ISSN 2220-3141 (online)

World Journal of

Critical Care Medicine

World J Crit Care Med 2022 July 9; 11(4): 201-310

Published by Baishideng Publishing Group Inc

World Journal of Critical Care Medicine

Contents

Bimonthly Volume 11 Number 4 July 9, 2022

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Observational Study

SYSTEMATIC REVIEWS

META-ANALYSIS

World Journal of Critical Care Medicine

Bimonthly Volume 11 Number 4 July 9, 2022

Contents

ABOUT COVER

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

AIMS AND SCOPE

The primary aim of the *World Journal of Critical Care Medicine* (*WJCCM*, *World J Crit Care Med*) is to provide scholars and readers from various fields of critical care medicine with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, sedation and analgesia, severe infection, *etc*.

INDEXING/ABSTRACTING

The *WJCCM* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Li-Li Wang*.

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Hua-Dong Wang

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

PUBLICATION DATE
July 9, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2022 July 9; 11(4): 201-218

DOI: 10.5492/wjccm.v11.i4.201

ISSN 2220-3141 (online)

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

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

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Bittner EA, United States; Wong YP, Malaysia
A-Editor: Liu X

Received: January 20, 2022
Peer-review started: January 20, 2022
First decision: February 8, 2022
Revised: February 24, 2022
Accepted: May 17, 2022
Article in press: May 17, 2022
Published online: July 9, 2022

Bruna Teixeira da Costa, Glauber Rocha Lima Araújo, Ronaldo Teixeira da Silva Júnior, Luana Kauany de Sá Santos, Daniel Bastos Alves Lima, Beatriz Rocha Cuzzuol, Jonathan Santos Apolonio, Lorena Sousa de Carvalho, Camilo Santana Silva, Isadora de Souza Barcelos, Márcio Vasconcelos Oliveira, Fabrício Freire de Melo, Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Vitória da Conquista 45029-094, Bahia, Brazil

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
URL: https://www.wjgnet.com/2220-3141/full/v11/i4/201.htm
DOI: https://dx.doi.org/10.5492/wjccm.v11.i4.201

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].

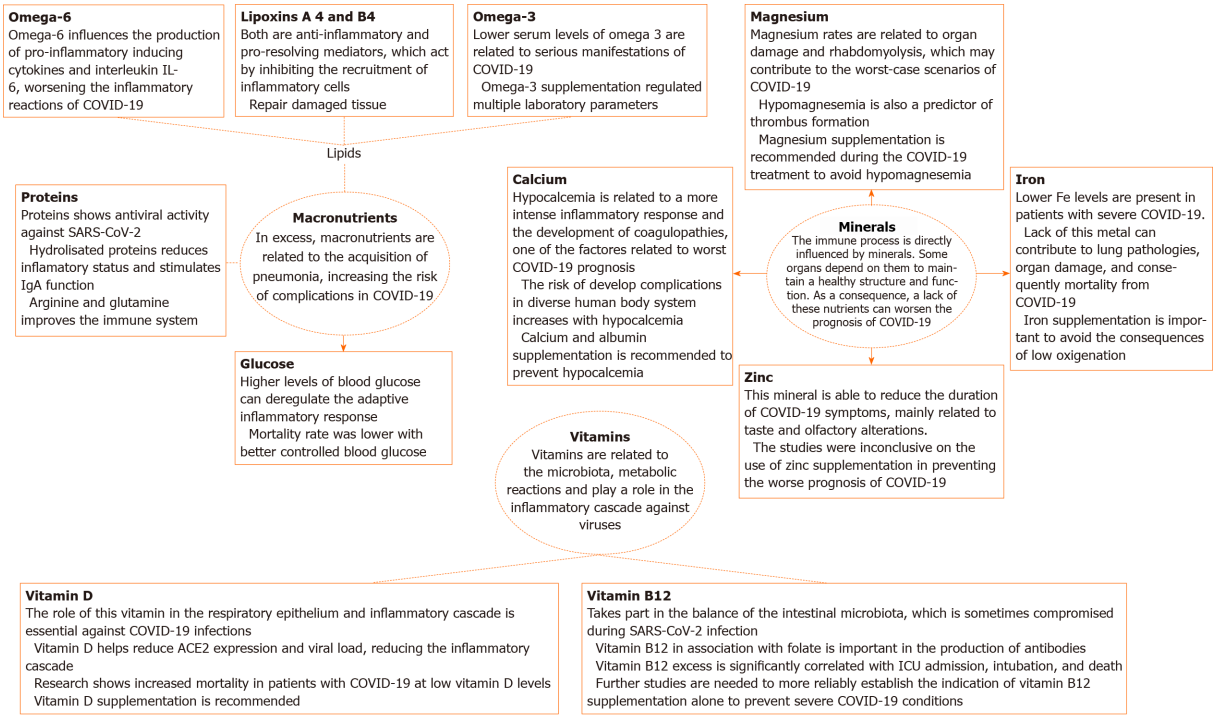
Figure 1 provides a summary of mechanisms of action of proteins and other nutrients in targeting SARS-CoV-2 infection.

