Sepsis OR "Septic Shock" in PubMed and Google Scholar and found a total of 17 RCTs suitable for the current analysis. Out of the 17, five were about the application of vitamin C alone in patients with sepsis[17-21]. The current study followed a heterogeneous design with different doses of vitamin C monotherapy *vs* combination therapy with thiamine and hydrocortisone and the timing of administration.

Isolated vitamin C therapy

Out of the RCTs considered, five compared vitamin C with placebo in patients with sepsis. Different doses were used in the studies under consideration[17-21]. All the studies, except one, failed to infer any clinically meaningful difference with the usage of vitamin C[18]. The CITRIS-ALI trial compared vitamin C (at a dose of 50 mg/kg q6h) with a placebo in patients with sepsis and acute respiratory distress syndrome. No significant difference was found in the mean change of sequential organ failure assessment (SOFA) scores between the groups considered, from baseline to 96 h. The changes in C-reactive protein (CRP) and thrombomodulin levels, at 168 h, were also statistically non-significant. In terms of subgroup analysis, the 28-d mortality rate (without adjustment for multiple comparisons) was found to be significantly lower in the vitamin C group (29.8% *vs* 46.3%; $P = 0.03$)[17].

The largest and the most recently published LOVIT study was a phase III, multicentre RCT that involved 35 medical-surgical ICUs which spanned across Canada, France, and New Zealand. The study included patients with suspected or proven infection and those who were on vasopressor support. Vitamin C was intravenously administered once for 6 h, at a dosage of 50 mg/kg, up to 96 h to 429 patients in the intervention group. On the other hand, a placebo was administered to 434 patients who belonged to the control group. The administration of thiamine and glucocorticoids was left to the clinical discretion of the treating physician. The primary outcome, *i.e.*, a composite of death or persistent organ dysfunction at 28 d, was significantly higher in the intervention (vitamin C) group *vs* the control group [44.5% *vs* 38.5%; risk ratio: 1.21; 95% confidence interval (CI): 1.04-1.40; $P = 0.01$]. However, no significant difference was found in the individual components of composite primary outcome: Mortality or persistent organ dysfunction, organ dysfunction-free days at 28 d, SOFA scores at pre-defined time intervals from days 1-8, 6-mo survival, and health-related quality of life. The study outcomes not only inferred the lack of benefit but also provided insights on possible harm caused by high dosage administration of vitamin C in patients with sepsis and septic shock[20].

Vitamin C as a part of combination therapy

Marik *et al*[22] conducted a single-centre retrospective study involving 47 patients. This study compared cocktail therapy that included hydrocortisone, ascorbic acid, and thiamine (HAT) with a control group (standard care) among patients with severe sepsis and septic shock. The authors recorded a low hospital mortality rate in the treatment group (8.5% *vs* 40.4%, $P < 0.001$). The dosage regimen was as follows: Vitamin C at 1.5 g/h q6h, hydrocortisone at 50 mg q6h, and thiamine at 200 mg/12 h. Moreover, the mean duration of the vasopressors, used for shock, was also significantly shorter in the intervention arm (18.3 h *vs* 54.9 h, $P = 0.001$)[22]. This observational study started a debate on the suggested possible benefits of cocktail therapy among patients with septic shock. Subsequently, multiple RCTs were conducted to validate the findings of this study.

Table 2 Randomized Trials of vitamin C in sepsis

No.	Title	Ref.	Acronym	Country of origin	Study design	Sample size in control arm	Sample size in intervention arm	Intervention summary	Results in brief
Studies using isolated vitamin C									
1	Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit	Lamontagne *et al*[20], 2022	**LOVIT Trial**	Canada	RCT	437	435	Intravenous vitamin C (at a dose of 50 mg/kg body weight) 6 hourly for 96 h	This trial reported significantly higher composite primary outcome (risk of mortality OR persistent organ dysfunction at 28 d) in vitamin C group. One patient had a severe hypoglycemic episode and another had a serious anaphylaxis event.
2	Intravenous vitamin C administration to patients with septic shock: a pilot randomised controlled trial	Rosengrave *et al*[19], 2022		New Zealand	RCT	20	20	Intravenous vitamin C (at a dose of 25 mg/kg of body weight every 6 h) for up to 96 h, or until death or discharge	Treatment with intravenous vitamin C did not result in reduction of mean dose and duration of vasopressor infusion. Both the groups were comparable for rise in inflammatory markers, length of ICU stay, length of hospital stay, and mortality.
3	Early use of high-dose vitamin C is beneficial in treatment of sepsis	Lv *et al*[18], 2020		China	RCT	56	61	Intravenous vitamin C 3.0 g in 5% dextrose (100 ml/time, 2 times/d)	Treatment with vitamin C resulted in a significant reduction in the 28-d mortality. There was a significant reduction in SOFA score at 72 h and duration of vasopressor use, also there was increased clearance of procalcitonin.
4	Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial	Fowler *et al* [17], 2019	**CITRIS-ALI RCT**	United States	RCT	83	84	Intravenous infusion of vitamin C (50 mg/kg in dextrose 5% in water, n = 84) every 6 h for 96 h	There was no significant difference in SOFA score at 96 h, and levels of marker of inflammation (CRP) and vascular injury (thrombomodulin) at 168 h.
5	Effect of vitamin C administration on neutrophil apoptosis in septic patients after abdominal surgery	Ferrón-Celma *et al*[21], 2008		Spain	PD interventions RCT study	10	10	The vitamin C group received 450 mg/d of the vitamin in 3 doses	Vitamin C treatment in postoperative septic abdominal surgery patients have an antiapoptotic effect on peripheral blood neutrophils, reducing caspase-3 and PARP levels, and increasing BCL-2 levels. However this effect is not maintained all the time.
Studies using vitamin C in combination therapy									
6	Effect of Supplementation of Vitamin C and Thiamine on the Outcome in Sepsis: South East Asian Region	Ap *et al*[27], 2022		India	RCT	20	20 + 20 + 20	Intervention group received vitamin C, thiamine, both, and neither, respectively. Vitamin C (2 g 8 hourly) and thiamine (200 mg 12 hourly) were given intravenously for 5 d	Intervention with vitamin C and thiamine did not reduce mortality. The vitamin C level and thiamine level were significantly lower than those in healthy controls.
7	Biomarker Analysis for Combination Therapy of Vitamin C and Thiamine	Park *et al*[34], 2022	**Post hoc ATESS**	South Korea	RCT (post hoc analysis)	52	45	Intravenous vitamin C (50 mg/kg, maximum single dose 3 g) and thiamine	Baseline biomarker levels (IL-6, IL-10, AP2, and S100β) at 72 h were not significantly different

	in Septic Shock: A Post-Hoc Study of the ATESS Trial							(200 mg) administration every 12 h for a total of 48 h	between the treatment and the placebo groups, also the rate of reduction was not significantly different between the two groups.
8	Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis: The VICTAS Randomized Clinical Trial	Sevransky JE *et al*[25], 2021	**VICTAS Trial**	United States	RCT	252	249	Vitamin C (1.5 G), thiamine (100 mg), and hydrocortisone (50 mg) every 6 h	In patients with sepsis and septic shock, treatment with combination therapy did not reduce ventilator days and vasopressor use. Mortality at 30 d was also comparable between the groups.
9	Vitamin C Therapy for Routine Care in Septic Shock (ViCTOR) Trial: Effect of Intravenous Vitamin C, Thiamine, and Hydrocortisone Administration on Inpatient Mortality among Patients with Septic Shock	Mohamed *et al*[33], 2020	**ViCTOR Trial**	India	RCT	43	45	Intravenous combination of vitamin C (1.5 g every 6 h), thiamine (200 mg every 12 h), and hydrocortisone (50 mg every 6 h) within 6 h of onset of septic shock admission	This trial found no difference in all-cause mortality in the two groups. The data reported earlier reversal of septic shock but no difference in improvement of SOFA score at 72 h, use of vasoactive substances, or use of mechanical ventilation.
10	Combined Treatment with Hydrocortisone, Vitamin C, and Thiamine for Sepsis and Septic Shock: A Randomized Controlled Trial	Chang *et al*[32], 2020	**HYVCTTSSS**	China	RCT	40	40	Combination therapy with hydrocortisone (50 mg every 6 h for 7 d), vitamin C (1.5 g every 6 h for 4 d), and thiamine (200 mg every 12 h for 4 d)	Combination therapy did not reduce 28 d all-cause mortality in sepsis and septic shock patients. However, it was associated with 72-h change in Sequential Organ Failure Assessment score improvement. The treatment group exhibited more incidents of hypernatremia.
11	Usefulness of Antioxidants as Adjuvant Therapy for Septic Shock: A Randomized Clinical Trial	Aisa-Alvarez *et al*[28], 2020		Mexico	RCT	18	18 + 18 + 18 + 18	Enterally administered tablets of NAC 600 mg every 12 hourly. Further, 50 mg of MT in capsules of 5 mg were given to patients once a day, and 1 mg vitamin C tablets were administered every 6 h. Vitamin E capsules of 400 units were given every 8 h for 5 d	Antioxidant therapy helps to regulate inflammation in septic patients with shock. Vitamin C therapy in pulmonary sepsis increases vitamin C serum levels and decreases levels of inflammatory marker like CRP, PCT, and NO^{3-}/NO^{2-}.
12	Effect of Ascorbic Acid, Corticosteroids, and Thiamine on Organ Injury in Septic Shock: The ACTS Randomized Clinical Trial	Moskowitz *et al*[24], 2020	**ACTS RCT**	United States	RCT	102	103	Parenteral vitamin C (1500 mg), hydrocortisone (50 mg), and thiamine (100 mg) every 6 h for 4 d	Combination therapy with ascorbic acid, corticosteroids, and thiamine did not lead to a significant reduction of SOFA score in septic shock patients during the first 72 h after enrolment. Data from this trial do not support routine use of combination therapy in septic shock.
13	Combination therapy of vitamin C and thiamine for septic shock: a multicentre, double-blinded randomized, controlled study	Hwang *et al*[26], 2020	**ATESS Trial**	South Korea	RCT	58	53	Vitamin C (50 mg/kg, maximum single dose 3 g) and thiamine (200 mg) administration every 12 h for a total of 48 h intravenously	Vitamin C therapy and thiamine administration did not improve organ function and need for organ support despite improvement in levels of these vitamins in early phase of septic shock.
14	Outcomes of Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in the Early Treatment of Sepsis: The ORANGES Trial	Iglesias *et al*[29], 2020	**ORANGES trial**	United States	RCT	69	68	Ascorbic acid 1500 mg q6h, thiamine 200 mg every 12 h, and hydrocortisone 50 mg q6h for a maximum of 4 d	Combination therapy resulted in quicker reversal of shock; however, no difference was found in reversal of organ dysfunction or other secondary outcomes.
15	Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients	Fujii *et al*[23], 2020	**VITMAINS RCT**	Japan	RCT	107	109	Intravenous vitamin C (1.5 g every 6 h), hydrocortisone (50 mg every 6 h), and thiamine (200 mg every 12 h), given in intervention group and intravenous	Findings from this trial suggest that combination therapy does not lead to rapid resolution of septic shock in comparison to hydrocortisone alone with no significant improvement in overall mortality

	With Septic Shock: The VITAMINS Randomized Clinical Trial						hydrocortisone (50 mg every 6 h) alone in comparison group until shock resolution or up to 10 d	with intervention. No serious adverse events were reported.
16	Combination of vitamin C, thiamine and hydrocortisone added to standard treatment in the management of sepsis: results from an open label randomised controlled clinical trial and a review of the literature	Wani *et al* [30], 2020	India	RCT	50	50	Combination of vitamin C (1.5 g q6h for 4 d), thiamine (200 mg q12h for 4 d), and hydrocortisone (50 mg q6h for 7 d/ICU discharge, taper over 3 d)	Combination therapy does not improve in hospital mortality and mortality at 30 d. However, lactate clearance was faster and vasopressor use was lower in intervention group.
17	The effects of intravenous antioxidants in patients with septic shock	Galley HF *al* [31], 1997	United Kindom	RCT	14	16	Antioxidants (n-acetylcysteine 150 mg/kg for 30 min then 20 mg/kg/h plus bolus doses of 1 g ascorbic acid and 400 mg α-tocopherol)	Basal vitamin C was low and redox-reactive iron was elevated in all patients. Levels of vitamin C were increased but overall antioxidant capacity was unaffected after supplementation. Heart rate cardiac index increased and systemic vascular resistance index decreased in patients treated with antioxidants.

AP2: Angiopoietin-2; CRP: C-reactive Protein; DOI: Digital object identifier; ICU: Intensive care unit; IL-10: Interleukin-10; IL-6: Interleukin-6; MT: Melatonin; NAC: N-acetyl cysteine; NO2: Nitrite; NO3: Nitrate; PARP: Poly (ADP-ribose) polymerase; PCT: Procalcitonin; PMID: PubMed unique identifier; S100β: S100 calcium-binding protein B; SOFA: Sequential organ failure assessment score.

The VITAMINS trial, a multicentric RCT involving 211 patients, evaluated the effectiveness of a combination of vitamin C (1.5 g q6h), thiamine (200 mg q12h), and hydrocortisone (50 mg q6h) in patients suffering from septic shock. To conduct primary analysis, 107 patients were recruited for the intervention arm and 104 patients under the control arm. The eligibility criteria for this study were as follows: A primary diagnosis of septic shock with an acute increase in SOFA score by two points or more, a lactate level > 2 mmol/L, and the requirement for vasopressor support for at least 2 h, prior to enrolment. The study found no significant difference between the groups in terms of primary outcome, duration of time alive, and vasopressor-free days until day 7 [122.1 (76.3–145.4 h) *vs* 124.6 (82.1–147.0 h), $P = 0.83$)]. Among the secondary outcomes too, no significant difference was found in 28 d, 90 d, ICU-, or hospital-mortality between the groups. Further, the two groups also exhibited similar secondary outcomes like vasopressor-free days, mechanical ventilation-free days, and renal replacement-free days. While SOFA scores got reduced by day 3 in both the groups, the decline was marginally higher in the intervention group. In this study, two patients had adverse events (fluid overload and hyperglycemia, one each) in the intervention group[23].

A multicentre RCT (ACTS trial) was conducted among 205 septic shock patients randomised into either a placebo ($n = 102$) or an intervention arm ($n = 103$) with intravenous vitamin C (1500 mg q6h), hydrocortisone (50 mg q6h), and thiamine (100 mg q6h) for 4 d. No significant change was observed in SOFA score (difference between baseline and SOFA score at 72 h) between intervention *vs* placebo (-0.8; 95%CI: -1.7 to 0.2; $P = 0.12$). Further, no significant difference was found in the secondary outcomes too, such as incidence of acute kidney injury (AKI) and ventilator-free days. Shock-free days were found to be higher in the intervention group (median difference of 1 d; 95%CI: 0.2-1.8 d; $P < 0.01$)[24].

In another multicentric RCT (VICTAS trial) conducted among patients with sepsis and septic shock ($n = 252$), a cocktail of vitamin C (1.5 g q6h), thiamine (100 mg q6h), and hydrocortisone (50 mg q6h) was used, commencing within 4 h of randomization for 4 d. On the other hand, a matching placebo was

administered in the control group (n = 249). The trial was prematurely terminated due to the lack of funding though the actual plan was to recruit 2000 patients. No significant difference was found in terms of primary outcomes such as ventilator- and vasopressor-free days for the first 30 d [25 d (0-29 d) *vs* 26 d (0-28 d), P = 0.85]. Further, no significant difference was found between 30-d mortality between the groups (22% *vs* 24%). In addition to these, no serious adverse events were reported during the study. This study, although terminated early, did not reveal any difference with vitamin C cocktail in patients with sepsis, including respiratory or cardiovascular dysfunction[25].

Similar findings were reported in another multi-center RCT (ATESS trial) conducted in South Korea. Patients with septic shock in emergency department were randomized to receive either vitamin C (50 mg/kg) and thiamine (200 mg q6h for 48 h) in the intervention arm (n = 53) or placebo (n = 58) in the control group. Hydrocortisone (200 mg/d) and intravenous vasopressin infusion were administered in both the arms of patients who required high dosage norepinephrine. No statistically significant difference was found in the primary outcome whereas the SOFA score (difference between the baseline and 72-h score) significantly changed between the intervention and placebo groups [3, (- 1 to 5) *vs* 3, (0–4), P = 0.96]. Further, there was no significant difference between the intervention arm and placebo in baseline vitamin C or thiamine levels. After the treatment, vitamin C and thiamine levels were found to have increased in the intervention group. However, there was no significant difference observed in any of the secondary outcomes, including mortality at day 7, 28, or 90, shock reversal, ventilator-free days, incidence of AKI, and reduction of CRP or procalcitonin[26].

Several non-randomized trials have also been conducted earlier to evaluate the role of vitamin C, either as a single entity or as a part of combination therapy, in the management of sepsis (Table 3).

Meta-analysis of vitamin C in sepsis

Various systematic reviews and meta-analyses have been published on vitamin C in sepsis, with conflicting results on the short-term mortality (Table 4). However, no effect was found in the trials with long-term mortality. A recent metanalysis by Agarwal *et al*[44], with 41 RCTs and 4915 patients (including recently published LOVIT trial), explored the effect of intravenous vitamin C as monotherapy or combination therapy among hospitalized patients with severe infection. With low-certainty evidence, there was a trend towards reduced in-hospital mortality [21 RCTs, 2762 patients, risk ratio (RR) = 0.88 (95%CI, 0.73-1.06)], 30-d mortality [24 RCTs, 3436 patients, RR = 0.83 (0.71-0.98)], and early mortality [34 RCTs, 4366 patients, RR = 0.80 (0.68-0.93)] with vitamin C. However, on sensitivity analysis involving published trials which were blinded and with a low risk of bias, the impact of vitamin C was attenuated with no statistical significance. The RR of hospital mortality (6 RCTs, 1371 patients) was 1.07 (0.92-1.24), with moderate certainty evidence; that of 30-day mortality (9 RCTs, 2057 patients) was 0.88 (0.71-1.10), with low certainty evidence; and that of early mortality (11 RCTs, 2214 patients) was 0.88 (0.73-1.06), with low certainty evidence. With moderate certainty evidence, increased 90-d mortality was suggested in five RCTs, including 1722 patients (RR = 1.07, 0.94-1.21). The reason for heterogeneity was that few trials with large treatment effects were either single centre, or had small sample size. The RR of early mortality in trials reporting 90-d mortality was 1.05 (0.91-1.21). Among the adverse events, there were no major adverse events, except an increased risk of hypoglycemia (1 RCT, 862 patients, RR = 1.20 [0.69-2.08]), with moderate certainty of evidence. The result of other secondary outcomes was mixed with reduction of duration and use of mechanical ventilation and increased risk of AKI or need of RRT, based on low-certainty evidence. No credible subgroup effects were observed related to cointerventions (monotherapy *vs* combined therapy), dose of vitamin C, or the type of infection (SARS-CoV-2 *vs* others) [44].

DOSING

Different authors have tried several different dosing regimens. Higher doses of intravenous vitamin C are also being prescribed regularly, with doses up to 100 g/d used to manage patients with sepsis[50]. Even "high-dose" is not clearly defined and is arbitrarily considered a dose of more than 2-10 g/d in adults, by different authors[57,58].

The current literature suggests using six-hourly dosage for vitamin C in order to alleviate the deficiency, achieve steady plasma levels rapidly, and maintain normal serum levels. This dosing schedule may also be able to rapidly normalize the neutrophil ascorbic acid levels[36,39]. Even though intravenous formulations are generally preferred in critically ill patients, especially those in shock, and may rapidly increase the serum vitamin C levels, no difference in clinical efficacy has been reported between intravenous and oral formulations of vitamin C[59,60].