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].



DOI: 10.5492/wjccm.v11.i4.201

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

Author contributions: All authors equally contributed to this paper with the conception and design of the study, literature review and analysis, manuscript drafting, critical revision, and editing, and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest exist.

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.

S-Editor: Wang LL
L-Editor: Wang TQ
P-Editor: Wang LL

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]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2022 July 9; 11(4): 219-227

DOI: 10.5492/wjccm.v11.i4.219

ISSN 2220-3141 (online)

MINIREVIEWS

Challenges in hyperglycemia management in critically ill patients with COVID-19

Rajesh Kethireddy, Darshan Gandhi, Asim Kichloo, Love Patel

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

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Papadopoulos VP, Greece; Sivanand N, India

Received: April 2, 2021
Peer-review started: April 2, 2021
First decision: July 31, 2021
Revised: August 10, 2021
Accepted: May 8, 2022
Article in press: May 8, 2022
Published online: July 9, 2022

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.

Citation: Kethireddy R, Gandhi D, Kichloo A, Patel L. Challenges in hyperglycemia management in critically ill patients with COVID-19. *World J Crit Care Med* 2022; 11(4): 219-227
URL: https://www.wjgnet.com/2220-3141/full/v11/i4/219.htm
DOI: https://dx.doi.org/10.5492/wjccm.v11.i4.219

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

Author contributions: Kethireddy R conceived the idea of this article and contributed to the writing and revision of the manuscript substantially; Gandhi D contributed to the discussion and revision of the manuscript substantially; Kichloo A contributed to the manuscript format and editing of the manuscript substantially; Patel L contributed to the manuscript formation and reference numbering of the manuscript.

Conflict-of-interest statement: The authors declare that they have no competing or conflicts of interests.

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.

S-Editor: Wu YXJ
L-Editor: A
P-Editor: Wu YXJ

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]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2022 July 9; 11(4): 228-235

DOI: 10.5492/wjccm.v11.i4.228

ISSN 2220-3141 (online)

MINIREVIEWS

Medicinal nicotine in COVID-19 acute respiratory distress syndrome, the new corticosteroid

Farrukh Ahmad

Specialty type: Critical care medicine

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Juneja D, India

Received: November 14, 2021
Peer-review started: November 14, 2021
First decision: April 7, 2022
Revised: April 23, 2022
Accepted: June 18, 2022
Article in press: June 18, 2022
Published online: July 9, 2022

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.

Citation: Ahmad F. Medicinal nicotine in COVID-19 acute respiratory distress syndrome, the new corticosteroid. *World J Crit Care Med* 2022; 11(4): 228-235
URL: https://www.wjgnet.com/2220-3141/full/v11/i4/228.htm
DOI: https://dx.doi.org/10.5492/wjccm.v11.i4.228

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

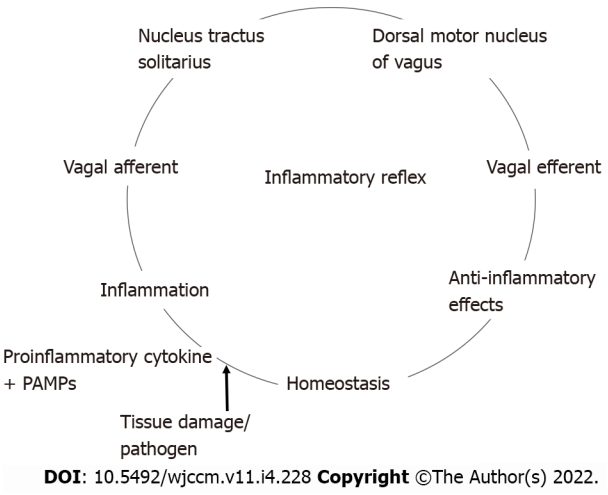
The systemic anti-inflammatory effects of CAP are thought to exert its effects *via* the spleen[23,24]. The efferent limb originates at the DMV, the motor nuclei of the vagus nerve. Motor signals are transmitted *via* cholinergic fibers down the vagus nerve to mount an anti-inflammatory response, reestablishing 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