ADVERSE EFFECTS

As a water-soluble vitamin, vitamin C is generally considered safe, even when used at high doses. Most

Table 3 Non randomized studies of vitamin C in sepsis

No.	Title	Ref.	Country of origin	Study design	Sample size in control arm	Sample size in intervention arm	Intervention summary	Results in brief
Studies using isolated vitamin C								
1	High dose intravenous vitamin C treatment in Sepsis: associations with acute kidney injury and mortality	McCune *et al*[35], 2021	United States	Cohort study (retrospective cohort)	1178	212	Cohort of patients who have received at least one dose of 1.5 g IV vitamin C	Vitamin C therapy was associated with significant chances of AKI and death.
2	Effect of high-dose intravenous vitamin C on point-of-care blood glucose level in septic patients: a retrospective, single-center, observational case series	He *et al* [38], 2020	China	Observational case series		82	Patients with septic shock on admission received 100 mg/kg/d, while other patients received < 100 mg/kg/d	High-dose vitamin C therapy may interfere with point-of-care glucose testing results.
3	Pharmacokinetic data support 6-hourly dosing of intravenous vitamin C to critically ill patients with septic shock	Hudson EP *et al* [36], 2019	Australia	Observational PK study		11	Patients received 1.5 g intravenous vitamin C every 6 h	Injectable vitamin C 1.5 g every 6 h helps in correction of vitamin C deficiency and hypovit-aminosis C, and it also provides appropriate dosing schedule for vitamin C supplementation in septic shock.
4	Accuracy of Point-of-Care Blood Glucose Level Measurements in Critically Ill Patients with Sepsis Receiving High-Dose Intravenous Vitamin C	Smith *et al* [37], 2018	United States	Observational PK study		5	Patients who have received vitamin C 1500 mg intravenously two or more doses and had point of care blood glucose checked and laboratory venous BG levels measured within 1 h of each other during vitamin C therapy	The accuracy and agreement of POC BG did not have significant interreference during vitamin C treatment in sepsis.
5	Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis	Fowler *et al*[39], 2014	United States	Phase I safety trial		24 total in 1:1:1 ratio	Patients with severe sepsis in the medical intensive care unit were randomized 1:1:1 to receive intravenous infusions every 6 h for 4 d of ascorbic acid: Lo-AscA (50 mg/kg/24 h, *n* = 8), or Hi-AscA (200 mg/kg/24 h, *n* = 8), or placebo (5% dextrose/water, *n* = 8)	Intravenous vitamin C infusion is safe and tolerated well and may have a positive impact on endothelial injury, the extent of multiple organ failure, and levels of inflammatory biomarkers.
Studies using combination therapies including vitamin C								
6	Adding vitamin C to hydrocortisone lacks benefit in septic shock: a historical cohort study	Chang *et al* [40], 2020	Canada	Cohort study (retrospective cohort)	88	52	Retrospective cohorts of vitamin C with hydrocortisone and hydrocortisone therapies for 72 h were compared in patients with sepsis or septic shock	Outcomes for hospital mortality, ICU mortality, ventilator free days, vasopressor free days, dialysis use, and duration of ICU admission were comparable between the groups.
7	Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study	Marik *et al* [22], 2017	United States	Cohort study (before and after study)	47	47	Intravenous vitamin C (1.5 g q6h for 4 d or until ICU discharge), hydrocortisone (50 mg q6h for 7 d or until ICU discharge followed by a taper over 3 d) as well as intravenous thiamine (200 mg q12h for 4 d or until ICU discharge)	Results of this study suggest that the early use of intravenous vitamin C, together with corticosteroids and thiamine, prevents progressive organ dysfunction, including acute kidney injury, and reduces the mortality of patients with severe sepsis and septic shock.
Other studies								

9	Plasma Cortisol, Aldosterone, and Ascorbic Acid Concentrations in Patients with Septic Shock Do Not Predict Treatment Effect of Hydrocortisone on Mortality. A Nested Cohort Study	Cohen *et al* [42], 2020	Australia and NZ	Cohort Study (nested cohort study)			Levels of total and free plasma cortisol and aldosterone were measured along with quantitatively measured vitamin C levels	In patients with septic shock, plasma aldosterone and ascorbic acid concentrations are not associated with outcome.
10	Vitamin C levels amongst initial survivors of out of hospital cardiac arrest	Gardner *et al*[43], 2020	United States	Observational study	34	25 post arrest, 25 post sepsis	Observational	Vitamin C levels are lower in cardiac arrest patients in comparison to healthy patients.
11	Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes	Carr *et al* [8], 2017	New Zealand	Observational study	20	24	Patients with septic shock and non-septic aetiology	Critically sick patients have low levels of vitamin C, and septic shock patients have significantly depleted levels.
12	Colistin-associated Acute Kidney Injury in Severely Ill Patients: A Step Toward a Better Renal Care? A Prospective Cohort Study	Dalfino *et al*[41], 2015	Italy	Cohort (prospective cohort)	39 non AKI	31 AKI	Intervention cohort patients have received colistin at a median daily dose of 9 million IU	Independent renal-protective role emerged for ascorbic acid among other factors responsible for higher chances of AKI.

AKI: Acute kidney injury; Hi-AscA: High dose ascorbic acid; ICU: Intensive care unit; Lo-AscA: Low dose ascorbic acid; POC BG: Point of care blood glucose.

of the large trials evaluating the efficacy of vitamin C have not assessed adverse effects as a primary objective. Hence, the data regarding adverse events has largely come from case reports, case series, and meta-summary of case reports[61]. Most commonly reported side effects are mild and include interference with laboratory tests, lethargy, fatigue, phlebitis, glycemic disturbances (hypo- or hyperglycemia), hypernatremia, muscle cramps, nausea, vomiting, headache, altered mental status, syncope, methemoglobinemia, oxalosis, and renal stones. However, rarely patients may develop life-threatening complications like haemolysis, AKI, and disseminated intravascular coagulation[62,63]. The probability of developing complications is reported to be higher in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and in those with underlying renal dysfunction[61]. Even though vitamin C has anti-oxidant properties, when used at higher doses, it may deplete the intra-erythrocyte glutathione stores and cause oxidative stress. Patients with G6PD deficiency are unable to replenish these glutathione stores and develop haemolysis secondary to oxidative damage[64,65].

DISCUSSION

Despite a pathophysiological rationale, the current clinical evidence does not support the use of vitamin C in sepsis. Indeed, there was a trend towards harm observed in the LOVIT trial. However, the primary outcome was composite, and its components did not reach statistical significance. The harm was not seen in other RCTs. In the LOVIT trial, the intervention arm had more patients in shock and on invasive mechanical ventilation at the baseline compared to the control arm. This imbalance in baseline characteristics between the groups may explain the higher incidence of organ dysfunction. Furthermore, despite excluding patients staying > 24 h in ICU, the time gap between the actual onset of sepsis and administration of vitamin C is unclear[20].

Table 4 Meta-analyses of trials on vitamin C in sepsis

No.	Title	Ref.	Country of origin	Study design	Included studies	Included sample size	Intervention summary	Results in brief
Studies with isolated vitamin C therapy								
1	IV Vitamin C in Critically Ill Patients: A Systematic Review and Meta-Analysis	Patel *et al* [45], 2022	United States	Meta-analysis	15 RCTs	2490 participants	Compared intravenous vitamin C at high and low doses with placebo among pooled study participants	Intravenous vitamin C therapy is associated with a trend toward reduced overall mortality. Data further reveals that High-dose IV vitamin C was associated with a significant reduction in overall mortality. None of the included trials reported an increase in adverse events related to IV vitamin C therapy.
2	Efficacy of intravenous vitamin C intervention for septic patients: A systematic review and meta-analysis based on randomized controlled trials	Li *et al*[47], 2021	China	Meta-analysis of RCTs	10 RCTs	1400 patients	Studies that have intravenous vitamin C supplementation were included	Data from this meta-analysis reports improved SOFA score within 72 h but no significant improvement in short term (28-30 d) mortality, long term mortality (90 d), hospital stay, ventilator-free days, ICU-stay in sepsis or septic shock patients.
3	Effect of vitamin C in critically ill patients with sepsis and septic shock: A meta-analysis	Feng *et al* [48], 2021	China	Meta-analysis of RCTs	9 RCTs	584 patients	Studies with vitamin C treatment in critically sick sepsis and septic shock patients were included	Data from this study finds significant differences in 28-d mortality and dose of vasopressors. However, the ICU length of stay was the same between the two groups.
4	Efficacy of vitamin C in patients with sepsis: An updated meta-analysis	Wei *et al* [46], 2020	China	Meta-analysis	6 RCTs and 6 observational studies	1176 in control group	This analysis included data from RCTs and observational studies that evaluated the effect of vitamin C in patients with sepsis	This study reports no significant improvement in 28-d or in-hospital mortality. There was also no difference in vasopressor duration and ICU or hospital stay.
Vitamin C as a combination therapy								
5	Thiamine, Ascorbic Acid, and Hydrocortisone As a Metabolic Resuscitation Cocktail in Sepsis: A Meta-Analysis of Randomized Controlled Trials With Trial Sequential Analysis	Assouline B *et al*[49], 2021	Switzerland	Meta-analysis	8 RCTs	1335 patients	Combination of thiamine, ascorbic acid, and hydrocortisone compared to in patients with sepsis or septic shock	Data in this study was homogenous and intervention led to improved change in SOFA score at 72 h; however, there was no difference in ICU mortality and renal composite outcome (incidence of AKI 3 or need for Renal replacement therapy).
6	The Efficacy of vitamin C, thiamine, and corticosteroid therapy in adult sepsis patients: a systematic review and meta-analysis	Somagutta *et al*[50], 2021	United States	Meta-analysis	15 studies (8 RCTs and 7 cohort studies)	67349 patients	Combination of HAT treatment in patients with sepsis	Meta-analysis from RCTs concluded that hospital mortality, ICU stay, hospital stay, and renal replacement therapy was not significant. Results from cohort studies have also concluded that hospital mortality, ICU mortality, ICU length of stay, length of hospital stay, change in SOFA score, the use of renal replacement therapy, or vasopressor duration was not significant.
7	Vitamin C, Thiamine, and Hydrocortisone in the Treatment of Sepsis: A Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials	Zayed *et al* [51], 2021	United States	Meta-analysis	6 RCTs	839 patients	Vitamin C, thiamine, and steroid in combination for sepsis and septic shock	Data from this study concluded that there is no significant difference in long term mortality, ICU mortality, incidence of acute kidney injury, hospital length of stay, ICU length of stay, and ICU free days on day 28 between the intervention and control groups. However, there was a significant reduction in SOFA score on 3rd day.

8	Mortality in septic patients treated with vitamin C: a systematic meta-analysis	Scholz *et al* [52], 2021	Germany	Meta-analysis	17 studies (randomized and non-randomized, blinded and unblinded, prospective and retrospective, and single- and multi-centre studies)	3133 patients	Vitamin C 1.5 g every 6 h, 100 mg thiamine every 6 h, and 50 mg hydrocortisone every 6 h. However, initiation and duration of the intervention differed considerably within the studies	Pooled analysis in this study indicated no mortality benefit; however, a subgroup analyses revealed an improved survival, if vitamin C treatment was applied for 3-4 d.
9	Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer-term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis	Fujii *et al* [53], 2021	Japan	Meta-analysis (network meta-analysis)	43 RCTs	10257 patients	Compared networked interventions of very high dose vitamin C, high dose vitamin C, vitamin C, vitamin B1, and glucocorticoids	This study found that metabolic resuscitation with vitamin C, glucocorticoids, vitamin B1, or combinations of these drugs have no difference in long term mortality. Also they did not find effect of vitamin C or B1 on organ dysfunction or ICU length of stay. However, adding glucocorticoid to the combination therapies reduces the duration of vasopressor therapy and ICU stay.
10	Steroid, ascorbic acid, and thiamine in adults with sepsis and septic shock: a systematic review and component network meta-analysis	Fong *et al* [54], 2021	Hong Kong	Meta-analysis (component network meta-analysis)	33 RCTs	9898 patients	Additive network meta -analysis was performed, adding vitamin C, glucose corticoid, and thiamine sequentially	Data from this study reveals that combination of glucocorticoid and fludrocortisone improved short-term and longer-term mortality in sepsis and septic shock patients. Steroids shortened the time to resolution of shock and duration of mechanical ventilation. However, there was no evidence to support use of thiamine and vitamin C in sepsis and septic shock.
11	Effect of Combined Hydrocortisone, Ascorbic Acid and Thiamine for Patients with Sepsis and Septic Shock: A Systematic Review and Meta-Analysis	Wu *et al* [55], 2021	China	Meta-analysis of RCT and observational studies	6 RCTs and 7 observational studies	1559 participants.	This study compared hydrocortisone, thiamine, and ascorbic acid use to usual care or hydrocortisone	Combination therapy associated with significant reductions in duration of vasopressor in RCTs, but not in observational studies. It was associated with lower SOFA score at 72 h both in RCTs and observational studies. Combination therapy associated with lower hospital mortality and higher PCT clearance in observational studies.
12	Thiamine combined with vitamin C in sepsis or septic shock: a systematic review and meta-analysis	Ge *et al*[56], 2021	China	Systematic review and meta-analysis	7 RCTs	868 patients	Thiamine combined with vitamin C in patients with sepsis or septic shock	Data from this study found no significant differences for in hospital mortality, but have shorter duration of vasopressor use and reduced SOFA score during 72 h.

HAT: Hydrocortisone; ascorbic acid and thiamine combination; ICU: Intensive care unit; IV: Intravenous; RCT: Randomized control trial; SOFA: Sequential organ failure assessment score.

We know that sepsis is a syndrome and has proven to be a graveyard of various therapies modulating inflammation. The role of vitamin C, if there is, may be in the initial phase of hyperinflammation or cytokine storm associated with release of ROS. Besides, these RCTs used the heterogeneous cohort and failed to consider the sepsis phenotypes based on the level of inflammation. Finally, baseline vitamin C levels were not measured in all the trials, and a fixed dose therapy without measuring therapeutic levels may have caused inconsistent results.

In the absence of current evidence showing any clinical benefits, the recent surviving sepsis guidelines suggest against using vitamin C for managing patients with sepsis and septic shock[4]. The clinical practice at our institute is also in accordance to these latest recommendations and we refrain from making vitamin C a part of our routine sepsis management regimen. The future may be the individualization of these therapies using different disease models based on the aetiology of sepsis, illness severity, and degree of inflammation.

FURTHER TRIALS

Presently, there are more than 30 ongoing clinical trials to evaluate the effect of vitamin C in the management of sepsis and septic shock, in different parts of the world. These trials are evaluating the role of different doses (up to 12 g/d), different patient populations (alcoholic hepatitis, acute lung injury, and patients on invasive mechanical ventilation), and different combinations (along with steroids, thiamine, pyridoxine, or cyanocobalamine). Many of these are randomized multi-center trials (CEMVIS, REVISTA-DOSE, and C-EASIE) which may shed light on many of the unanswered questions regarding the utility of vitamin C in sepsis management. Ongoing studies in different cohorts, like patients with COVID-19 (LOVIT-COVID and REMAP-CAP), burn (VICTORY), post-cardiac arrest (VITaCCA), and/or cardiac surgery patients (advanceCSX) may answer the question of whether vitamin C can produce clinically meaningful outcomes in more specific patient populations.

CONCLUSION

Theoretically, vitamin C has been established to protect cells from oxidative damage, reduce inflammatory response, maintain immune functions, and increase the hemodynamic reserve. All these biological actions may be beneficial in the management of sepsis and septic shock. However, in the aftermath of recent interests and several multi-center trials, it can be concluded that there is still a lack of strong evidence to prove its clinical benefits. Contrary to popular belief, use of intravenous HDVC may rarely be associated with adverse effects like haemolysis, especially in vulnerable patients like those with G6PD deficiency or underlying renal dysfunction. Hence, routine use of HDVC is presently not recommended in the management of sepsis or septic shock.

FOOTNOTES

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Country/Territory of origin: India

ORCID number: Deven Juneja 0000-0002-8841-5678; Prashant Nasa 0000-0003-1948-4060; Ravi Jain 0000-0001-9260-479X.

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REFERENCES

1 **Gao L**, Chong E, Pendharkar S, Phillips A, Ke L, Li W, Windsor JA. The Challenges and Effects of Ascorbic Acid Treatment of Acute Pancreatitis: A Systematic Review and Meta-Analysis of Preclinical and Clinical Studies. *Front Nutr* 2021; **8**: 734558 [PMID: 34765629 DOI: 10.3389/fnut.2021.734558]
2 **Martimbianco ALC**, Pacheco RL, Bagattini ÂM, de Fátima Carreira Moreira Padovez R, Azevedo LCP, Riera R. Vitamin C-based regimens for sepsis and septic shock: Systematic review and meta-analysis of randomized clinical trials. *J Crit Care* 2022; **71**: 154099 [PMID: 35763993 DOI: 10.1016/j.jcrc.2022.154099]
3 **Zasowska-Nowak A**, Nowak PJ, Ciałkowska-Rysz A. High-Dose Vitamin C in Advanced-Stage Cancer Patients. *Nutrients* 2021; **13** [PMID: 33652579 DOI: 10.3390/nu13030735]
4 **Evans L**, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Joost Wiersinga W, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Yataco AC, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Møller MH, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Executive Summary: Surviving Sepsis Campaign: International Guidelines for the Management of Sepsis and Septic Shock

2021. *Crit Care Med* 2021; **49**: 1974-1982 [PMID: 34643578 DOI: 10.1097/CCM.0000000000005357]

5 **Ranieri VM**, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Finfer S, Gårdlund B, Marshall JC, Rhodes A, Artigas A, Payen D, Tenhunen J, Al-Khalidi HR, Thompson V, Janes J, Macias WL, Vangerow B, Williams MD; PROWESS-SHOCK Study Group. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med* 2012; **366**: 2055-2064 [PMID: 22616830 DOI: 10.1056/NEJMoa1202290]

6 **Wang H**, Liu B, Tang Y, Chang P, Yao L, Huang B, Lodato RF, Liu Z. Improvement of Sepsis Prognosis by Ulinastatin: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Front Pharmacol* 2019; **10**: 1370 [PMID: 31849646 DOI: 10.3389/fphar.2019.01370]

7 **European Food Safety Authority Panel on Dietetic Products, Nutrition and Allergies**. Scientific opinion on dietary reference values for vitamin C. *EFSA J* 2013; **11**: 3418 [DOI: 10.2903/j.efsa.2013.3418]

8 **Carr AC**, Rosengrave PC, Bayer S, Chambers S, Mehrtens J, Shaw GM. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. *Crit Care* 2017; **21**: 300 [PMID: 29228951 DOI: 10.1186/s13054-017-1891-y]

9 Hyaluronidase therapy for acute myocardial infarction: results of a randomized, blinded, multicenter trial. MILIS Study Group. *Am J Cardiol* 1986; **57**: 1236-1243 [PMID: 2872794 DOI: 10.1177/0884533617716618]

10 **Carr AC**, Shaw GM, Fowler AA, Natarajan R. Ascorbate-dependent vasopressor synthesis: a rationale for vitamin C administration in severe sepsis and septic shock? *Crit Care* 2015; **19**: 418 [PMID: 26612352 DOI: 10.1186/s13054-015-1131-2]

11 **Marik PE**. Vitamin C for the treatment of sepsis: The scientific rationale. *Pharmacol Ther* 2018; **189**: 63-70 [PMID: 29684467 DOI: 10.1016/j.pharmthera.2018.04.007]

12 **Wilson JX**. Mechanism of action of vitamin C in sepsis: ascorbate modulates redox signaling in endothelium. *Biofactors* 2009; **35**: 5-13 [PMID: 19319840 DOI: 10.1002/biof.7]