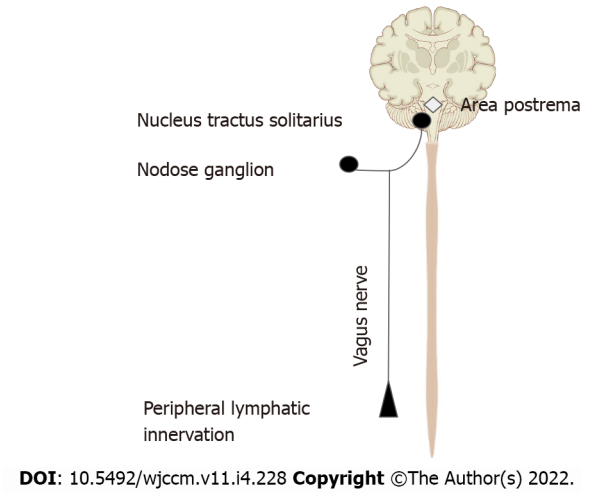
Augmenting the CAP offers an effective tool in controlling maladaptive inflammatory responses[25,26]. Modulating the cholinergic tone, irrespective of the modality used, has been shown to suppress inflammation[27]. Direct electrical stimulation of the vagus nerve aims to trigger an action potential that 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].



DOI: 10.5492/wjccm.v11.i4.228 **Copyright** ©The Author(s) 2022.

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.



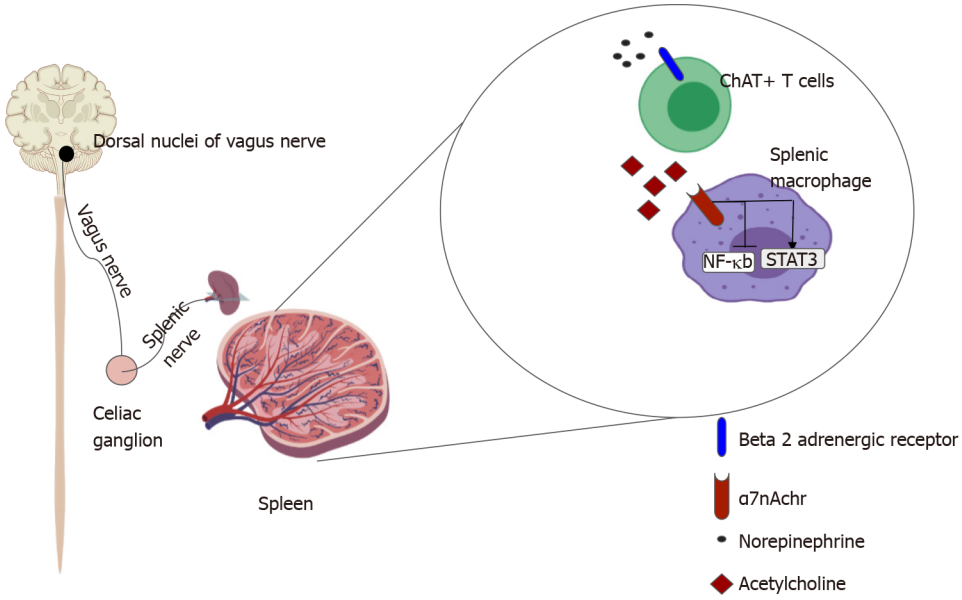
DOI: 10.5492/wjccm.v11.i4.228 **Copyright** ©The Author(s) 2022.

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



DOI: 10.5492/wjccm.v11.i4.228 **Copyright** ©The Author(s) 2022.

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

Author contributions: Ahmad F contributed hypothesis generation, evidence gathering, drafting and editing of manuscript.

Conflict-of-interest statement: The author reports no relevant conflicts of interest for this article.

Country/Territory of origin: United States

ORCID number: Farrukh Ahmad 0000-0003-0004-441X.

S-Editor: Gao CC
L-Editor: A
P-Editor: Gao CC

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]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2022 July 9; 11(4): 236-245

DOI: 10.5492/wjccm.v11.i4.236

ISSN 2220-3141 (online)

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

Specialty type: Critical care medicine

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: El-Gendy HA, Egypt; Gupta L, Indonesia

Received: February 3, 2022
Peer-review started: February 3, 2022
First decision: April 13, 2022
Revised: April 16, 2022
Accepted: May 28, 2022
Article in press: May 28, 2022
Published online: July 9, 2022

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.