13 **Peng Y**, Kwok KH, Yang PH, Ng SS, Liu J, Wong OG, He ML, Kung HF, Lin MC. Ascorbic acid inhibits ROS production, NF-kappa B activation and prevents ethanol-induced growth retardation and microencephaly. *Neuropharmacology* 2005; **48**: 426-434 [PMID: 15721175 DOI: 10.1016/j.neuropharm.2004.10.018]

14 **Kornberg MD**, Bhargava P, Kim PM, Putluri V, Snowman AM, Putluri N, Calabresi PA, Snyder SH. Dimethyl fumarate targets GAPDH and aerobic glycolysis to modulate immunity. *Science* 2018; **360**: 449-453 [PMID: 29599194 DOI: 10.1126/science.aan4665]

15 **Levine M**. New concepts in the biology and biochemistry of ascorbic acid. *N Engl J Med* 1986; **314**: 892-902 [PMID: 3513016 DOI: 10.1056/NEJM198604033141407]

16 **Lavillegrand JR**, Raia L, Urbina T, Hariri G, Gabarre P, Bonny V, Bigé N, Baudel JL, Bruneel A, Dupre T, Guidet B, Maury E, Ait-Oufella H. Vitamin C improves microvascular reactivity and peripheral tissue perfusion in septic shock patients. *Crit Care* 2022; **26**: 25 [PMID: 35062987 DOI: 10.1186/s13054-022-03891-8]

17 **Fowler AA 3rd**, Truwit JD, Hite RD, Morris PE, DeWilde C, Priday A, Fisher B, Thacker LR 2nd, Natarajan R, Brophy DF, Sculthorpe R, Nanchal R, Syed A, Sturgill J, Martin GS, Sevransky J, Kashiouris M, Hamman S, Egan KF, Hastings A, Spencer W, Tench S, Mehkri O, Bindas J, Duggal A, Graf J, Zellner S, Yanny L, McPolin C, Hollrith T, Kramer D, Ojielo C, Damm T, Cassity E, Wieliczko A, Halquist M. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. *JAMA* 2019; **322**: 1261-1270 [PMID: 31573637 DOI: 10.1001/jama.2019.11825]

18 **Lv SJ**, Zhang GH, Xia JM, Yu H, Zhao F. Early use of high-dose vitamin C is beneficial in treatment of sepsis. *Ir J Med Sci* 2021; **190**: 1183-1188 [PMID: 33094466 DOI: 10.1007/s11845-020-02394-1]

19 **Rosengrave P**, Spencer E, Williman J, Mehrtens J, Morgan S, Doyle T, Van Der Heyden K, Morris A, Shaw G, Carr AC. Intravenous vitamin C administration to patients with septic shock: a pilot randomised controlled trial. *Crit Care* 2022; **26**: 26 [PMID: 35073968 DOI: 10.1186/s13054-022-03900-w]

20 **Lamontagne F**, Masse MH, Menard J, Sprague S, Pinto R, Heyland DK, Cook DJ, Battista MC, Day AG, Guyatt GH, Kanji S, Parke R, McGuinness SP, Tirupakuzhi Vijayaraghavan BK, Annane D, Cohen D, Arabi YM, Bolduc B, Marinoff N, Rochwerg B, Millen T, Meade MO, Hand L, Watpool I, Porteous R, Young PJ, D'Aragon F, Belley-Cote EP, Carbonneau E, Clarke F, Maslove DM, Hunt M, Chassé M, Lebrasseur M, Lauzier F, Mehta S, Quiroz-Martinez H, Rewa OG, Charbonney E, Seely AJE, Kutsogiannis DJ, LeBlanc R, Mekontso-Dessap A, Mele TS, Turgeon AF, Wood G, Kohli SS, Shahin J, Twardowski P, Adhikari NKJ; LOVIT Investigators and the Canadian Critical Care Trials Group. Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit. *N Engl J Med* 2022; **386**: 2387-2398 [PMID: 35704292 DOI: 10.1056/NEJMoa2200644]

21 **Ferrón-Celma I**, Mansilla A, Hassan L, Garcia-Navarro A, Comino AM, Bueno P, Ferrón JA. Effect of vitamin C administration on neutrophil apoptosis in septic patients after abdominal surgery. *J Surg Res* 2009; **153**: 224-230 [PMID: 18952228 DOI: 10.1016/j.jss.2008.04.024]

22 **Marik PE**, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. *Chest* 2017; **151**: 1229-1238 [PMID: 27940189 DOI: 10.1016/j.chest.2016.11.036]

23 **Fujii T**, Luethi N, Young PJ, Frei DR, Eastwood GM, French CJ, Deane AM, Shehabi Y, Hajjar LA, Oliveira G, Udy AA, Orford N, Edney SJ, Hunt AL, Judd HL, Bitker L, Cioccari L, Naorungroj T, Yanase F, Bates S, McGain F, Hudson EP, Al-Bassam W, Dwivedi DB, Peppin C, McCracken P, Orosz J, Bailey M, Bellomo R; VITAMINS Trial Investigators. Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial. *JAMA* 2020; **323**: 423-431 [PMID: 31950979 DOI: 10.1001/jama.2019.22176]

24 **Moskowitz A**, Huang DT, Hou PC, Gong J, Doshi PB, Grossestreuer AV, Andersen LW, Ngo L, Sherwin RL, Berg KM, Chase M, Cocchi MN, McCannon JB, Hershey M, Hilewitz A, Korotun M, Becker LB, Otero RM, Uduman J, Sen A, Donnino MW; ACTS Clinical Trial Investigators. Effect of Ascorbic Acid, Corticosteroids, and Thiamine on Organ Injury in Septic Shock: The ACTS Randomized Clinical Trial. *JAMA* 2020; **324**: 642-650 [PMID: 32809003 DOI: 10.1001/jama.2020.11946]

25 **Sevransky JE**, Rothman RE, Hager DN, Bernard GR, Brown SM, Buchman TG, Busse LW, Coopersmith CM, DeWilde C, Ely EW, Eyzaguirre LM, Fowler AA, Gaieski DF, Gong MN, Hall A, Hinson JS, Hooper MH, Kelen GD, Khan A, Levine MA, Lewis RJ, Lindsell CJ, Marlin JS, McGlothlin A, Moore BL, Nugent KL, Nwosu S, Polito CC, Rice TW, Ricketts EP, Rudolph CC, Sanfilippo F, Viele K, Martin GS, Wright DW; VICTAS Investigators. Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis: The VICTAS Randomized Clinical Trial. *JAMA* 2021; **325**: 742-750 [PMID: 33620405 DOI: 10.1001/jama.2020.24505]

26 **Hwang SY**, Ryoo SM, Park JE, Jo YH, Jang DH, Suh GJ, Kim T, Kim YJ, Kim S, Cho H, Jo IJ, Chung SP, Choi SH, Shin TG, Kim WY; Korean Shock Society (KoSS). Combination therapy of vitamin C and thiamine for septic shock: a multi-centre, double-blinded randomized, controlled study. *Intensive Care Med* 2020; **46**: 2015-2025 [PMID: 32780166 DOI: 10.1007/s00134-020-06191-3]

27 **Ap GR**, Daga MK, Mawari G, Koner BC, Singh VK, Kumar N, Rohatgi I, Mishra R. Effect of Supplementation of Vitamin C and Thiamine on the Outcome in Sepsis: South East Asian Region. *J Assoc Physicians India* 2022; **70**: 11-12 [PMID: 35438278]

28 **Aisa-Alvarez A**, Soto ME, Guarner-Lans V, Camarena-Alejo G, Franco-Granillo J, Martínez-Rodríguez EA, Gamboa Ávila R, Manzano Pech L, Pérez-Torres I. Usefulness of Antioxidants as Adjuvant Therapy for Septic Shock: A Randomized Clinical Trial. *Medicina (Kaunas)* 2020; **56** [PMID: 33213070 DOI: 10.3390/medicina56110619]

29 **Iglesias J**, Vassallo AV, Patel VV, Sullivan JB, Cavanaugh J, Elbaga Y. Outcomes of Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in the Early Treatment of Sepsis: The ORANGES Trial. *Chest* 2020; **158**: 164-173 [PMID: 32194058 DOI: 10.1016/j.chest.2020.02.049]

30 **Wani SJ**, Mufti SA, Jan RA, Shah SU, Qadri SM, Khan UH, Bagdadi F, Mehfooz N, Koul PA. Combination of vitamin C, thiamine and hydrocortisone added to standard treatment in the management of sepsis: results from an open label randomised controlled clinical trial and a review of the literature. *Infect Dis (Lond)* 2020; **52**: 271-278 [PMID: 31990246 DOI: 10.1080/23744235.2020.1718200]

31 **Galley HF**, Howdle PD, Walker BE, Webster NR. The effects of intravenous antioxidants in patients with septic shock. *Free Radic Biol Med* 1997; **23**: 768-774 [PMID: 9296454 DOI: 10.1016/s0891-5849(97)00059-2]

32 **Chang P**, Liao Y, Guan J, Guo Y, Zhao M, Hu J, Zhou J, Wang H, Cen Z, Tang Y, Liu Z. Combined Treatment With Hydrocortisone, Vitamin C, and Thiamine for Sepsis and Septic Shock: A Randomized Controlled Trial. *Chest* 2020; **158**: 174-182 [PMID: 32243943 DOI: 10.1016/j.chest.2020.02.065]

33 **Mohamed ZU**, Prasannan P, Moni M, Edathadathil F, Prasanna P, Menon A, Nair S, Greeshma CR, Sathyapalan DT, Menon V. Vitamin C Therapy for Routine Care in Septic Shock (ViCTOR) Trial: Effect of Intravenous Vitamin C, Thiamine, and Hydrocortisone Administration on Inpatient Mortality among Patients with Septic Shock. *Indian J Crit Care Med* 2020; **24**: 653-661 [PMID: 33024370 DOI: 10.5005/jp-journals-10071-23517]

34 **Park JE**, Jo YH, Hwang SY, Kim WY, Ryoo SM, Jang DH, Kim T, Kim YJ, Kim S, Cho H, Lee GT, Chung SP, Choi SH, Shin TG, Suh GJ; Korean Shock Society (KoSS) Investigators. Biomarker Analysis for Combination Therapy of Vitamin C and Thiamine in Septic Shock: A Post-Hoc Study of the ATESS Trial. *Shock* 2022; **57**: 81-87 [PMID: 34482319 DOI: 10.1097/SHK.0000000000001850]

35 **McCune TR**, Toepp AJ, Sheehan BE, Sherani MSK, Petr ST, Dodani S. High dose intravenous vitamin C treatment in Sepsis: associations with acute kidney injury and mortality. *BMC Nephrol* 2021; **22**: 387 [PMID: 34800992 DOI: 10.1186/s12882-021-02599-1]

36 **Hudson EP**, Collie JT, Fujii T, Luethi N, Udy AA, Doherty S, Eastwood G, Yanase F, Naorungroj T, Bitker L, Abdelhamid YA, Greaves RF, Deane AM, Bellomo R. Pharmacokinetic data support 6-hourly dosing of intravenous vitamin C to critically ill patients with septic shock. *Crit Care Resusc* 2019; **21**: 236-242 [PMID: 31778629]

37 **Smith KE**, Brown CS, Manning BM, May T, Riker RR, Lerwick PA, Hayes TL, Fraser GL. Accuracy of Point-of-Care Blood Glucose Level Measurements in Critically Ill Patients with Sepsis Receiving High-Dose Intravenous Vitamin C. *Pharmacotherapy* 2018; **38**: 1155-1161 [PMID: 30230568 DOI: 10.1002/phar.2182]

38 **He J**, Zheng G, Qian X, Sheng H, Chen B, Zhao B, Chen E, Mao E, Bian X. Effect of high-dose intravenous vitamin C on point-of-care blood glucose level in septic patients: a retrospective, single-center, observational case series. *Curr Med Res Opin* 2021; **37**: 555-565 [PMID: 33560893 DOI: 10.1080/03007995.2021.1887832]

39 **Fowler AA 3rd**, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, Farthing CA, Larus TL, Martin E, Brophy DF, Gupta S; Medical Respiratory Intensive Care Unit Nursing, Fisher BJ, Natarajan R. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med* 2014; **12**: 32 [PMID: 24484547 DOI: 10.1186/1479-5876-12-32]

40 **Chang K**, Harbin M, Shuster C, Griesdale DEG, Foster D, Sweet D, Wood MD, Dhingra VK. Adding vitamin C to hydrocortisone lacks benefit in septic shock: a historical cohort study. *Can J Anaesth* 2020; **67**: 1798-1805 [PMID: 32939746 DOI: 10.1007/s12630-020-01814-1]

41 **Dalfino L**, Puntillo F, Ondok MJ, Mosca A, Monno R, Coppolecchia S, Spada ML, Bruno F, Brienza N. Colistin-associated Acute Kidney Injury in Severely Ill Patients: A Step Toward a Better Renal Care? *Clin Infect Dis* 2015; **61**: 1771-1777 [PMID: 26354965 DOI: 10.1093/cid/civ717]

42 **Cohen J**, Bellomo R, Billot L, Burrell LM, Evans DM, Finfer S, Hammond NE, Li Q, Liu D, McArthur C, McWhinney B, Moore J, Myburgh J, Peake S, Pretorius C, Rajbhandari D, Rhodes A, Saxena M, Ungerer JPJ, Young MJ, Venkatesh B. Plasma Cortisol, Aldosterone, and Ascorbic Acid Concentrations in Patients with Septic Shock Do Not Predict Treatment Effect of Hydrocortisone on Mortality. A Nested Cohort Study. *Am J Respir Crit Care Med* 2020; **202**: 700-707 [PMID: 32396775 DOI: 10.1164/rccm.202002-0281OC]

43 **Gardner R**, Liu X, Wang Y, Cole A, Heydrick S, Donnino MW, Moskowitz A. Vitamin C levels amongst initial survivors of out of hospital cardiac arrest. *Resuscitation* 2020; **156**: 190-193 [PMID: 32946985 DOI: 10.1016/j.resuscitation.2020.09.005]

44 **Agarwal A**, Basmaji J, Fernando SM, Ge FZ, Xiao Y, Faisal H, Honarmand K, Hylands M, Lau VI, Lewis K, Couban R, Lamontagne F, Adhikari NK. Parenteral Vitamin C in Patients with Severe Infection: A Systematic Review. NEJM Evidence 2022 ahead of print. [DOI: 10.1056/EVIDoa2200105]

45 **Patel JJ**, Ortiz-Reyes A, Dhaliwal R, Clarke J, Hill A, Stoppe C, Lee ZY, Heyland DK. IV Vitamin C in Critically Ill

Patients: A Systematic Review and Meta-Analysis. *Crit Care Med* 2022; **50**: e304-e312 [PMID: 34637420 DOI: 10.1097/CCM.0000000000005320]

46 **Wei XB**, Wang ZH, Liao XL, Guo WX, Wen JY, Qin TH, Wang SH. Efficacy of vitamin C in patients with sepsis: An updated meta-analysis. *Eur J Pharmacol* 2020; **868**: 172889 [PMID: 31870831 DOI: 10.1016/j.ejphar.2019.172889]

47 **Li T**, Zeng J, Li DH, Yang GY, Wang K, Deng HF, Jiang H. Efficacy of intravenous vitamin C intervention for septic patients: A systematic review and meta-analysis based on randomized controlled trials. *Am J Emerg Med* 2021; **50**: 242-250 [PMID: 34416515 DOI: 10.1016/j.ajem.2021.08.012]

48 **Feng F**, Yang H, Yang W, Li M, Chang X, Chen Y. Effect of vitamin C in critically ill patients with sepsis and septic shock: A meta-analysis. *Sci Prog* 2021; **104**: 36850421998175 [PMID: 33787414 DOI: 10.1177/0036850421998175]

49 **Assouline B**, Faivre A, Verissimo T, Sangla F, Berchtold L, Giraud R, Bendjelid K, Sgardello S, Elia N, Pugin J, de Seigneux S, Legouis D. Thiamine, Ascorbic Acid, and Hydrocortisone As a Metabolic Resuscitation Cocktail in Sepsis: A Meta-Analysis of Randomized Controlled Trials With Trial Sequential Analysis. *Crit Care Med* 2021; **49**: 2112-2120 [PMID: 34582409 DOI: 10.1097/CCM.0000000000005262]

50 **Somagutta MKR**, Pormento MKL, Khan MA, Hamdan A, Hange N, Kc M, Pagad S, Jain MS, Lingarajah S, Sharma V, Kaur J, Emuze B, Batti E, Iloeje OJ. The Efficacy of vitamin C, thiamine, and corticosteroid therapy in adult sepsis patients: a systematic review and meta-analysis. *Acute Crit Care* 2021; **36**: 185-200 [PMID: 34185986 DOI: 10.4266/acc.2021.00108]

51 **Zayed Y**, Alzghoul BN, Banifadel M, Venigandla H, Hyde R, Sutchu S, Khasawneh M, Borok Z, Urbine D, Jantz M, Reddy R. Vitamin C, Thiamine, and Hydrocortisone in the Treatment of Sepsis: A Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials. *J Intensive Care Med* 2022; **37**: 327-336 [PMID: 33511898 DOI: 10.1177/0885066620987809]

52 **Scholz SS**, Borgstedt R, Ebeling N, Menzel LC, Jansen G, Rehberg S. Mortality in septic patients treated with vitamin C: a systematic meta-analysis. *Crit Care* 2021; **25**: 17 [PMID: 33407793 DOI: 10.1186/s13054-020-03438-9]

53 **Fujii T**, Salanti G, Belletti A, Bellomo R, Carr A, Furukawa TA, Luethi N, Luo Y, Putzu A, Sartini C, Tsujimoto Y, Udy AA, Yanase F, Young PJ. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer-term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis. *Intensive Care Med* 2022; **48**: 16-24 [PMID: 34750650 DOI: 10.1007/s00134-021-06558-0]

54 **Fong KM**, Au SY, Ng GWY. Steroid, ascorbic acid, and thiamine in adults with sepsis and septic shock: a systematic review and component network meta-analysis. *Sci Rep* 2021; **11**: 15777 [PMID: 34349184 DOI: 10.1038/s41598-021-95386-9]

55 **Wu T**, Hu C, Huang W, Xu Q, Hu B, Li J. Effect of Combined Hydrocortisone, Ascorbic Acid and Thiamine for Patients with Sepsis and Septic Shock: A Systematic Review and Meta-Analysis. *Shock* 2021; **56**: 880-889 [PMID: 34529397 DOI: 10.1097/SHK.0000000000001781]

56 **Ge Z**, Huang J, Liu Y, Xiang J, Gao Y, Walline JH, Lu X, Yu S, Zhao L, Li Y. Thiamine combined with vitamin C in sepsis or septic shock: a systematic review and meta-analysis. *Eur J Emerg Med* 2021; **28**: 189-195 [PMID: 33709993 DOI: 10.1097/MEJ.0000000000000812]

57 **Kwak SG**, Choo YJ, Chang MC. The effectiveness of high-dose intravenous vitamin C for patients with coronavirus disease 2019: A systematic review and meta-analysis. *Complement Ther Med* 2022; **64**: 102797 [PMID: 34953366 DOI: 10.1016/j.ctim.2021.102797]

58 **Wang Y**, Lin H, Lin BW, Lin JD. Effects of different ascorbic acid doses on the mortality of critically ill patients: a meta-analysis. *Ann Intensive Care* 2019; **9**: 58 [PMID: 31111241 DOI: 10.1186/s13613-019-0532-9]

59 **Hemilä H**, Chalker E. Vitamin C Can Shorten the Length of Stay in the ICU: A Meta-Analysis. *Nutrients* 2019; **11** [PMID: 30934660 DOI: 10.3390/nu11040708]

60 **Hemilä H**, Chalker E. Vitamin C may reduce the duration of mechanical ventilation in critically ill patients: a meta-regression analysis. *J Intensive Care* 2020; **8**: 15 [PMID: 32047636 DOI: 10.1186/s40560-020-0432-y]

61 **Juneja D**, Jain R, Nasa P. Vitamin C-induced Hemolysis: Meta-summary and Review of Literature. *Indian J Crit Care Med* 2022; **26**: 224-227 [PMID: 35712748 DOI: 10.5005/jp-journals-10071-24111]

62 **Padayatty SJ**, Sun AY, Chen Q, Espey MG, Drisko J, Levine M. Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects. *PLoS One* 2010; **5**: e11414 [PMID: 20628650 DOI: 10.1371/journal.pone.0011414]

63 **Yanase F**, Fujii T, Naorungroj T, Belletti A, Luethi N, Carr AC, Young PJ, Bellomo R. Harm of IV High-Dose Vitamin C Therapy in Adult Patients: A Scoping Review. *Crit Care Med* 2020; **48**: e620-e628 [PMID: 32404636 DOI: 10.1097/CCM.0000000000004396]

64 **Zhang ZZ**, Lee EE, Sudderth J, Yue Y, Zia A, Glass D, Deberardinis RJ, Wang RC. Glutathione Depletion, Pentose Phosphate Pathway Activation, and Hemolysis in Erythrocytes Protecting Cancer Cells from Vitamin C-induced Oxidative Stress. *J Biol Chem* 2016; **291**: 22861-22867 [PMID: 27660392 DOI: 10.1074/jbc.C116.748848]

65 **Wilson JX**. The physiological role of dehydroascorbic acid. *FEBS Lett* 2002; **527**: 5-9 [PMID: 12220624 DOI: 10.1016/s0014-5793(02)03167-8]

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ORIGINAL ARTICLE

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Scoring systems in critically ill: Which one to use in cancer patients?

Anisha Beniwal, Deven Juneja, Omender Singh, Amit Goel, Akhilesh Singh, Hemant Kumar Beniwal

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Anisha Beniwal, Deven Juneja, Omender Singh, Amit Goel, Akhilesh Singh, Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket, New Delhi 110017, India

Hemant Kumar Beniwal, Department of Neurosurgery, Dr SNMC Hospital, Jodhpur 342001, India

Corresponding author: Deven Juneja, DNB, FCCP, MBBS, Director, Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket 1, Press Enclave Road, New Delhi 110017, India. devenjuneja@gmail.com

Abstract

BACKGROUND

Scoring systems have not been evaluated in oncology patients. We aimed to assess the performance of Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE III, APACHE IV, Simplified Acute Physiology Score (SAPS) II, SAPS III, Mortality Probability Model (MPM) II_0 and Sequential Organ Failure Assessment (SOFA) score in critically ill oncology patients.

AIM

To compare the efficacy of seven commonly employed scoring systems to predict outcomes of critically ill cancer patients.

METHODS

We conducted a retrospective analysis of 400 consecutive cancer patients admitted in the medical intensive care unit over a two-year period. Primary outcome was hospital mortality and the secondary outcome measure was comparison of various scoring systems in predicting hospital mortality.

RESULTS

In our study, the overall intensive care unit and hospital mortality was 43.5% and 57.8%, respectively. All of the seven tested scores underestimated mortality. The mortality as predicted by MPM II_0 predicted death rate (PDR) was nearest to the actual mortality followed by that predicted by APACHE II, with a standardized mortality rate (SMR) of 1.305 and 1.547, respectively. The best calibration was shown by the APACHE III score ($\chi^2 = 4.704$, $P = 0.788$). On the other hand, SOFA score ($\chi^2 = 15.966$, $P = 0.025$) had the worst calibration, although the difference was not statistically significant. All of the seven scores had acceptable discrimination with good efficacy however, SAPS III PDR and MPM II_0 PDR (AUROC = 0.762),

had a better performance as compared to others. The correlation between the different scoring systems was significant ($P < 0.001$).

CONCLUSION

All the severity scores were tested under-predicted mortality in the present study. As the difference in efficacy and performance was not statistically significant, the choice of scoring system used may depend on the ease of use and local preferences.

Key Words: APACHE score; Intensive care unit; Medical oncology; SOFA score; Scoring systems; Severity of illness index

Core Tip: Scoring systems are important for patient triaging, benchmarking intensive care unit (ICU) performance, comparing different ICUs and may also help in patient prognostication, selecting treatment options and resource utilization. However, validity and utility of these scores may be questionable in the patient population apart from where they were developed. Hence, these scores need to be tested and validated in different patient populations, in different geographical areas and over different time periods. There is a lack of an ideal score for prognostication of critically ill cancer patients. In our retrospective study, analyzing data from 400 patients and comparing seven commonly employed critical illness scores, we observed that all the scores had similar efficacy and under-predicted mortality. Therefore, the selection of severity of illness score should depend on the ease of use and local preferences.

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INTRODUCTION

The application of prognosticating scoring systems is considered as an important phase in intensive care units (ICUs) since these severity scoring systems estimate the probability of mortality for patients. These scores help the physicians to facilitate resource utilization or continuous quality improvement and to stratify the patients for clinical research[1,2]. ICU scoring systems can help both patients as well as their attendants to select from further treatment options. Further, the scores calculated by these scoring systems help in evaluating the impact of newer treatment modalities and organizational changes which in turn contributes towards the development of treatment standards. In addition to the above, the scoring systems' outcomes also help in benchmarking ICU performance and comparing the scores secured by different ICU patient populations so as to find out the differences in mortality. However, these systems are unreliable in predicting the clinical outcomes of an individual though it has proven efficacy in predicting mortality for a particular patient cohort[3].

Acute Physiology and Chronic Health Evaluation (APACHE) II and Simplified Acute Physiology Score (SAPS) II are arguably the two most-commonly used and validated tools used in the prediction of ICU patient outcomes[4,5]. These scoring systems were developed in the 1980s and have become outdated due to technological and clinical advancements in critical care management of patients in recent years. Hence, there is a need to develop new scoring systems that include APACHE IV, SAPS III and Mortality Probability Model (MPM) II0[6-9]. Such newly-created systems encompass a large number of variables and are highly complicated to compute.

In addition, both validity and utility of the existing scoring systems may be questionable in terms of current patient population compared to the patient population during which they were developed. These scores are widely used and the scoring systems have been validated for a notable time to predict the outcome in general medical or surgical procedures conducted upon critically ill patients. However, whether these systems can predict the mortality accurately among cancer patients remains unknown [10]. There is a dearth of studies that compare different generations of scoring systems and especially the ones used upon cancer patients admitted in medical oncology ICUs. Only a few studies have assessed their usefulness in cancer patients with conflicting results. Moreover, geographic variations in patient populations and the types of cancer necessitate that these scores should be evaluated for different populations[11]. Therefore, the current study is aimed at analyzing the efficacy of seven commonly-used scoring systems to predict the mortality amongst patients admitted in oncology ICUs.

MATERIALS AND METHODS

A retrospective observational cohort study was carried out at a multi-disciplinary onco-medical ICU of a tertiary care center in India. We have an advanced ICU setup and 24-h intensivist coverage with state-of-the-art facilities. Approval for the study and a consent waiver from the institutional ethics committee was obtained.

The data from the records of adult patients who were admitted between January 2018 and February 2020, *i.e.*, 2 years, was collected and analyzed. If the patient was readmitted to the ICU more than once during his/her hospital stay, only the first admission was included in the study. Patients who had ICU stays of less than 12 h, post-operative patients and those admitted from or discharged to another ICU were excluded from the study. Patients fulfilling inclusion criteria were serially recruited. The researchers collected the following data; baseline patient characteristics, indication for ICU admission, type of malignancy, presence of metastasis, need for vasopressor, renal and mechanical ventilation (MV), length of ICU and hospital stay, and ICU and hospital mortality. The data, required to compute various scores, was collected and calculated specified by the procedures.

Statistical analysis

The collected data was then transformed into variables, coded and entered in Microsoft Excel. Then, it was statistically analyzed using SPSS software (version. PC-25). Quantitative data was expressed in mean ± SD or median with an interquartile range. Normality distribution difference between two comparable groups was measured using student's *t*-test or Mann Whitney '*U*' test. Qualitative data was expressed in percentage whereas the statistical differences between the proportions were tested using chi square or Fisher's exact test, as appropriate.

Standardized Mortality Ratio (SMR) was computed by dividing the observed 28 d' mortality by predicted hospital mortality based on different scores. Further, 95% confidence interval (CI) was calculated for SMR by considering the observed mortality as a Poisson variable and then dividing its 95%CI by predicted mortality.

The calibration of the scores was executed using Hosmer-Lemeshow goodness-of-fit statistics which divides the subjects into deciles based on the predicted probabilities of death. Afterwards, it computes a Chi-square value from the observed and expected frequencies. Low Chi-square values and high *P* values ($P > 0.5$) correspond to a better fit. The ability of the scores to predict ICU mortality was explored and discrimination was tested using Area Under Receiver Operating Characteristic (AUROC) curves. If the AUROC curves are more than 0.8, it denotes excellent outcome while 0.6-0.8 are considered to be acceptable. The cut-off values were calculated for different scores using Youden's index based on which sensitivity and specificity of the scores were calculated.

Clinically-relevant variables that produced $P < 0.05$ during univariate analyses and are easily accessible on admission were also entered into multiple logistic regression models as the outcome variable of interest. Odds ratio (OR) was calculated along with 95%CI. A *P* value < 0.05 was considered to be statistically significant.

Sample size calculation

The sample size calculation was done for the estimation of the AUROC curve for APACHE 2 score, using the following formula:

$n \geq Z^2_{\alpha/2} V(AUC) \div d^2$

Where, $V(AUC) = 0.0099 \times e^{-a2/2} \times (6a^2 + 16)$, $a = \phi^{-1}(AUC) \times 1.414$ and ϕ^{-1} is the inverse of standard cumulative normal distribution for AUC.

For a 95% level of confidence $Z_{\alpha/2=1.96}$; d = 0.05 which is the margin of error in estimation and AUC was obtained from a similar study conducted by Schellongowski *et al*[12] who reported an AUC of 0.776 for the APACHE II score.

Substituting these values in the above formula gives $n \geq 196$. As our study was retrospective in nature, we included 400 patients.

RESULTS

During the study period, the data from 400 patients who fulfilled the inclusion criteria were included in the final analysis. Thirty-eight patients were excluded because 31 were admitted from or discharged to another ICU, five were post-operative patients and two had ICU stays less than 12 h. Their baseline characteristics are given in Table 1 and the comparison between various scores is given in Table 2.

Predicted mortality

All of the scoring systems tested in the current study underestimated the mortality (Table 3). The mortality, predicted by MPM II_0 PDR, was nearest to the actual mortality with an SMR of 1.305, followed by APACHE II (1.547) and SAPS II (1.74).

Table 1 Comparison of baseline variables among survivors and non-survivors

Parameters	Survivors, *n* = 169	Non-survivors, *n* = 231	Total, *n* = 400	*P* value
Age in yr	62.85 ± 12.49	61.45 ± 14.82	62.04 ± 13.88	0.527
Male	98 (58.0%)	142 (61.5%)	240 (60.0%)	0.48
Female	71 (42.0%)	89 (38.5%)	160 (40.0%)	
DM	56 (33.1%)	62 (26.8%)	118 (29.5%)	0.17
Hypertension	61 (36.1%)	63 (27.3%)	124 (31.0%)	0.06
Reason for ICU admission				
Sepsis	42 (24.9%)	68 (29.4%)	110 (27.5%)	0.31
Respiratory distress/failure	76 (45.0%)	93 (40.3%)	169 (42.2%)	0.34
Cardiac arrest	1 (0.6%)	8 (3.5%)	9 (2.2%)	0.08
Gastrointestinal bleed	15 (8.9%)	14 (6.1%)	29 (7.2%)	0.33
Altered sensorium	33 (19.5%)	45 (19.5%)	78 (19.5%)	1
Acute kidney injury	2 (1.2%)	3 (1.3%)	5 (1.2%)	1
Type of malignancy				
Solid organ	135 (79.9%)	187 (81.0%)	322 (80.5%)	0.78
Hematological	34 (20.1%)	44 (19.0%)	78 (19.5%)	
Metastasis	80 (59.3%)	145 (77.5%)	225 (69.9%)	0.001
Previous history of surgery for CA				
Yes	72 (42.6%)	74 (32.0%)	146 (36.5%)	0.03
No	97 (57.4%)	157 (68.0%)	254 (63.5%)	
ICU stay	5 (3-8)	4 (2-10)	5 (3-9)	0.58
Hospital stay	14 (8-21)	11 (5-22)	12 (7-21)	0.006
Use of MV	24 (14.2%)	130 (56.3%)	154 (38.5%)	< 0.001
Days of MV	5 (3-7.75)	3 (2-6)	3 (2-7)	0.002
Use of renal support	7 (4.1%)	29 (12.6%)	36 (9.0%)	0.004
Days of renal support	2.14 ± 0.90	2.48 ± 2.06	2.42 ± 1.88	0.786
Use of vasopressor support	26 (15.4%)	174 (75.3%)	200 (50.0%)	< 0.001
Days of vasopressor support	3 (2-4)	2 (1.75-4.0)	2 (2-4)	0.276

ICU: Intensive care unit; MV: Mechanical ventilation.

Calibration

Using the Lemeshow-Hosmer goodness-of fit test, APACHE III (4.704) achieved the best calibration with $P = 0.788$ whereas SOFA score (15.966) was the worst with $P = 0.025$ (Table 4). The least statistically significant discrepancy between the predicted and observed mortality was shown by the APACHE III score.

Discrimination

The efficacy of various scores is given in Figure 1. All the scores tested in the current study exhibited good efficacy, even though there was no statistically significant difference between AUROCs and SAPS III PDR. On the other hand, MPM II_0 PDR (AUROC = 0.762) yielded the best performance (Table 5).

Correlation between various scoring systems

As shown in Table 6, there was a significant correlation found among various scoring systems ($P <$ 0.001) as assessed by linear regression analysis.

Factors associated with hospital mortality

Five factors that showed significance in univariate analysis such as hypertension, surgery for cancer, use

Table 2 Comparison between survivors and non-survivors for various scores

Scoring system	Survivors, *n* = 169	Non-survivors, *n* = 231	Total, *n* = 400	*P* value
APACHE II	17.66 ± 4.96	22.82 ± 8.34	20.64 ± 7.55	< 0.001
APACHE II PDR	28.10 ± 17.74	44.04 ± 25.88	37.30 ± 24.10	< 0.001
APACHE III	59.01 ± 16.95	81.36 ± 31.37	71.92 ± 28.46	< 0.001
APACHE III PDR	17.59 ± 15.80	37.59 ± 28.51	29.14 ± 25.91	< 0.001
APACHE IV	58.80 ± 16.98	80.45 ± 31.70	71.30 ± 28.55	< 0.001
APACHE IV PDR	20.45 ± 14.99	40.45 ± 27.91	32.00 ± 25.33	< 0.001
SAPS II	34.67 ± 11.83	49.20 ± 19.87	43.06 ± 18.39	< 0.001
SAPS II PDR	19.81 ± 16.97	42.83 ± 30.51	33.10 ± 28.06	< 0.001
SAPS III PDR	18.12 ± 16.95	34.66 ± 24.12	27.67 ± 22.88	< 0.001
SOFA Score	5.76 ± 2.80	9.02 ± 4.58	7.64 ± 4.24	< 0.001
MPM II_0 PDR	33.39 ± 15.08	52.16 ± 26.63	44.23 ± 24.31	< 0.001

APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; MPM: Mortality Probability Model; PDR: Predicted death rate.

Table 3 Comparison of the actual and predicted mortality rates for the various scoring systems

Scoring system	Actual mortality	Predicted mortality	SMR	95%CI
APACHE II	0.577	0.373	1.547	1.423-1.678
APACHE III	0.577	0.291	1.982	1.824-2.151
APACHE IV	0.577	0.320	1.803	1.659-1.956
SAPS II	0.577	0.331	1.743	1.604-1.891
SAPS III	0.577	0.277	2.083	1.917-2.26
MPM II_0 PDR	0.577	0.442	1.305	1.201-1.416

SMR: Standardized mortality rate; CI: Confidence interval; APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; MPM: Mortality Probability Model; PDR: Predicted death rate.

of MV, vasopressors and renal support were used in multivariate analysis as well. Out of the five factors, two factors, *i.e.* need for MV (OR 2.437, 95%CI = 1.315-4.515, *P* = 0.005) and vasopressor support (OR 10.465, 95%CI = 5.901-18.557, *P* = 0.000) were statistically associated with hospital mortality.

DISCUSSION

The current study compared various mortality prediction scoring systems and found that all the scores under-predicted the mortality in critically-ill cancer patients. Amongst the scoring systems considered, mortality predicted by MPM PDR was the closest to that of the actual mortality with an SMR of 1.305. AUROC values showed that all of the seven scoring systems had good efficacy and acceptable discrimination. MPM PDR and SAPS III PDR achieved the best discrimination. We found the best sensitivity in SAPS II score (76.2%) and best specificity in SAPS III PDR score (92%). The Lemeshow-Hosmer goodness-of fit tests showed that the APACHE III score had the best calibration although there was no statistically significant difference.

In the current study, all of the scores were significantly higher among non-survivors (*P* value < 0.001) as reported in the literature[13-18]. However, all the scores tested in this study underestimated the mortality (SMR > 1), like previous studies[14,15,19,20].

Discrimination is the ability to determine the patients who may die and who will survive. Measures of discrimination include sensitivity, specificity and AUROC curve. But no single scoring system excelled in all of the three areas. SAPS III PDR and MPM II_0 PDR (AUROC = 0.762) had the best AUROC values whereas sensitivity was at its best for SAPS II and specificity was at its best for SAPS III PDR.

Table 4 Lemeshow-Hosmer goodness-of-fit tests for evaluating the calibration of the scoring systems

Scoring system	Chi square value	*P* value
APACHE II	9.366	0.312
APACHE II PDR	12.159	0.144
APACHE III	4.707	0.788
APACHE III PDR	6.471	0.595
APACHE IV	9.331	0.315
APACHE IV PDR	10.763	0.216
SAPS II	9.479	0.304
SAPS II PDR	10.410	0.237
SAPS III PDR	10.787	0.214
SOFA Score	15.966	0.025
MPM II_0 PDR	11.265	0.187

APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; MPM: Mortality Probability Model; PDR: Predicted death rate.

Table 5 Area under curve for predicting hospital mortality for various scoring system

Scoring system	AUC	*P* value	95%CI	Cut off	Sensitivity	Specificity
APACHE II	0.688	< 0.001	0.637-0.739	> 18.5	67.5%	62.7%
APACHE III	0.720	< 0.001	0.672-0.769	> 78.5	46.8%	87.6%
APACHE IV	0.708	< 0.001	0.659-0.758	> 72.5	53.7%	79.3%
SAPS II	0.734	< 0.001	0.685-0.782	> 34.5	76.2%	60.4%
SAPS III PDR	0.762	< 0.001	0.715-0.808	39.0	44.3%	92.0%
SOFA Score	0.715	< 0.001	0.665-0.764	> 7.5	58.0%	79.3%
MPM II_0 PDR	0.762	< 0.001	0.714-0.810	36.45	71.3%	69.9%

AUC: Area under the curve; CI: Confidence interval; APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; MPM: Mortality Probability Model; PDR: Predicted death rate.

However, these differences were not statistically significant. In the current study, AUROC outcomes showed that discrimination is acceptable in all the scoring systems tested as reported in the literature [14-16,20-22]. All the severity illness scores showed good efficacy with no statistically significant difference in AUROCs.