Citation: Lau VI, Johnson JA, Bagshaw SM, Rewa OG, Basmaji J, Lewis KA, Wilcox ME, Barrett K, Lamontagne F, Lauzier F, Ferguson ND, Oczkowski SJW, Fiest KM, Niven DJ, Stelfox HT, Alhazzani W, Herridge M, Fowler R, Cook DJ, Rochwerg B, Xie F. Health-related quality-of-life and health-utility reporting in critical care. *World J Crit Care Med* 2022; 11(4): 236-245
URL: https://www.wjgnet.com/2220-3141/full/v11/i4/236.htm
DOI: https://dx.doi.org/10.5492/wjccm.v11.i4.236

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

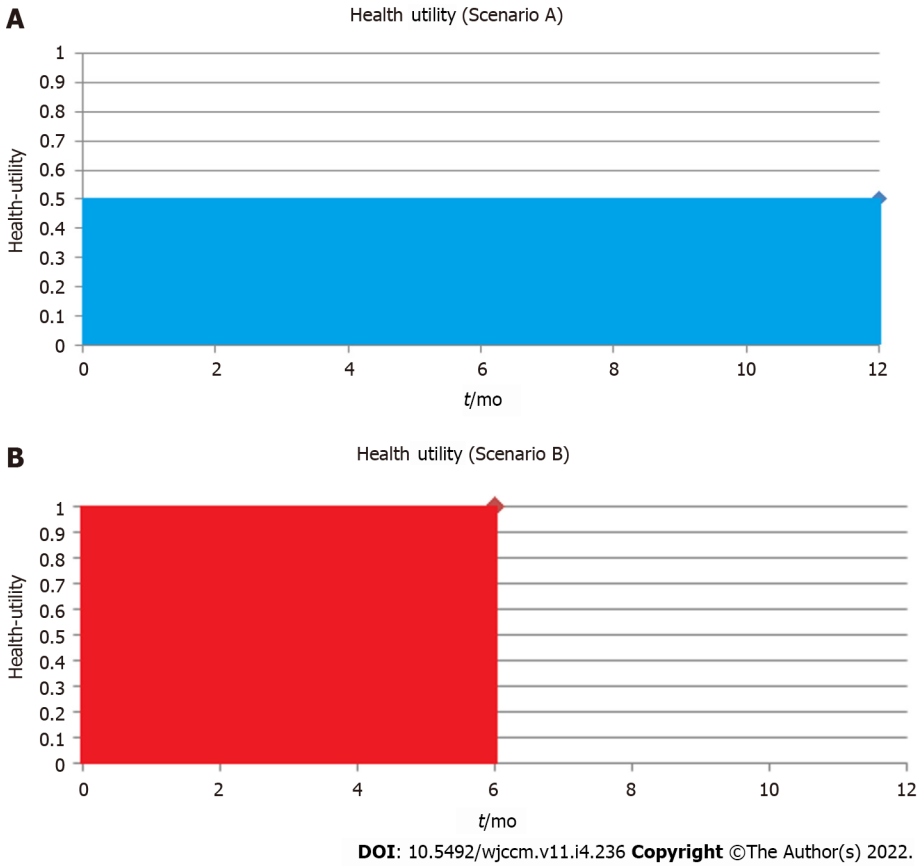
EQ-5D: EuroQoL-5 domains; HUI: Health utility index mark; ICU: Intensive care unit; QALY: Quality-adjusted life year; QoL: Quality of life; SF-12: Short form-12; SF-36: Short form-36; SF-6D: Short form-6 domains.

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.



DOI: 10.5492/wjccm.v11.i4.236

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.

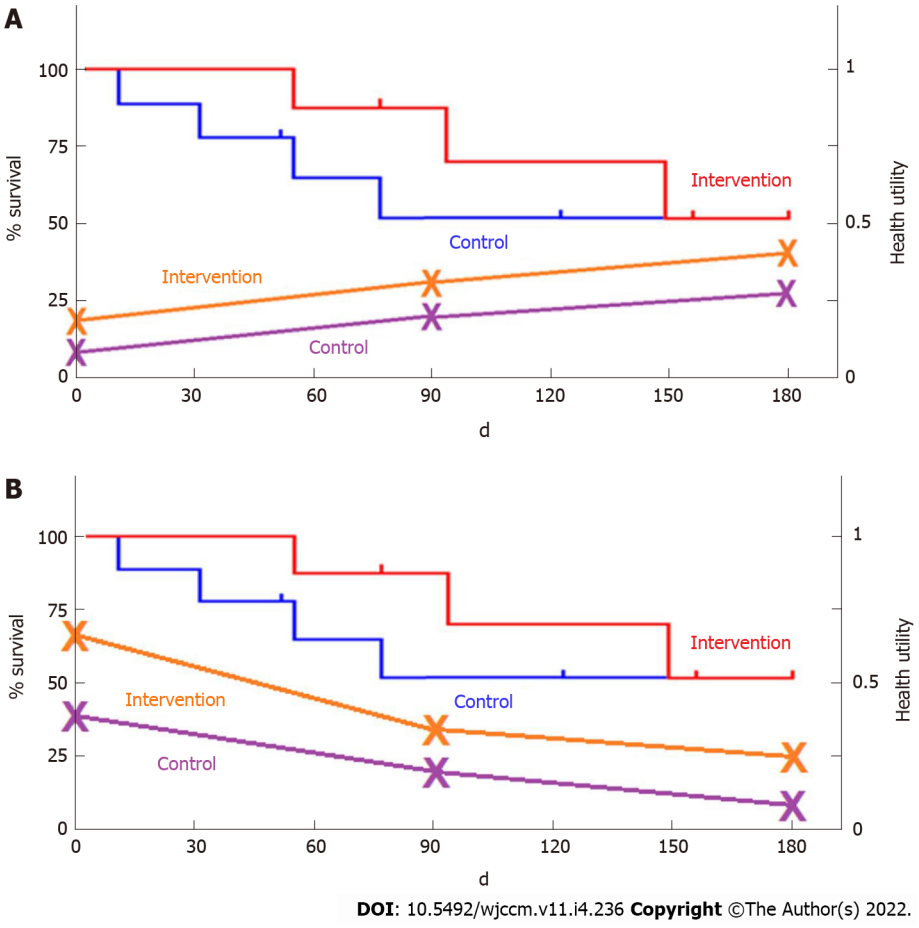
HRQOL IMPLEMENTATION AND MEASUREMENT

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 (



DOI: 10.5492/wjccm.v11.i4.236 **Copyright** ©The Author(s) 2022.

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.

ACKNOWLEDGEMENTS

We also wish to acknowledge the support and contributions from the University of Alberta Department of Critical Care Medicine Research Office (Nadia Baig, Teresa Lawrence, Dawn Opgenorth, Lily Guan) and McMaster University's Guidelines in Intensive Care, Development and Evaluation (GUIDE) group members (Sarah Culgin, Kate Nelson).

FOOTNOTES

Author contributions: Lau VI, Johnson JA, Bagshaw SM, Rewa OG, Basmaji J, Lewis KA, Wilcox ME, Barrett K, Lamontagne F, Lauzier F, Ferguson ND, Oczkowski SJW, Fiest KM, Niven DJ, HT Stelfox, Alhazzani W, Herridge M, Fowler R, Cook DJ, Rochwerg B, and Xie F had (1) made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; (2) drafted the submitted article and revised it critically for important intellectual content; and (3) provided final approval of the version to be published; Lau VI, Johnson JA, Cook DJ, Rochwerg B, Xie F contributed to conception and background; All the authors contributed to drafting the manuscript and revising the manuscript.

Supported by the EuroQol Research Foundation, No. 299-RA.

Conflict-of-interest statement: Drs. Lau, Xie and Johnson have received funding from EuroQoL Foundation. All other authors declare that they have no conflict of interest.

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.

S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2022 July 9; 11(4): 246-254

DOI: 10.5492/wjccm.v11.i4.246

ISSN 2220-3141 (online)

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

Specialty type: Critical care medicine

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Deshwal H, United States; Solanki SL; India

Received: November 6, 2021
Peer-review started: November 6, 2021
First decision: January 12, 2022
Revised: January 17, 2022
Accepted: June 24, 2022
Article in press: June 24, 2022
Published online: July 9, 2022

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.