Calibration evaluates the accuracy of the degree of correspondence between the estimated probability of mortality and the observed actual mortality. Calibration is good if the predicted mortality is close to the observed mortality. APACHE III (4.704) had the best calibration with $P = 0.788$. This infers that it had the least statistically significant discrepancy between the predicted and observed mortality. Good calibration of these scores have also been reported by other authors[14-16,20].

A significant correlation was found among various scoring systems ($P < 0.001$) as per linear regression analysis. This correlation may be attributed to the overlap of multiple variables, considered for calculating the scores. Sculier *et al*[21] also reported an excellent correlation between APACHE II and SAPS II in their study on oncology patients. ICU mortality rate among cancer patients was reportedly high and in the range of 30% to 77%[23-26]. The overall ICU mortality rate in the current study was 43.5%. Even though it is higher, the ICU mortality of the current cohort does not differ from the mortality reported in similar studies conducted earlier[23,24]. The hospital mortality rate in the current study was 57.8% which is again similar as reported earlier[27,28].

Use of MV and vasopressor support have a direct association with hospital mortality. Similar studies conducted earlier have also reported the need for organ support in the form of MV. At times, vasopressor use is directly associated with increased mortality among cancer patients[29]. An ideal scoring system is the need of the hour. This system should be well calibrated, easy to compute, able to have high

Table 6 Correlation of different scoring system with each other

Scoring system		APACHE II Score	A2 PDR	APACHE III Score	A3 PDR	APACHE IV Score	A4 PDR	SAPS II Score	SAPS2 PDR	SAPS 3 PDR	SOFA score
APACHE II Score	*r* value		0.898	0.892	0.836	0.883	0.826	0.820	0.812	0.748	0.679
	P value		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
A2 PDR	*r* value	0.898		0.824	0.832	0.814	0.805	0.751	0.752	0.716	0.635
	P value	0.000		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
APACHE III Score	*r* value	0.892	0.824		0.929	0.966	0.895	0.910	0.902	0.820	0.753
	P value	0.000	0.000		0.000	0.000	0.000	0.000	0.000	0.000	0.000
A3 PDR	*r* value	0.836	0.832	0.929		0.897	0.895	0.851	0.852	0.763	0.711
	P value	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000	0.000
APACHE IV Score	*r* value	0.883	0.814	0.966	0.897		0.915	0.890	0.877	0.821	0.762
	P value	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000
A4 PDR	*r* value	0.826	0.805	0.895	0.895	0.915		0.836	0.839	0.782	0.727
	P value	0.000	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000
SAPS II Score	*r* value	0.820	0.751	0.910	0.851	0.890	0.836		0.972	0.814	0.756
	P value	0.000	0.000	0.000	0.000	0.000	0.000		0.000	0.000	0.000
SAPS 2 PDR	*r* value	0.812	0.752	0.902	0.852	0.877	0.839	0.972		0.813	0.773
	P value	0.000	0.000	0.000	0.000	0.000	0.000	0.000		0.000	0.000
SAPS 3 PDR	*r* value	0.748	0.716	0.820	0.763	0.821	0.782	0.814	0.813		0.684
	P value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000		0.000
SOFA score	*r* value	0.679	0.635	0.753	0.711	0.762	0.727	0.756	0.773	0.684	
	P value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	
MPM II_0 PDR	*r* value	0.704	0.653	0.777	0.729	0.759	0.734	0.790	0.805	0.714	0.700
	P value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; MPM: Mortality Probability Model; PDR: Predicted death rate.

levels of discrimination and predict mortality rates with high accuracy based on the easily-available patient parameters. Additionally, an ideal score also needs to be dynamic, reflecting the change in management and case mix over time. In this search for an ideal scoring system, newer scoring systems have been developed. However, these systems are highly complex in nature, demand huge sets of patient data and need computer assistance to calculate the scores. Hence, the development of an ideal scoring system has a long way to go.

The accuracy of scoring systems may differ over a period of time and may produce varied results in different countries due to differences in ethnicity, patient population, healthcare systems, ICU structure and organization. So, its accuracy cannot be generalized and all such models need external validation in independent patient populations to prove its reproducibility. Therefore, it becomes imperative to compare and test the validity of scoring systems under different geographical areas and upon different patient populations. The current study is one of the few studies conducted on the Indian subcontinent and the researchers have compared a huge number of scoring systems developed for cancer patients in a significantly large cohort of patients.

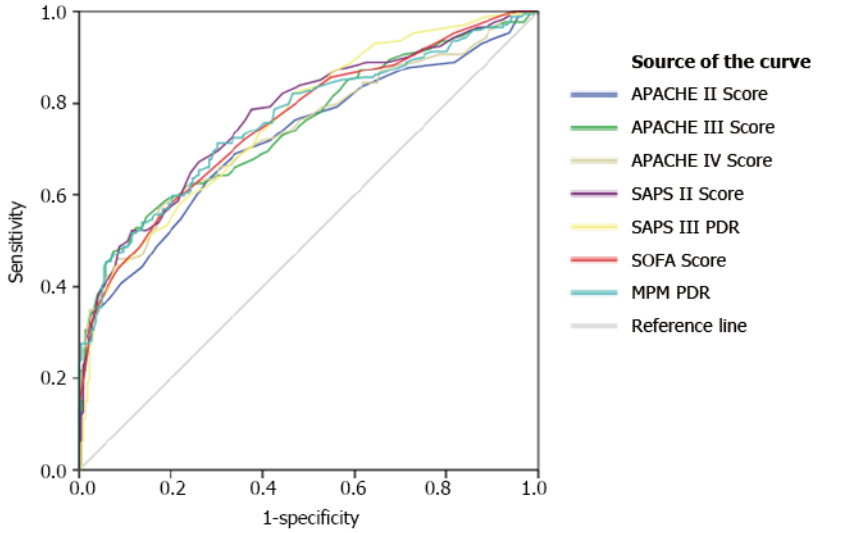

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Figure 1 Comparison between the area under the receiver operating characteristic curves of APACHE II, APACHE III, APACHE IV SAPS-II, SAPS-III, SOFA score and MPM II_0-PDR in discriminating survivors from non-survivors. APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; MPM: Mortality Probability Model.

The current study has a limitation to address, *i.e.* being a single center retrospective study where concerns may arise in terms of generalizing the conclusions arrived in this study. The missing data may have also led to information bias. Nonetheless, the study has several salient features such as the comparison of seven scoring systems, fairly large sample size, well-defined study protocol and the inclusion of only medical oncology patients.

CONCLUSION

The current study concludes that all of the scoring systems considered for this study cohort underpredicted the mortality. However, the APACHE III score had the least discrepancy between the predicted and observed mortality. There was no statistically significant difference in efficacy and all the scores tested had good calibration and acceptable discrimination. Hence, the choice of scoring system in critically-ill oncology patients should not only be based on the performance of the score, but also on other factors such as ease of use and local preferences.

ARTICLE HIGHLIGHTS

Research background

The application of prognosticating scoring systems is considered as an important phase in intensive care units (ICUs) since these severity scoring systems estimate the probability of mortality for patients. These scores help the physicians to facilitate resource utilization or continuous quality improvement and to stratify the patients for clinical research. ICU scoring systems can help both patients as well as their attendants to select from further treatment options. Further, the scores calculated by these scoring systems help in evaluating the impact of newer treatment modalities and organizational changes which in turn contributes towards the development of treatment standards. In addition to the above, the scoring systems' outcomes also help in benchmarking ICU performance and comparing the scores secured by different ICU patient populations so as to find out the differences in mortality.

Research motivation

There is a dearth of studies that compare different generations of scoring systems especially the ones used upon cancer patients admitted in medical oncology ICUs. Only a few studies have assessed their usefulness in cancer patients with conflicting results.

Research objectives

To compare the efficacy of seven commonly employed scoring systems to predict outcomes of critically ill cancer patients.

Research methods

We conducted a retrospective analysis of 400 consecutive cancer patients admitted in the medical intensive care unit over a 2-year period. The primary outcome was hospital mortality and the secondary outcome measure was comparison of various scoring systems in predicting hospital mortality.

Research results

Overall ICU mortality in our study was 43.5% whereas hospital mortality was 57.8%. All scoring systems tested underestimated the mortality. Mortality predicted by MPM II_0 predicted death rate (PDR), was closest to that of the actual mortality followed by that of APACHE II, with a standardized mortality rate (SMR) of 1.305 and 1.547, respectively. APACHE III (χ^2 = 4.704, P = 0.788) had the best calibration and SOFA score (χ^2 = 15.966, P = 0.025) had the worst calibration, but the difference was not statistically significant. All the scores tested had good efficacy and acceptable discrimination, however SAPS III PDR and MPM II_0 PDR (AUROC = 0.762), performed better than others. There was a significant correlation between the various scoring systems (P < 0.001).

Research conclusions

Overall, all the scores in our study cohort under-predicted the mortality. The difference in efficacy was not statistically significant in all scores. The choice of scoring system should depend on the ease of use and local preferences as all the scores tested had similar performance.

Research perspectives

There is a lack of an ideal score for prognostication of critically ill cancer patients. In our retrospective study, analyzing data from 400 patients and comparing seven commonly employed critical illness scores, we observed that all the scores had similar efficacy but under-predicted mortality. Therefore, the choice of scoring system should depend on the ease of use and local preferences.

FOOTNOTES

Author contributions: Beniwal A and Juneja D designed the study; Beniwal A, Juneja D and Beniwal HK collected the data, analyzed the results, performed the majority of the writing and prepared the tables; Singh O, Goel A and Singh A provided critical input in writing the paper and reviewed the manuscript.

Institutional review board statement: Approved by Institutional Scientific Committee of Max Super Speciality Hospital, No. 1944105991.

Informed consent statement: As this was a retrospective study, the need for consent was waived off by the institute's ethical committee.

Conflict-of-interest statement: All authors report no relevant conflict of interest for this article.

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ORCID number: Anisha Beniwal 0000-0003-1139-0692; Deven Juneja 0000-0002-8841-5678; Omender Singh 0000-0002-3847-4645; Amit Goel 0000-0002-9509-5705; Akhilesh Singh 0000-0001-6192-140X; Hemant Kumar Beniwal 0000-0002-7052-0146.

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REFERENCES

1 **Sakr Y**, Krauss C, Amaral AC, Réa-Neto A, Specht M, Reinhart K, Marx G. Comparison of the performance of SAPS II, SAPS 3, APACHE II, and their customized prognostic models in a surgical intensive care unit. *Br J Anaesth* 2008; **101**: 798-803 [PMID: 18845649 DOI: 10.1093/bja/aen291]

2 **Moreno R**, Matos R. New issues in severity scoring: interfacing the ICU and evaluating it. *Curr Opin Crit Care* 2001; **7**: 469-474 [PMID: 11805554 DOI: 10.1097/00075198-200112000-00018]

3 **Aygencel G**, Turkoglu M, Turkoz Sucak G, Benekli M. Prognostic factors in critically ill cancer patients admitted to the intensive care unit. *J Crit Care* 2014; **29**: 618-626 [PMID: 24612762 DOI: 10.1016/j.jcrc.2014.01.014]

4 **Knaus WA**, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818-829 [PMID: 3928249 DOI: 10.1097/00003246-198510000-00009]

5 **Le Gall JR**, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; **270**: 2957-2963 [PMID: 8254858 DOI: 10.1001/jama.270.24.2957]

6 **Zimmerman JE**, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med* 2006; **34**: 1297-1310 [PMID: 16540951 DOI: 10.1097/01.CCM.0000215112.84523.F0]

7 **Metnitz PG**, Moreno RP, Almeida E, Jordan B, Bauer P, Campos RA, Iapichino G, Edbrooke D, Capuzzo M, Le Gall JR; SAPS 3 Investigators. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 1: Objectives, methods and cohort description. *Intensive Care Med* 2005; **31**: 1336-1344 [PMID: 16132893 DOI: 10.1007/s00134-005-2762-6]

8 **Moreno RP**, Metnitz PG, Almeida E, Jordan B, Bauer P, Campos RA, Iapichino G, Edbrooke D, Capuzzo M, Le Gall JR; SAPS 3 Investigators. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med* 2005; **31**: 1345-1355 [PMID: 16132892 DOI: 10.1007/s00134-005-2763-5]

9 **Higgins TL**, Teres D, Copes WS, Nathanson BH, Stark M, Kramer AA. Assessing contemporary intensive care unit outcome: an updated Mortality Probability Admission Model (MPM0-III). *Crit Care Med* 2007; **35**: 827-835 [PMID: 17255863 DOI: 10.1097/01.CCM.0000257337.63529.9F]

10 **Juneja D**, Singh O, Nasa P, Dang R. Comparison of newer scoring systems with the conventional scoring systems in general intensive care population. *Minerva Anestesiol* 2012; **78**: 194-200 [PMID: 22095102]

11 **Torre LA**, Siegel RL, Ward EM, Jemal A. Global Cancer Incidence and Mortality Rates and Trends--An Update. *Cancer Epidemiol Biomarkers Prev* 2016; **25**: 16-27 [PMID: 26667886 DOI: 10.1158/1055-9965.EPI-15-0578]

12 **Schellongowski P**, Benesch M, Lang T, Traunmüller F, Zauner C, Laczika K, Locker GJ, Frass M, Staudinger T. Comparison of three severity scores for critically ill cancer patients. *Intensive Care Med* 2004; **30**: 430-436 [PMID: 14598029 DOI: 10.1007/s00134-003-2043-1]

13 **Adam AK**, Soubani AO. Outcome and prognostic factors of lung cancer patients admitted to the medical intensive care unit. *Eur Respir J* 2008; **31**: 47-53 [PMID: 17715168 DOI: 10.1183/09031936.00031607]

14 **Kopterides P**, Liberopoulos P, Ilias I, Anthi A, Pragkastis D, Tsangaris I, Tsaknis G, Armaganidis A, Dimopoulou I. General prognostic scores in outcome prediction for cancer patients admitted to the intensive care unit. *Am J Crit Care* 2011; **20**: 56-66 [PMID: 21196571 DOI: 10.4037/ajcc2011763]

15 **Soares M**, Silva UV, Teles JM, Silva E, Caruso P, Lobo SM, Dal Pizzol F, Azevedo LP, de Carvalho FB, Salluh JI. Validation of four prognostic scores in patients with cancer admitted to Brazilian intensive care units: results from a prospective multicenter study. *Intensive Care Med* 2010; **36**: 1188-1195 [PMID: 20221751 DOI: 10.1007/s00134-010-1807-7]

16 **Berghmans T**, Paesmans M, Sculier JP. Is a specific oncological scoring system better at predicting the prognosis of cancer patients admitted for an acute medical complication in an intensive care unit than general gravity scores? *Support Care Cancer* 2004; **12**: 234-239 [PMID: 14740281 DOI: 10.1007/s00520-003-0580-3]

17 **Xia R**, Wang D. Intensive care unit prognostic factors in critically ill patients with advanced solid tumors: a 3-year retrospective study. *BMC Cancer* 2016; **16**: 188 [PMID: 26946297 DOI: 10.1186/s12885-016-2242-0]

18 **Vincent F**, Soares M, Mokart D, Lemiale V, Bruneel F, Boubaya M, Gonzalez F, Cohen Y, Azoulay E, Darmon M; GrrrOH: Groupe de recherche respiratoire en réanimation en Onco-Hématologie (Group for respiratory research in intensive care in Onco-Hematology, http://www. grrroh.com/). In-hospital and day-120 survival of critically ill solid cancer patients after discharge of the intensive care units: results of a retrospective multicenter study-A Groupe de recherche respiratoire en réanimation en Onco-Hématologie (Grrr-OH) study. *Ann Intensive Care* 2018; **8**: 40 [PMID: 29582210 DOI: 10.1186/s13613-018-0386-6]

19 **Soares M**, Fontes F, Dantas J, Gadelha D, Cariello P, Nardes F, Amorim C, Toscano L, Rocco JR. Performance of six severity-of-illness scores in cancer patients requiring admission to the intensive care unit: a prospective observational study. *Crit Care* 2004; **8**: R194-R203 [PMID: 15312218 DOI: 10.1186/cc2870]

20 **Xing X**, Gao Y, Wang H, Huang C, Qu S, Zhang H, Sun K. Performance of three prognostic models in patients with cancer in need of intensive care in a medical center in China. *PLoS One* 2015; **10**: e0131329 [PMID: 26110534 DOI: 10.1371/journal.pone.0131329]

21 **Sculier JP**, Paesmans M, Markiewicz E, Berghmans T. Scoring systems in cancer patients admitted for an acute complication in a medical intensive care unit. *Crit Care Med* 2000; **28**: 2786-2792 [PMID: 10966251 DOI: 10.1097/00003246-200008000-00018]

22 **Staudinger T**, Stoiser B, Müllner M, Locker GJ, Laczika K, Knapp S, Burgmann H, Wilfing A, Kofler J, Thalhammer F, Frass M. Outcome and prognostic factors in critically ill cancer patients admitted to the intensive care unit. *Crit Care Med* 2000; **28**: 1322-1328 [PMID: 10834673 DOI: 10.1097/00003246-200005000-00011]

23 **Anisoglou S**, Asteriou C, Barbetakis N, Kakolyris S, Anastasiadou G, Pnevmatikos I. Outcome of lung cancer patients admitted to the intensive care unit with acute respiratory failure. *Hippokratia* 2013; **17**: 60-63 [PMID: 23935346]

24 **Müller AM**, Gazzana MB, Silva DR. Outcomes for patients with lung cancer admitted to intensive care units. *Rev Bras Ter Intensiva* 2013; **25**: 12-16 [PMID: 23887754 DOI: 10.1590/s0103-507x2013000100004]

25 **Ostermann M**, Raimundo M, Williams A, Whiteley C, Beale R. Retrospective analysis of outcome of women with breast or gynaecological cancer in the intensive care unit. *JRSM Short Rep* 2013; **4**: 2 [PMID: 23413404 DOI: 10.1258/shorts.2012.012036]

26 **Yoo H**, Suh GY, Jeong BH, Lim SY, Chung MP, Kwon OJ, Jeon K. Etiologies, diagnostic strategies, and outcomes of

diffuse pulmonary infiltrates causing acute respiratory failure in cancer patients: a retrospective observational study. *Crit Care* 2013; **17**: R150 [PMID: 23880212 DOI: 10.1186/cc12829]

27 **Wang YG**, Zhou JC, Wu KS. High 28-day mortality in critically ill patients with sepsis and concomitant active cancer. *J Int Med Res* 2018; **46**: 5030-5039 [PMID: 30088429 DOI: 10.1177/0300060518789040]

28 **Shin SH**, Lee H, Kang HK, Park JH. Twenty-eight-day mortality in lung cancer patients with metastasis who initiated mechanical ventilation in the emergency department. *Sci Rep* 2019; **9**: 4941 [PMID: 30894559 DOI: 10.1038/s41598-019-39671-8]

29 **Kostakou E**, Rovina N, Kyriakopoulou M, Koulouris NG, Koutsoukou A. Critically ill cancer patient in intensive care unit: issues that arise. *J Crit Care* 2014; **29**: 817-822 [PMID: 24857640 DOI: 10.1016/j.jcrc.2014.04.007]

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SYSTEMATIC REVIEWS

Postoperative complications and critical care management after cytoreduction surgery and hyperthermic intraperitoneal chemotherapy: A systematic review of the literature

Anjana S Wajekar, Sohan Lal Solanki, Vijaya P Patil

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

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Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

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Anjana S Wajekar, Sohan Lal Solanki, Vijaya P Patil, Department of Anaesthesiology, Critical Care and Pain, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai 400012, Maharashtra, India

Corresponding author: Sohan Lal Solanki, MD, Professor, Department of Anaesthesiology, Critical Care and Pain, Tata Memorial Hospital, Homi Bhabha National Institute, 2nd Floor, Main Building, Tata Memorial Hospital, Dr E Borges Marg, Parel, Mumbai 400012, Maharashtra, India. me_sohans@yahoo.co.in

Abstract

BACKGROUND

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a comprehensive treatment option performed for peritoneal surface malignancies. Postoperatively almost all patients are transferred to the intensive care unit electively.

AIM

To describe the common and rare postoperative complications, postoperative mortality and their critical care management after CRS-HIPEC.

METHODS

The authors assessed 54 articles for eligibility. Full text assessment identified 14 original articles regarding postoperative complications and critical care management for inclusion into the final review article.

RESULTS

There is an exaggerated metabolic and inflammatory response after surgery which may be termed as physiological in view of the nature of surgery combined with the use of heated intraperitoneal chemotherapy with/out early postoperative intravenous chemotherapy. The expected postoperative course is further discussed. CRS-HIPEC is a complex procedure with some life-threatening complications in the immediate postoperative period, reported morbidity rates between 12%-60% and a mortality rate of 0.9%-5.8%. Over the years, since its inception in the 1980s, postoperative morbidity and survival have significantly improved. The commonest postoperative surgical complications and systemic toxicity due to chemotherapy as reported in the last decade are discussed.

CONCLUSION
CRS-HIPEC is associated with a varying rate of postoperative complications including postoperative deaths and needs early suspicion and intensive care monitoring.

Key Words: Intensive care units; Hyperthermic intraperitoneal chemotherapy; Morbidity; Peritoneal neoplasms; Postoperative period

Core Tip: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is a complex procedure with some life-threatening complications in the immediate postoperative period, reported morbidity rates between 12%-60% and a mortality rate of 0.9%-5.8%. There is an exaggerated metabolic and inflammatory response after surgery which may be termed as physiological in view of the nature of surgery combined with use of heated intraperitoneal chemotherapy.

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INTRODUCTION

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a comprehensive treatment option performed for peritoneal surface malignancies (PSM), both primary peritoneal cancers and peritoneal metastasis secondary to colorectal, appendiceal, ovarian, gastric and other malignancies. CRS comprises the surgical removal of visible tumour from peritoneal surfaces as well as abdomino-pelvic organs. CRS includes a wide spectrum which ranges from excision of a single peritoneal nodule to complete peritonectomy along with multi-visceral resections and up to 3-5 anastomoses. It is followed by HIPEC which involves pumping highly concentrated chemotherapy drugs heated to 41°C–43°C into the peritoneal cavity. HIPEC can be performed either with closed or open abdominal techniques. The advantages of a closed abdominal HIPEC are increased intraabdominal pressure leading to increased tissue penetration and prevention of heat loss whereas the advantage of open abdominal HIPEC is better distribution of the chemotherapeutic drugs. The primary disease and institutional protocol dictate the type of HIPEC treatment used in various institutes. The duration of surgery can vary from eight to fifteen hours, with longer duration being the norm rather than an exception.

CRSHIPEC is a complex procedure with some life-threatening complications in the immediate postoperative period, reported morbidity rates between 12%-60% and a mortality rate of 0.9%-5.8%[1-4]. The postsurgical complications have been reported as late as 90 d after surgery[1,5]. Over the years since its introduction in 1980's, better patient selection, improvements in surgical techniques, surgical skills and perioperative management strategies, have further reduced the morbidity and improved the survival after CRS-HIPEC. Additionally, disease progression even after comprehensive treatment, necessitating a repeat CRS-HIPEC procedure has been reported to be useful in selected patients with recurrent peritoneal malignancies[6].

The present article reviews the early postoperative management and common complications after CRS-HIPEC, reported in the last decade.

MATERIALS AND METHODS

Literature search strategy

An electronic literature search was conducted using the databases of 'PubMed' and 'Google Scholar'. The 'Reference Citation Analysis', an artificial intelligence technology-based open citation analysis database was employed. The period of the search was from 2010 to 2021. The search terms included, "Peritoneal Cancer", "Hyperthermic", "Intraperitoneal", "HIPEC", Critical Care, Intensive Care, Postoperative Care, Perioperative Care, Postoperative Complications and their synonyms in various combinations. The extracted articles were further reviewed in a step-wise manner for identification of relevant studies. The titles and abstracts were inspected independently by two authors.

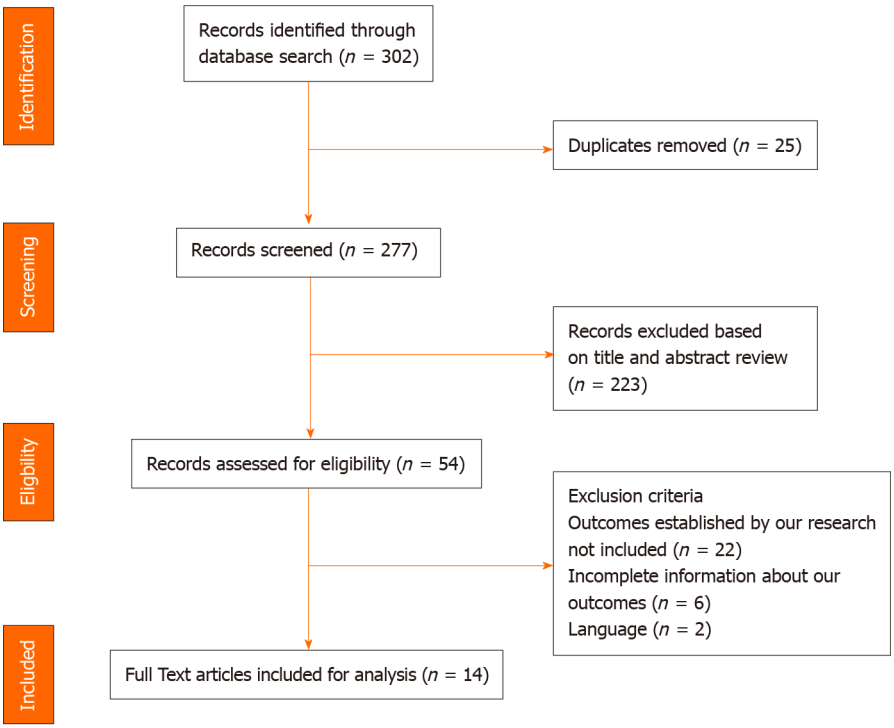

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Figure 1 PRISMA flow diagram.

Study selection criteria

Only full text articles published in English were included for review. Only articles which reported postoperative critical care management and complications were included. Articles regarding only preoperative and intraoperative management were excluded. Only original research articles were included for analysis. Meta-analyses and review articles were excluded.

RESULTS

Literature search results

A total of 277 articles were identified after the initial literature search. Initial review included screening of article titles for relevance and identifying duplicates. A further screening of abstracts identified articles for full text review. Full text assessment identified 14 original articles regarding postoperative complications and critical care management for inclusion into the final review article (Table 1, Figure 1).

DISCUSSION

Critical care management

Postoperatively almost all the patients were transferred to the intensive care unit (ICU) electively. Only a few selected patients with limited CRS and short duration HIPEC may be amenable for high dependency unit (HDU) management. There is an exaggerated metabolic and inflammatory response after surgery which may be termed as physiological in view of the nature of surgery combined with use of heated intraperitoneal chemotherapy with/out early postoperative intravenous chemotherapy.

At the end of surgery, the decision to extubate or electively ventilate depends upon patient comorbidities, duration of surgery, degree of cytoreduction, haemodynamic instability, vasopressor use, blood loss and the need for massive blood transfusion, and metabolic derangement. Even in the ICU, it is quite common to extubate the patients to a high flow nasal cannula or non-invasive ventilation depending upon the extent of diaphragmatic peritonectomy, breathing efforts of the patients and site of gastrointestinal anastomosis. Preoperative malnutrition and anaemia, long duration of surgery, fluid overload, poorly controlled pain leading to diaphragmatic splinting, lithotomy with steep Trendelenburg positioning, preoperative pleural effusion, ascites or presence of preoperative compromised pulmonary functions predispose a patient to postoperative pulmonary complications. Adherence to enhanced recovery after surgery (ERAS) protocols including preoperative incentive

Table 1 Demographic details and disease load

Ref.	Data duration	Type of Cohort/Study	No of Institutes (Country)	PSM	No of procedures	Age		PCI	
Cavaliere *et al* [35], 2011	1995-2007	Prospective	Five (Italy)	Colorectal	146	56 (19-76)	median (range)	< 11-48, 11-20-72, > 20-26	Range
Glehen *et al*[36], 2010	1989-2007	Retrospective	Twenty-five (Europe and Canada)	Non-ovarian	1154, 190(EPIC)	52 (12)	mean (SD)	13.1 (8.9)	mean (SD)
Cooksley *et al*[7], 2011	2009-2010	Retrospective	Single (England)	Mixed	69	53.3 (30-73)	mean (range)	10.5	Mean
Mizumoto *et al* [37], 2012	2007-2011	Retrospective	Single (Japan)	Mixed	284	57 (13) (23–88)	mean (SD) (range)	20 (13) (0–39)	mean (SD) (range)
Bakrin *et al*[1], 2012	1991-2008	Retrospective	Two (France)	Ovarian	246	57.5 (28.6-77.6)	Mean (range)	10.8 (1-31)	Mean (range)
Baratti *et al*[17], 2012	1995-2011	Prospective	Single (Italy)	Mixed	426	53.4 (12.7)	mean (SD)	18.7 (10.8)	mean (SD)
Bakrin *et al*[16], 2013	1991-2010	Retrospective	Thirteen (France)	Ovarian	566	57.89 (22-77)	Median (range)	8.5 (0-31)	Median (range)
Canda *et al*[27], 2013	2007-2012	Retrospective	Single (Turkey)	Mixed	118	53.4 (20-82)	Mean (range)	14.7 (3-28)	Mean (range)
Jafari *et al*[15], 2014	2005-2011	Retrospective	> 500 (USA)	Mixed	694	55 (10)	mean (SD)	NA	
Levine *et al*[30], 2014	1991-2013	Prospective	Single (USA)	Mixed	1000	52.9 (12.4)	mean (SD)	12	Mean
Cascales-Campos *et al* [24], 2016	2008-2014	Prospective	Single (Spain)	Mixed	156	57 (33-79)	Median (range)	8 (0-13)	Median (range)
Martin *et al*[25], 2016	1991-2014	Retrospective	Single (USA)	Mixed	302	54% (40-60)	Percent (range)	13 (6-18)	Median (IQR)
Elekonawo *et al* [38], 2019	2010-2015	Case matched RCT	Two centres in Netherlands	Colorectal	223	61.4(10.7)	mean (SD)	9.0 (0–24)	Median (range)
Kelly *et al*[39], 2018	2007-2014	Retrospective	Single (USA)	Mixed	226	53 (20-66)	Median (range)	14 (0-27)	Median (range)

RCT: Randomised controlled trial; PCI: Peritoneal carcinomatosis index; EPIC: Early postoperative intravenous chemotherapy; SD: Standard Deviation; PSM: Peritoneal surface malignancies; NA: Not available.

spirometry and respiratory muscle training and its continuation in the postoperative period have been proven to reduce pulmonary complications. Cooksley *et al*[7] extubated all their HIPEC patients at the end of surgery with the use of good epidural analgesia and goal-directed fluid therapy.

Massive fluid shifts, third spacing and blood loss are quite common in the CRS phase of the surgery whereas the HIPEC phase can lead to extensive vasodilatation necessitating use of vasopressors. The fluid losses, both external and internal (third space), continue in the immediate postoperative period. The abdominal drain losses can be as high as 40% of the total output, in the first 72 h after surgery[3,8]. Continuous monitoring and assessment of fluid status guided by various static and dynamic parameters such as cardiac output monitoring, central venous pressure, serum lactate, urine output, abdominal drain and nasogastric losses need to be conducted. Adequate and timely resuscitation with crystalloids, colloids, blood and blood products helps reduce postoperative morbidity and mortality. In view of the increased risk of postoperative sepsis, acute kidney injury and coagulopathy, it is advisable to avoid use of hydroxylethyl starches in the perioperative period. There is a significant protein loss secondary to the exudating ascitic fluid and extensive surgical dissection. Postoperative decline in albumin levels is common, which starts intraoperatively and continues postoperatively, with the need for exogenous replacement. The routine use of furosemide, mannitol or low doses of dopamine to prevent renal injury is no longer recommended.

Malfroy *et al*[8] found that abdominal drain output more than 1500 mL, postoperative fluid resuscitation > 70 mL/kg or the need for vasopressors in the first 24 h after surgery are predictors of increased 30-d morbidity and mortality. Earlier concerns regarding chemotherapy-induced nephropathy, replacement of large volume ascites and dehydration due to preoperative bowel preparations, led to liberal fluid replacement during the intraoperative period with resultant postoperative

fluid overload leading to tissue and bowel edema and increased abdominal, respiratory and cardiac complications. In CRSHIPEC procedures, Colantonio *et al*[9] found that patients in the protocolised goal-directed therapy (GDT) group received significantly less fluids in the intraoperative period, had lower abdominal and other systemic morbidity and postoperative length of stay but with no significant difference in mortality. They reported that GDT with individualised therapeutic end points can be achieved using a combination of colloids, crystalloids and vasopressors.

Coagulopathy during the perioperative period is multifactorial which includes the length of surgery, extent of resection, both hypothermia and hyperthermia, blood loss and massive blood transfusion. There may be prolongation of prothrombin time, activated partial thromboplastin time and/or reduction in platelet count. Monitoring viscoelastic properties of clots with the use of thromboelastography both intra- and postoperatively can help with management. The coagulation profile generally normalises by the third to sixth postoperative day. Platelet transfusion is rarely required and should only be considered when platelet levels fall below 50000 with associated bleeding or additional surgical procedures become imminent.

Electrolyte abnormalities may be common due to perioperative massive fluid shifts. Sodium, chloride, potassium, calcium, magnesium and phosphate should be measured periodically and replacement should be done in the ICU.

Extensive CRS and HIPEC can cause wide fluctuations in temperature. The hyperdynamic alterations secondary to hyperthermia generally reverse once the temperature normalises. Hyperthermia can also cause coagulopathies, renal tubulopathy, liver dysfunction, neuropathies and seizures. Delta temperature (difference between lowest and highest temperatures) during CRSHIPEC was found to be a significant predictor of ICU stay > 5 d[3]. This is highest in patients with a high peritoneal carcinomatosis index (PCI) necessitating longer, aggressive resection. Hypothermia during the CRS phase is associated with cardiac morbidity, decreased humoral and cellmediated immunity and worsen metabolic acidosis and may be responsible for increased ICU stay. The lactate levels after HIPEC should be interpreted with caution and along with other markers of perfusion as the inflammatory state itself can be responsible for hyperlactatemia.

Perioperative fluid shifts and hypoperfusion combined with nephrotoxic chemotherapy especially cisplatin predisposes to acute kidney injury. The critical time for renal perfusion is generally the first 2 postoperative days. Transient severe hypophosphatemia may be observed on the first two-three postoperative days due to hyperthermia-related renal tubulopathy. It can lead to decreased diaphragm mobility leading to atelectasis and increased insulin requirements. Transaminitis (2to 3fold rise) is common during the first four postoperative days. Diarrhoea can occur in the first week due to digestive hypersecretion secondary to the hyper inflammatory status.

Initiation of enteral feed should depend on the extent of bowel resection, presence or absence of inflammation and haemodynamic stability. Parenteral nutrition should be initiated early and switched to enteral nutrition as soon as possible. The decisions regarding nutrition should consider patients baseline nutritional status, and surgical and medical concerns. Dieticians should be actively involved from the preoperative phase. Preoperative nutritional status may predict length of stay, risk of infectious complications and possibly long-term survival.

The anticipated postoperative course includes lowgrade fever up to 38°C, even in the absence of infection, during the first 7-10 postoperative days. Leukocyte counts and platelet counts progressively decrease in the first two weeks followed by a progressive increase. Inflammatory markers such as Creactive protein, interleukins and elastase increase during surgery and return to normal within 12-24 h. Hyperglycaemia can be a common finding due to surgical stress and hypercatabolic state, necessitating insulin infusions. The glycaemic targets are set at blood sugar levels between 140 to 180 mg/dL. Routine postsurgical antibiotic prophylaxis is recommended. An escalation after appropriate cultures may be required in the event of infections.

Moderate to severe pain is quite common. Use of thoracic epidural anaesthesia (TEA) is desirable in these patients for management of postoperative analgesia, prevention of respiratory complications and reduction in rates of paralytic ileus. Thoracic epidural analgesia with local anaesthetics and short acting opioids up to 72-96 h after surgery have been found to be useful. Owusu-Agyemang *et al*[10] in their study of 215 patients reported that intraoperative initiation of continuous epidural infusions pre-HIPEC was associated with significantly less blood loss and decreased intraoperative fluid requirements. Despite common postoperative coagulation abnormalities and an increased incidence of sepsis, no epidural hematomas or abscesses were reported in their study. A single centre retrospective analysis reported improved survival and reduced grade III/IV postoperative morbidity after HIPEC when TEA was used compared to patient-controlled opioid analgesia[11]. Along with thoracic epidural analgesia, adjuncts such as paracetamol as a component of multimodal analgesia are recommended. Opioid usage needs to be minimised. The use of truncal blocks such as transversus abdominis block or quadratus lumborum blocks in the absence of epidurals are encouraged.

Adherence to ERAS protocols in the perioperative period have helped to considerably decrease the grade III/IV complications and associated morbidity, length of ICU and hospital stays and improve the survival rates[3,12-14]. Mechanical and pharmacological deep vein thrombosis prophylaxis should be considered as appropriate during the entire perioperative period if not contraindicated. The first dose of low molecular weight heparin is generally given the previous night as part of ERAS and continued

postoperatively. Implementation of ERAS protocols in the postoperative period such as early extubation, early removal of drains and urinary catheter, and early mobilisation are recommended. Stress ulcer prophylaxis can be followed as per institutional protocols.

Compliance to ERAS protocols have been found to reduce the major postoperative complication rate from 33% to 21% due to early detection and reversal of the pathophysiological cascade after this major surgery, consequently reducing the length of stay from 13.1 ± 9.5 d to 8.6 ± 4.9 d[12]. A more recent National Surgical Quality Improvement Program review reported an average length of stay of 13 d[15].

Complications in the postoperative period

The extent of peritoneal disease as scored by the PCI, the completeness of the cytoreduction (CC) score and dose of intraperitoneal platinum chemotherapy are important prognostic factors of both morbidity and survival[1,8,16]. PCI > 8-10 and CC-1/CC-2 have been found to have an increased incidence of postoperative grade III/IV complications. The risk of complications increased by 3.5% for every single point increase in PCI[17]. Additionally, initial indication of surgery, ECOG score, number of organ resections *etc* may help further prognostication[1,17]. Tao *et al*[18] in their meta-analysis, reported a similar incidence of anastomotic leaks and duration of hospital stay between younger (< 65 years) and elderly (> 65 years) patients but the morbidity outcomes and mortality were higher in elderly patients. Cooksley *et al*[7] found that the higher the vasopressor requirement intra- and postoperatively, the higher the risk of postoperative complications.

In recent years, a gamut of studies investigated the utility of inflammatory markers to predict the postoperative course as well as survival. Inflammation plays an important role not only in carcinogenesis but also during CRS-HIPEC surgery. Some inflammatory biomarkers have been found to have an increased association with postoperative infective complications. Kim *et al*[19] reported that higher values of preoperative neutrophil to lymphocyte ratio (NLR) and mean platelet volume (MPV), platelet to lymphocyte ratio (PLR), and MPV on postoperative days 2, 3, and 5 were associated with decreased 1-year survival after CRS-HIPEC. C-reactive protein (CRP), an acute phase inflammation protein, is a highly sensitive but nonspecific biomarker of systemic inflammatory response. van Kooten *et al*[20] reported an increasing value of CRP after postoperative day (POD) 2 or CRP > 166 mg/L at POD3 or > 116 mg/L at POD4, had a predictive value for early detection of severe adverse events. Saeed *et al*[21] studied the dynamics of precalcitonin (PCT) pre and postoperative in CRS-HIPEC patients and compared them to CRP and white cell counts (WCC) in patients who developed infective complications postoperatively. They found a trend for faster rise in serum PCT on POD1 as compared to CRP and WCC, along with a faster PCT decline following appropriate therapy on POD3 and 6 when infected cases were clinically resolving while WCC and CRP continued to rise, particularly in non-splenectomised patients. Splenectomised patients had an increase in PCT postoperatively even in the absence of infection. Although all three, namely PCT, WCC and CRP showed an increase postoperatively consequent to systemic inflammatory response syndrome (SIRS) post CRS-HIPEC surgery, PCT had the highest negative predictive value to rule out bacterial infectious complications. Finally, they cautioned the interpretation of postoperative PCT in predicting infectious complications only in association with other clinical, biochemical, microbiological and radiological findings. Viyuela García *et al*[22] reported that CRP on POD7 and 8 had best accuracy, with an optimal cut-off value of 88 mg/L and 130 mg/L, respectively, to predict postoperative infective complications in ovarian cancer patients who underwent CRS-HIPEC.

The complications are commonly graded on two main classification systems – Clavien Dindo classification and National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCICTCAE). Major surgical complications generally include those requiring interventional endoscopy or CT-scan/ultrasound-guided procedures (grade 3), return to the operating room or ICU (grade 4), and death (grade 5). It has been found that conventional 30-d mortality underestimates post-operative mortality by 50% in CRS-HIPEC patients[5]. In their study, Alyami *et al*[5] found that most major complications occurred within 30 d, but more than 50% of deaths related to postoperative complications occurred after 30 d. Various studies have suggested evaluating morbidity and mortality related to complex surgical procedures such as CRS-HIPEC, using a 90-d time period for its definition[5,17,23].

CRS-HIPEC, being a major abdominal surgery, is associated with a gamut of postoperative complications. Grade III/IV complications are most common in the first 2 wk after surgery (Table 2). Malfroy *et al*[8] reported a median time to complications post-surgery of 2.5 d.

Gastrointestinal complications

CRS with HIPEC involves extensive abdominal surgery with major handling of small bowel, several visceral resections, anastomosis and peritonectomy. The major complications include anastomotic leaks, gastrointestinal perforations distant from the suture line, abdominal abscess, sepsis, haemorrhage, biliary, pancreatic or ureteral leakage, pancreatitis, paralytic ileus, diarrhoea *etc.* An important consideration is the timing of the anastomosis vis-à-vis HIPEC. There is no evidence in the literature to suggest an increased risk of anastomotic leaks or isolated disease recurrence on suture lines if anastomosis is performed at the completion of the cytoreduction and prior to HIPEC[6]. Some authors prefer bowel anastomoses to be performed before HIPEC in closed procedures to avoid reopening the patient but after HIPEC in cases of open procedure[16]. Malfroy *et al*[8] found that septic shock was the commonest

Table 2 Surgical complications

Ref.	N	Mortality (%)	Days	Morbidity (Grade III/IV), %	Complication classification	Commonest complications			Re-operations (%)
						First (%)	Second (%)	Third (%)	
Cavaliere *et al*[35], 2011	146	2.7	30	27.4	WHO	GI perforation/anastomotic leak (7.4)	Sepsis (4.1)	Pancreatitis/pancreatic fistula (1.4)	NA
Glehen *et al*[36], 2010	1154, 190 (EPIC)	4.1	30	33.6	NCICTCAE	GI perforation/anastomotic leak (9.7)	Pneumonia (9.1)	Intraabdominal bleeding (7.7)	14
Cooksley *et al*[7], 2011	69	0	30	5.79	NA	Pneumonia (2.9)	Central line infection (1.5)	Uncontrolled hypertension (1.5)	NA
Mizumoto *et al*[37], 2012	284	3.5	30	17	NCICTCAE	GI perforation/anastomotic leak (6.7)	Sepsis (4.6)	Intraabdominal bleeding (2.1)	11
Bakrin *et al* [1], 2012	246	0.37	30	11.6	NCICTCAE	GI perforation/anastomotic leak (4.9)	Intraabdominal bleeding (2.4)		4.9
Baratti *et al* [17], 2012	426	2.6	90	25.3	NCICTCAE	GI perforation/anastomotic leak (11.03)	Sepsis (3.76)	Intraabdominal bleeding (3.3)	10.7
Bakrin *et al* [16], 2013	566	0.8	30	31.3	NCICTCAE	Intraabdominal bleeding (8)	GI perforation/anastomotic leak (3)		8
Canda *et al* [27], 2013	118	7.6	30	31.35	NCICTCAE	Sepsis (7.6)	Pneumonia (2.5)	Ileus (2.5)	5.08
Jafari *et al* [15], 2014	694	2.3	30	32.9	NA	Intraabdominal bleeding (17)	Sepsis (15.9)	Pneumonia (4.8)	9.8
Levine *et al*[30], 2014	1000	3.8	30	42	NA	Sepsis	GI perforation/anastomotic leak	Pneumonia	NA
Cascales-Campos *et al*[24], 2016	156	0.6	30	11.5	NCICTCAE	Pleural effusion (4.49)	Sepsis (3.8)	GI perforation/anastomotic leak (1.9)	NA
Martin *et al*[25], 2016	302	3	30		NA	Pleural effusion (10.8)	Thrombosis (6.8)	Sepsis (5.4)	NA
Elekonawo *et al*[38], 2019	223	1.5	30	17.6	Clavien Dindo	Sepsis (14.7)	GI perforation/anastomotic leak		NA
Kelly *et al* [39], 2018	226		30	NA	NA	Ileus (31)	Sepsis (21)	Thrombosis (15)	16

EPIC: Early postoperative intravenous chemotherapy; GI: Gastrointestinal; NA: Not available; NCICTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCICTCAE).

factor for postoperative ICU re-admission (28.1%) with gastrointestinal origin of sepsis to be the highest (64.3%). Paralytic ileus is the commonest morbidity observed postoperatively, classified as Grade I-III morbidity[24]. One meta-analysis showed an incidence of prolonged postoperative ileus of 10.2% following elective colonic surgery, with potential higher rates with added effects of the hyperthermic bath, chemotherapy and peritoneal carcinomatosis[14]. The use of thoracic epidural analgesia, postoperative use of prokinetics, laxatives and adjuncts such as coffee or chewing gum, and early mobilisation have all been recommended to hasten gut recovery after such major surgery. ICU readmissions occur in 11%-25% of patients and in one study, ileus/dehydration was responsible for one third of readmissions[14]. The rate of re-operations increases in patients with postoperative complications due to sepsis, anastomotic leaks, *etc*.

Sepsis both abdominal and unrelated to the surgical site is the commonest complication post-surgery. It is also the commonest cause of mortality. Infections with resistant organisms are also common[8].

Martin *et al*[25] reported 30- and 90-d readmission rates after CRS-HIPEC to be 14.9% (n = 32), and 21.4% (n = 46), respectively. The main factor implicated in re-admissions was the presence of enterocutaneous fistula. They did not find any association between factors such as age, sex, race, intraoperative

blood loss, pancreatic or hepatic resection at the index operation, and postoperative complications of surgical site infection, line infection, and thromboembolic events with higher re-admission rates.

Respiratory complications

Common postoperative grade III/IV respiratory complications include pneumonia, pleural effusions, respiratory failure, and pulmonary embolism[8,23,26]. These can prolong the ICU stay or cause ICU re-admissions. Respiratory sepsis is the second most common cause of septic shock at 28.6%[8]. The massive fluid shifts during CRS-HIPEC are most commonly responsible for the increased incidence of unplanned intubations, prolonged ventilations and pulmonary interventions. Preti *et al*[26] reported an incidence of pulmonary adverse events of 10% which included 4.6% pleural effusions, 4.2% respiratory distress necessitating oxygen supplementation and intubations and 3.2% pneumonia. Martin *et al*[25] reported pleural effusions in 10.8% of patients postoperatively and mortality in two patients secondary to pulmonary embolism.

Cardiovascular complications

Hypovolemic shock especially in the first 48 h post-surgery secondary to exuding peritoneal surfaces and systemic inflammatory response can lead to higher rates of grade III/IV complications. The incidence of acute myocardial infarction and arrythmias is similar to any major gastrointestinal surgery. Jafari *et al*[15] reported a 0.3% incidence of postoperative myocardial infarction. Martin *et al*[25] reported a 4.4% incidence of cardiac arrythmias (atrial fibrillation, supraventricular tachycardia and pulseless electrical activity) and attributed one patient's mortality to cardiac dysrhythmia.

Miscellaneous

Sepsis (unrelated to abdominal complications), central line infections as well as urinary tract infection are common[6,17,25,27]. Some case reports have mentioned rare complications such as non-cirrhotic, non-total parenteral nutrition hyperammonia *etc*[28]. Prolonged postoperative acidosis has also been observed[8]. Multi-organ failure is common. The risk of pulmonary embolism, deep venous thrombosis and superior mesenteric vein thrombosis is in the range of 5%-10%[29]. The significant risk factors associated with the development of venous thromboembolism include advanced cancer stage at the time of diagnosis, prolonged immobilization, extensive surgical procedures, mucinous tumours of the gastrointestinal tract and the use of central venous catheters.

Systemic toxicity due to hyperthermic chemotherapy

Depending on the cancer histology, high concentrations of different chemotherapeutic agents (20-1000 times greater than plasma levels) are delivered into the abdominal cavity. Drugs which have a synergistic effect with heat, namely, mitomycinC and the platinumbased drugs, cisplatin, carboplatin, and oxaliplatin are used for intraperitoneal (IP) administration. The less commonly used drugs are doxorubicin, 5fluorouracil, docetaxel, paclitaxel and irinotecan.

Intraperitoneal chemotherapy is sometimes combined with concomitant or early postoperative administration of intravenous chemotherapy, aiming to create a bidirectional diffusion gradient through the cancer cells.

Most of the PSM are platinum-sensitive, with cisplatin being the commonest chemotherapeutic agent used for HIPEC. Common toxicities include nephropathy and haematological toxicity (Table 3). A cisplatin dose more than 240 mg was demonstrated to increase both surgical morbidity and systemic toxicity[17]. Some centres have used sodium thiosulphate for the prevention of cisplatininduced nephrotoxicity with promising results[3,14,30]. One of the considerations for patients with a second recurrence is platinum sensitivity. The progression-free interval since the most recent course of platinum chemotherapy may differentiate between platinum sensitive and platinum resistant disease [16]. Few studies have reported an increased rate of systemic complications with the combined use of cisplatin and mitomycin for IP chemotherapy[1,31]. Canda *et al*[27] found that patients with pre-operative renal dysfunction and previous chemotherapy may present with grade III/IV postoperative nephrotoxicity. Despite a 30% dose reduction in the chemotherapeutic agent doses during HIPEC in older patients (age > 70 years), patients with preoperative renal dysfunction or previous systemic/intraperitoneal chemotherapy, they found a high incidence of post-operative renal dysfunction with five patients requiring haemodialysis and two patients continuing with chronic haemodialysis[27]. Bakrin *et al*[16] suggested a 30% dose reduction in patients older than 70 years, with previous chemotherapy and/or extensive surgical cytoreduction as they found a higher incidence of postoperative renal dysfunction with 8% of patients (n = 51) suffering from postoperative renal insufficiency, 2% of patients (n = 15) chronic renal insufficiency and 1% of patients (n = 6) requiring long-term dialysis.

Haematological complications secondary to chemotherapeutic agents are also commonly reported in various studies[1,7,32]. Leukopenia and neutropenia have been frequently reported. Mitomycin-C (MMC), when dosed by body surface area or weight, has been attributed to leukopenia to the tune of 20%-40%[32]. In a study by Feferman *et al*[32], the use of MMC-HIPEC produced an incidence of 7% severe leukopenia and 4.5% neutropenia, with some patients requiring therapeutic granulocyte colony

Table 3 Systemic toxicities due to chemotherapy

Ref.	HIPEC drugs	EPIC	Nephrotoxicity, %	Haematological toxicity, %
Glehen *et al*[36], 2010	MMC + CDDP/Ox + 5FU/leucovorin	MMC+5FU	1	13.3
Bakrin *et al*[1], 2012	CDDP + MMC/DX			3
Baratti *et al*[17], 2012	CDDP + MMC/DX		5.4	5.9
Bakrin *et al*[16], 2013	CDDP/MMC/DX		11	11
Canda *et al*[27], 2013	CDDP + /MMC		25.8	19.8
Jafari *et al*[15], 2014	NA		3.7	0

EPIC: Early postoperative chemotherapy; HIPEC: Hyperthermic intraperitoneal chemotherapy; MMC: Mitomycin-C; CDDP-Cisplatin, 5FU" % flurouracil; Ox: Oxaloplatin; Dx: Adriamycin.

stimulating factor (GCSF). They reported that the risk of myelosuppression was reduced with a fixed 40 mg dose of MMC in HIPEC and routine use of GCSF for prophylaxis is not indicated. Bakrin *et al*[16] reported an 11% incidence of grade III/IV leukopenia in their cohort of 566 epithelial ovarian cancer patients undergoing CRS-HIPEC.

Limitations

The data provided in the included studies in this systematic review lacks standardisation in reporting of methodology, postoperative complications *etc*[33-37]. There is variance in the classification of complications, drugs used in HIPEC, *etc.* Although the first ERAS protocols for major abdominal surgery were developed in 2010, ERAS guidelines for CRS-HIPEC were recently published[14,38,39]. Hence the degree of adherence to ERAS in the studies included in our review and its effect on the rate of complications may vary in the future.

CONCLUSION

CRS-HIPEC for PSM has advantageous survival outcomes, and has become a common surgery in oncological centres all over the world. Being a complex surgery, with proven postoperative systemic inflammatory response, the focus in recent years has shifted to understanding the immediate postoperative pathophysiology and its management, early detection of complications and the institution of appropriate treatment to reduce morbidity and improve survival. The implementation of ERAS guidelines specific to CRS-HIPEC should help to further reduce postoperative complications.

ARTICLE HIGHLIGHTS

Research background

CRS-HIPEC is an aggressive option for the comprehensive management of all peritoneal surface malignancies. It can result in some life-threatening complications in the immediate postoperative period and reported higher morbidity and mortality rates. Postoperative morbidity and survival have significantly improved. The commonest postoperative surgical complications and systemic toxicity due to chemotherapy as reported in the last decade are discussed.

Research motivation

The number of patients undergoing CRS-HIPEC has increased in the last decade as have improvements in surgical techniques, surgical skills and perioperative management strategies. All these have led to improvements in post-surgical outcomes and survival rates. The present article reviews the early postoperative management and common complications after CRS-HIPEC, reported in the last decade.

Research objectives

To review early postoperative management after CRS-HIPEC. To review common im-mediate post-surgical complications, namely gastrointestinal, respiratory, cardiovascular, miscellaneous and systemic toxicity secondary to chemotherapy, in these patients.

Research methods

An electronic literature search was conducted using the databases of 'PubMed' and 'Google Scholar', during the period from 2010 to 2021. Postoperative complications and their synonyms in various combinations were searched. The extracted articles were further reviewed in a step-wise manner for the identification of relevant studies. The full-text assessment identified 14 original articles regarding postoperative complications and critical care management for inclusion in the final review article.

Research results

This article reviewed the early postoperative critical care management of such patients and the immediate post-surgical complications as reported in the gamut of studies included in the final review.

Research conclusions

CRS-HIPEC is a complex surgery, with a proven postoperative systemic inflammatory response. The focus in recent years has shifted to understanding the immediate postoperative pathophysiology and its management, early detection of complications and the institution of appropriate treatment to reduce morbidity and improve survival. The implementation of ERAS guidelines specific to CRS-HIPEC should help to further reduce postoperative complications.

Research perspectives

There are two major avenues for research in this area. One is the early prediction of postoperative complications and early intervention to reduce morbidity and mortality. Although numerous inflammatory markers such as mean platelet volume, CRP, procalcitonin *etc* have been studied, no single test is foolproof and they should be utilized in association with the clinical scenario, microbiological and biochemical investigations. The second avenue is the implementation of ERAS guidelines for CRS-HIPEC and its impact on postoperative outcomes and survival.

FOOTNOTES

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Country/Territory of origin: India

ORCID number: Sohan Lal Solanki 0000-0003-4313-7659.

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REFERENCES

1 **Bakrin N**, Cotte E, Golfier F, Gilly FN, Freyer G, Helm W, Glehen O, Bereder JM. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for persistent and recurrent advanced ovarian carcinoma: a multicenter, prospective study of 246 patients. *Ann Surg Oncol* 2012; **19**: 4052-4058 [PMID: 22825772 DOI: 10.1245/s10434-012-2510-4]

2 **Padmakumar AV**. Intensive Care Management of Patient After Cytoreductive Surgery and HIPEC - A Concise Review. *Indian J Surg Oncol* 2016; **7**: 244-248 [PMID: 27065716 DOI: 10.1007/s13193-016-0511-7]

3 **Solanki SL**, Mukherjee S, Agarwal V, Thota RS, Balakrishnan K, Shah SB, Desai N, Garg R, Ambulkar RP, Bhorkar NM, Patro V, Sinukumar S, Venketeswaran MV, Joshi MP, Chikkalingegowda RH, Gottumukkala V, Owusu-Agyemang P, Saklani AP, Mehta SS, Seshadri RA, Bell JC, Bhatnagar S, Divatia JV. Society of Onco-Anaesthesia and Perioperative Care consensus guidelines for perioperative management of patients for cytoreductive surgery and hyperthermic

intraperitoneal chemotherapy (CRS-HIPEC). *Indian J Anaesth* 2019; **63**: 972-987 [PMID: 31879421 DOI: 10.4103/ija.IJA_765_19]

4 **Solanki SL**, Jhingan MAK, Saklani AP. Rebound hypothermia after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) and cardiac arrest in immediate postoperative period: a report of two cases and review of literature. *Pleura Peritoneum* 2020; **5**: 20200126 [PMID: 33364341 DOI: 10.1515/pp-2020-0126]

5 **Alyami M**, Kim BJ, Villeneuve L, Vaudoyer D, Képénékian V, Bakrin N, Gilly FN, Cotte E, Glehen O, Passot G. Ninety-day post-operative morbidity and mortality using the National Cancer Institute's common terminology criteria for adverse events better describe post-operative outcome after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Int J Hyperthermia* 2018; **34**: 532-537 [PMID: 28838265 DOI: 10.1080/02656736.2017.1367846]

6 **Baratti D**, Kusamura S, Laterza B, Balestra MR, Deraco M. Early and long-term postoperative management following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *World J Gastrointest Oncol* 2010; **2**: 36-43 [PMID: 21160815 DOI: 10.4251/wjgo.v2.i1.36]

7 **Cooksley TJ**, Haji-Michael P. Post-operative critical care management of patients undergoing cytoreductive surgery and heated intraperitoneal chemotherapy (HIPEC). *World J Surg Oncol* 2011; **9**: 169 [PMID: 22182345 DOI: 10.1186/1477-7819-9-169]

8 **Malfroy S**, Wallet F, Maucort-Boulch D, Chardonnal L, Sens N, Friggeri A, Passot G, Glehen O, Piriou V. Complications after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis: Risk factors for ICU admission and morbidity prognostic score. *Surg Oncol* 2016; **25**: 6-15 [PMID: 26979635 DOI: 10.1016/j.suronc.2015.11.003]

9 **Colantonio L**, Claroni C, Fabrizi L, Marcelli ME, Sofra M, Giannarelli D, Garofalo A, Forastiere E. A randomized trial of goal directed vs. standard fluid therapy in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *J Gastrointest Surg* 2015; **19**: 722-729 [PMID: 25595308 DOI: 10.1007/s11605-015-2743-1]

10 **Owusu-Agyemang P**, Soliz J, Hayes-Jordan A, Harun N, Gottumukkala V. Safety of epidural analgesia in the perioperative care of patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 2014; **21**: 1487-1493 [PMID: 23982249 DOI: 10.1245/s10434-013-3221-1]

11 **Lorimier G**, Seegers V, Coudert M, Dupoiron D, Thibaudeau E, Pouplin L, Lebrec N, Dubois PY, Dumont F, Guérin-Meyer V, Capitain O, Campone M, Wernert R. Prolonged perioperative thoracic epidural analgesia may improve survival after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for colorectal peritoneal metastases: A comparative study. *Eur J Surg Oncol* 2018; **44**: 1824-1831 [PMID: 30213715 DOI: 10.1016/j.ejso.2018.08.012]

12 **Webb C**, Day R, Velazco CS, Pockaj BA, Gray RJ, Stucky CC, Young-Fadok T, Wasif N. Implementation of an Enhanced Recovery After Surgery (ERAS) Program is Associated with Improved Outcomes in Patients Undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy. *Ann Surg Oncol* 2020; **27**: 303-312 [PMID: 31605328 DOI: 10.1245/s10434-019-07900-z]

13 **Mao F**, Huang Z. Enhanced Recovery After Surgery for Patients Undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: A Systematic Review and Meta-Analysis. *Front Surg* 2021; **8**: 713171 [PMID: 34368219 DOI: 10.3389/fsurg.2021.713171]

14 **Hübner M**, Kusamura S, Villeneuve L, Al-Niaimi A, Alyami M, Balonov K, Bell J, Bristow R, Guiral DC, Fagotti A, Falcão LFR, Glehen O, Lambert L, Mack L, Muenster T, Piso P, Pocard M, Rau B, Sgarbura O, Somashekhar SP, Wadhwa A, Altman A, Fawcett W, Veerapong J, Nelson G. Guidelines for Perioperative Care in Cytoreductive Surgery (CRS) with or without hyperthermic IntraPEritoneal chemotherapy (HIPEC): Enhanced Recovery After Surgery (ERAS®) Society Recommendations - Part II: Postoperative management and special considerations. *Eur J Surg Oncol* 2020; **46**: 2311-2323 [PMID: 32826114 DOI: 10.1016/j.ejso.2020.08.006]

15 **Jafari MD**, Halabi WJ, Stamos MJ, Nguyen VQ, Carmichael JC, Mills SD, Pigazzi A. Surgical outcomes of hyperthermic intraperitoneal chemotherapy: analysis of the american college of surgeons national surgical quality improvement program. *JAMA Surg* 2014; **149**: 170-175 [PMID: 24352601 DOI: 10.1001/jamasurg.2013.3640]

16 **Bakrin N**, Bereder JM, Decullier E, Classe JM, Msika S, Lorimier G, Abboud K, Meeus P, Ferron G, Quenet F, Marchal F, Gouy S, Morice P, Pomel C, Pocard M, Guyon F, Porcheron J, Glehen O; FROGHI (FRench Oncologic and Gynecologic HIPEC) Group. Peritoneal carcinomatosis treated with cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for advanced ovarian carcinoma: a French multicentre retrospective cohort study of 566 patients. *Eur J Surg Oncol* 2013; **39**: 1435-1443 [PMID: 24209430 DOI: 10.1016/j.ejso.2013.09.030]

17 **Baratti D**, Kusamura S, Mingrone E, Balestra MR, Laterza B, Deraco M. Identification of a subgroup of patients at highest risk for complications after surgical cytoreduction and hyperthermic intraperitoneal chemotherapy. *Ann Surg* 2012; **256**: 334-341 [PMID: 22580946 DOI: 10.1097/SLA.0b013e31825704e3]

18 **Tao J**, Ji PT, Shen JJ, Lu Y. Survival and complications of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in elderly patients: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci* 2021; **25**: 5330-5348 [PMID: 34533809 DOI: 10.26355/eurrev_202109_26640]

19 **Kim NY**, Chun DH, Kim SY, Kim NK, Baik SH, Hong JH, Kim KS, Shin CS. Prognostic Value of Systemic Inflammatory Indices, NLR, PLR, and MPV, for Predicting 1-Year Survival of Patients Undergoing Cytoreductive Surgery with HIPEC. *J Clin Med* 2019; **8** [PMID: 31035703 DOI: 10.3390/jcm8050589]

20 **van Kooten JP**, Oemrawsingh A, de Boer NL, Verhoef C, Burger JWA, Madsen EVE, Brandt-Kerkhof ARM. Predictive Ability of C-Reactive Protein in Detecting Short-Term Complications After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: A Retrospective Cross-Sectional Study. *Ann Surg Oncol* 2021; **28**: 233-243 [PMID: 32524458 DOI: 10.1245/s10434-020-08619-y]

21 **Saeed K**, Dale AP, Leung E, Cusack T, Mohamed F, Lockyer G, Arnaudov S, Wade A, Moran B, Lewis G, Dryden M, Cecil T, Cepeda JA. Procalcitonin levels predict infectious complications and response to treatment in patients undergoing cytoreductive surgery for peritoneal malignancy. *Eur J Surg Oncol* 2016; **42**: 234-243 [PMID: 26560024 DOI: 10.1016/j.ejso.2015.10.004]

22 **Viyuela García C**, Medina Fernández FJ, Arjona-Sánchez Á, Casado-Adam Á, Sánchez Hidalgo JM, Rufián Peña S, Briceño Delgado J. Systemic inflammatory markers for the detection of infectious complications and safe discharge after

cytoreductive surgery and HIPEC. *Surg Oncol* 2020; **34**: 163-167 [PMID: 32891323 DOI: 10.1016/j.suronc.2020.04.013]

23 **Sinukumar S**, Mehta S, Damodaran D, Rajan F, Zaveri S, Ray M, Katdare N, Sethna K, Patel MD, Kammer P, Peedicayil A, Bhatt A. Failure-to-Rescue Following Cytoreductive Surgery with or Without HIPEC is Determined by the Type of Complication-a Retrospective Study by INDEPSO. *Indian J Surg Oncol* 2019; **10**: 71-79 [PMID: 30886497 DOI: 10.1007/s13193-019-00877-x]

24 **Cascales-Campos PA**, Sánchez-Fuentes PA, Gil J, Gil E, López-López V, Rodriguez Gomez-Hidalgo N, Fuentes D, Parrilla P. Effectiveness and failures of a fast track protocol after cytoreduction and hyperthermic intraoperative intraperitoneal chemotherapy in patients with peritoneal surface malignancies. *Surg Oncol* 2016; **25**: 349-354 [PMID: 27916165 DOI: 10.1016/j.suronc.2016.08.001]

25 **Martin AS**, Abbott DE, Hanseman D, Sussman JE, Kenkel A, Greiwe P, Saeed N, Ahmad SH, Sussman JJ, Ahmad SA. Factors Associated with Readmission After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Carcinomatosis. *Ann Surg Oncol* 2016; **23**: 1941-1947 [PMID: 26842489 DOI: 10.1245/s10434-016-5109-3]

26 **Preti V**, Chang D, Sugarbaker PH. Pulmonary Complications following Cytoreductive Surgery and Perioperative Chemotherapy in 147 Consecutive Patients. *Gastroenterol Res Pract* 2012; **2012**: 635314 [PMID: 22927838 DOI: 10.1155/2012/635314]

27 **Canda AE**, Sokmen S, Terzi C, Arslan C, Oztop I, Karabulut B, Ozzeybek D, Sarioglu S, Fuzun M. Complications and toxicities after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 2013; **20**: 1082-1087 [PMID: 23456387 DOI: 10.1245/s10434-012-2853-x]

28 **Sharma V**, Solanki SL, Saklani AP. Hyperammonemia after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: A Report of Three Cases with Unusual Presentation. *Indian J Crit Care Med* 2021; **25**: 590-593 [PMID: 34177182 DOI: 10.5005/jp-journals-10071-23821]

29 **Lanuke K**, Mack LA, Temple WJ. A prospective evaluation of venous thromboembolism in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Can J Surg* 2009; **52**: 18-22 [PMID: 19234647]

30 **Levine EA**, Stewart JH 4th, Shen P, Russell GB, Loggie BL, Votanopoulos KI. Intraperitoneal chemotherapy for peritoneal surface malignancy: experience with 1,000 patients. *J Am Coll Surg* 2014; **218**: 573-585 [PMID: 24491244 DOI: 10.1016/j.jamcollsurg.2013.12.013]

31 **Tan GHC**, Shannon NB, Chia CS, Soo KC, Teo MCC. Platinum agents and mitomycin C-specific complications in cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). *Int J Hyperthermia* 2018; **34**: 595-600 [PMID: 28633580 DOI: 10.1080/02656736.2017.1345014]

32 **Feferman Y**, Bhagwandin S, Kim J, Aycart SN, Feingold D, Labow DM, Sarpel U. Conflicting Data on the Incidence of Leukopenia and Neutropenia After Heated Intraperitoneal Chemotherapy with Mitomycin C. *Ann Surg Oncol* 2017; **24**: 3831-3836 [PMID: 29027153 DOI: 10.1245/s10434-017-6112-z]

33 **Bhandoria G**, Solanki SL, Bhavsar M, Balakrishnan K, Bapuji C, Bhorkar N, Bhandarkar P, Bhosale S, Divatia JV, Ghosh A, Mahajan V, Peedicayil A, Nath P, Sinukumar S, Thambudorai R, Seshadri RA, Bhatt A. Enhanced recovery after surgery (ERAS) in cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC): a cross-sectional survey. *Pleura Peritoneum* 2021; **6**: 99-111 [PMID: 34676283 DOI: 10.1515/pp-2021-0117]

34 **Hübner M**, Kusamura S, Villeneuve L, Al-Niaimi A, Alyami M, Balonov K, Bell J, Bristow R, Guiral DC, Fagotti A, Falcão LFR, Glehen O, Lambert L, Mack L, Muenster T, Piso P, Pocard M, Rau B, Sgarbura O, Somashekhar SP, Wadhwa A, Altman A, Fawcett W, Veerapong J, Nelson G. Guidelines for Perioperative Care in Cytoreductive Surgery (CRS) with or without hyperthermic IntraPEritoneal chemotherapy (HIPEC): Enhanced recovery after surgery (ERAS®) Society Recommendations - Part I: Preoperative and intraoperative management. *Eur J Surg Oncol* 2020; **46**: 2292-2310 [PMID: 32873454 DOI: 10.1016/j.ejso.2020.07.041]

35 **Cavaliere F**, De Simone M, Virzì S, Deraco M, Rossi CR, Garofalo A, Di Filippo F, Giannarelli D, Vaira M, Valle M, Pilati P, Perri P, La Pinta M, Monsellato I, Guadagni F. Prognostic factors and oncologic outcome in 146 patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy: Italian multicenter study S.I.T.I.L.O. *Eur J Surg Oncol* 2011; **37**: 148-154 [PMID: 21093205 DOI: 10.1016/j.ejso.2010.10.014]

36 **Glehen O**, Gilly FN, Boutitie F, Bereder JM, Quenet F, Sideris L, Mansvelt B, Lorimier G, Msika S, Elias D; French Surgical Association. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. *Cancer* 2010; **116**: 5608-5618 [PMID: 20737573 DOI: 10.1002/cncr.25356]

37 **Mizumoto A**, Canbay E, Hirano M, Takao N, Matsuda T, Ichinose M, Yonemura Y. Morbidity and mortality outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy at a single institution in Japan. *Gastroenterol Res Pract* 2012; **2012**: 836425 [PMID: 22778724 DOI: 10.1155/2012/836425]

38 **Elekonawo FMK**, van der Meeren MMD, Simkens GA, de Wilt JHW, de Hingh IH, Bremers AJA. Comparison of 2 Perioperative Management Protocols and Their Influence on Postoperative Recovery after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Standard Parenteral Nutrition, Selective Bowel Decontamination and Suprapubic Catheters? *Dig Surg* 2019; **36**: 394-401 [PMID: 29982248 DOI: 10.1159/000490068]

39 **Kelly KJ**, Cajas L, Baumgartner JM, Lowy AM. Factors Associated with 60-Day Readmission Following Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy. *Ann Surg Oncol* 2018; **25**: 91-97 [PMID: 29090402 DOI: 10.1245/s10434-017-6108-8]

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CORRECTION

Correction to "Retrospective analysis of anti-inflammatory therapies during the first wave of COVID-19 at a community hospital"

Jose I Iglesias, Andrew V Vassallo

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Jose I Iglesias, Department of Critical Care, Community Medical Center, Toms River, NJ 08757, United States

Andrew V Vassallo, Department of Pharmacy, Community Medical Center, Toms River, NJ 08757, United States

Corresponding author: Jose I Iglesias, DO, FASN, Department of Critical Care, Community Medical Center, 99 W Rt 37, Toms River, NJ 08757, United States. jiglesias23@gmail.com

Abstract

Correction to: "Iglesias JI *et al*. Retrospective analysis of anti-inflammatory therapies during the first wave of COVID-19 at a community hospital. *World J Crit Care Med* 2021 Sep 9; 10(5): 244-259. DOI: 10.5492/wjccm.v10.i5.244. PMID: 34616660; PMCID: PMC8462025." In this article, corrections were made to Tables.

Key Words: Corrections; COVID-19; Corticosteroids; Intensive care unit; Methylprednisolone; Tociluzimab; Anti-inflammatory

Core Tip: This manuscript is an author's correction for "Retrospective analysis of anti-inflammatory therapies during the first wave of COVID-19 at a community hospital." *World J Crit Care Med* 2021 Sep 9; 10(5): 244-259. DOI: 10.5492/wjccm.v10.i5.244. PMID: 34616660; PMCID: PMC8462025.

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TO THE EDITOR

Correction to: Iglesias JI, Vassallo AV, Sullivan JB, Elbaga Y, Patel VV, Patel N, Ayad

Table 1 Coronavirus disease 2019 patients admitted to intensive care unit characteristics of survivors and non-survivors

	Non-survivor (*n* = 167)	Survivors (*n* = 94)	*P* value	OR	95%CI
Age	72 (63-82)	65.5 (51-74)	< 0.001		
Race (Caucasian)	125 (74.9)	57 (60.6)	0.016	1.9	1.12-3.3
BMI	29 (23.9, 34.7)	28.6 (24, 33)	0.49		
Sex (male)	102 (61)	56 (60)	0.81	1.065	0.63-1.78
Diabetes	60 (35)	24 (26)	0.08	1.63	0.93-2.8
CHF	24 (15)	10 (11)	0.38	1.42	0.64-3.1
CAD	45 (27)	20 (21)	0.30	1.36	0.74-2.48
COPD	38 (23)	23 (25)	0.75	0.9	0.5-1.64
CKD	25 (15)	13 (14)	0.8	1.09	0.53-2.26
HTN	100 (60)	45 (48)	0.061	1.62	0.97-2.70
AKI	87 (52)	30 (32)	0.002	2.3	1.21-2.5
Mechanical ventilation	134 (80)	44 (47)	< 0.001	4.6	2.64-8
Hemodialysis	29(18)	10 (11)	0.13	1.8	0.83-3.8
Neutrophils × 10^9/L	7.4 (5-11.79)	7.8 4.4-12.9	0.92		
Lymphocytes	0.7 (0.5, 1.2)	0.9 (0.6, 1.6)	0.011		
Neutrophil/lymphocyte	10 (6, 18.5)	7.54 4.3-14.2	0.017		
SCr (mg/dL)	1.2 (0.8-1.8)	1.1 (0.8, 0.8)	0.49		
Plts (× 10^9/L)	202 (166-268)	232 (155-301)	0.27		
Tbili (mg/dl)	0.5 (0.4, 0.8)	0.5 (0.4, 0.8)	0.65		
SOFA admit	4 (3-7)	4 (2, 6)	0.095		
PaO2/FIO2	190 (76, 285)	232 (123, 307)	0.039		
PaO2	69 (55-86)	73 (59-96)	0.083		
FIO2	0.44 (0.24-1)	0.36 (0.21-0.97)	0.12		

OR: Odds ratio; CI: Confidence interval; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; CHF: Congestive heart failure; AKI: Acute kidney injury; HD: Hemodialysis; tBili: Total bilirubin; Plts: Platelets INR: International normalized ratio; PaO2/FiO2: Partial pressure of oxygen/inspired concentration of oxygen ratio; SOFA: Sequential Organ Failure Assessment; BMI: Body mass index; SCr: Serum creatinine.

L, Benson P, Pittiglio M, Gobran E, Clark A, Khan W, Damalas K, Mohan R, Singh SP. Retrospective analysis of anti-inflammatory therapies during the first wave of COVID-19 at a community hospital. *World J Crit Care Med* 2021 Sep 9; 10(5): 244-259. DOI: 10.5492/wjccm.v10.i5.244. PMID: 34616660; PMCID: PMC8462025[1].

In the original manuscript, there are some errors in the table data presented, which need to be modified. The corrected tables are shown as Table 1 (original Table 1) and Table 2 (original Table 4). These errors do not change the ultimate results and conclusion of the paper but have been provided for clarification and overall accuracy.

Patient characteristics are described in Table 1. Univariate predictors of decreased survival included the need for mechanical ventilation, acute kidney injury, Caucasian race, older age, lower total lymphocyte count, higher neutrophil/Lymphocyte ratio, and a greater degree of respiratory failure manifested by a lower PaO2/FIO2 ratio. As anticipated non-survivors demonstrated a higher degree of elevated inflammatory and pro-thrombotic markers, D-Dimer at 24 h (Table 2, Original Table 4).

Table 2 Inflammatory markers in coronavirus disease 2019 survivors and non-survivors

	Non-survivors (*n* = 167)	Survivors (*n* = 94)	*P* value
IL-6 day 1 (pg/mL)	116 (33, 410)	72 (45, 210)	0.75
IL-6 day 2	470 (36, 1299)	153 (10, 280)	0.38
D-Dimer day 1 (ng/mL)	855 (522, 2434)	595 (337, 1349)	0.013
D-Dimer day 2	691 (436, 1743)	1040 (550, 3431)	0.11
CRP day 1 (mg/L)	125 (61, 179)	130 (89, 185)	0.55
CRP day 2	116 (82, 185)	119 (47, 175)	0.29
Ferritin day 1 (ng/mL)	869 (406, 1467)	995 (488, 1571)	0.35
Ferritin day 2	822 (447, 1432)	1053 (712, 2057)	0.05

IL-6: Interleukin 6, CRP: C-reactive protein.

FOOTNOTES

Author contributions: Iglesias JI did the formal analysis; Vassallo AV did the original draft editing and project administration; all authors participate in the manuscript conceptualization, methodology and original draft writing.

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Country/Territory of origin: United States

ORCID number: Jose I Iglesias 0000-0001-7851-0498.

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REFERENCES

1 **Iglesias JI**, Vassallo AV, Sullivan JB, Elbaga Y, Patel VV, Patel N, Ayad L, Benson P, Pittiglio M, Gobran E, Clark A, Khan W, Damalas K, Mohan R, Singh SP. Retrospective analysis of anti-inflammatory therapies during the first wave of COVID-19 at a community hospital. *World J Crit Care Med* 2021; **10**: 244-259 [PMID: 34616660 DOI: 10.5492/wjccm.v10.i5.244]

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