Citation: Cidade JP, Coelho L, Costa V, Morais R, Moniz P, Morais L, Fidalgo P, Tralhão A, Paulino C, Nora D, Valério B, Mendes V, Tapadinhas C, Povoa P. Septic shock 3.0 criteria application in severe COVID-19 patients: An unattended sepsis population with high mortality risk. *World J Crit Care Med* 2022; 11(4): 246-254
URL: https://www.wjgnet.com/2220-3141/full/v11/i4/246.htm
DOI: https://dx.doi.org/10.5492/wjccm.v11.i4.246

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

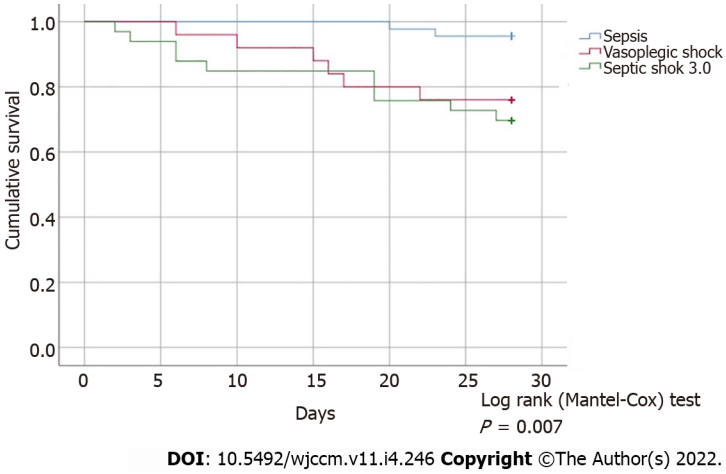
IQR: Interquartile range; SD: Standard deviation.

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

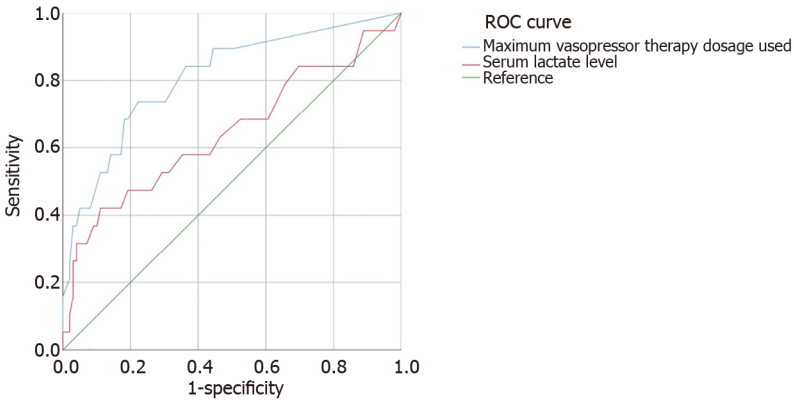
SD: Standard deviation.

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.



DOI: 10.5492/wjccm.v11.i4.246 **Copyright** ©The Author(s) 2022.

Figure 1 Kaplan-Meier Survival curves of Sepsis, Vasoplegic shock and Septic shock 3.0 groups.



DOI: 10.5492/wjccm.v11.i4.246 **Copyright** ©The Author(s) 2022.

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

Author contributions: Cidade JP, Coelho L, Costa V, Morais R, Moniz P, Morais L, Fidalgo P, Tralhão A, Paulino C, Nora D, Valério B, Mendes V, Tapadinhas C, and Póvoa P contributed to conceptualization, data curation and statistical analysis; Cidade JP, Coelho L; and Póvoa P designed the research; Cidade JP wrote the paper; Coelho L and

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.

Data sharing statement: The datasets generated and/or analyzed during the current study are not publicly available due to privacy issues but are available from the corresponding author on reasonable request.

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: 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.

S-Editor: Ma YJ
L-Editor: Webster JR
P-Editor: Ma YJ

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]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2022 July 9; 11(4): 255-268

DOI: 10.5492/wjccm.v11.i4.255

ISSN 2220-3141 (online)

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

Specialty type: Critical care medicine

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Karim HMR, India; Saaiq M, Pakistan; Surani S, United States

Received: March 1, 2022
Peer-review started: March 1, 2022
First decision: April 13, 2022
Revised: May 6, 2022
Accepted: June 18, 2022
Article in press: June 18, 2022
Published online: July 9, 2022

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.

Citation: Shahid A, Sept B, Kupsch S, Brundin-Mather R, Piskulic D, Soo A, Grant C, Leigh JP, Fiest KM, Stelfox HT. Development and pilot implementation of a patient-oriented discharge summary for critically Ill patients. *World J Crit Care Med* 2022; 11(4): 255-268

URL: https://www.wjgnet.com/2220-3141/full/v11/i4/255.htm

DOI: https://dx.doi.org/10.5492/wjccm.v11.i4.255

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

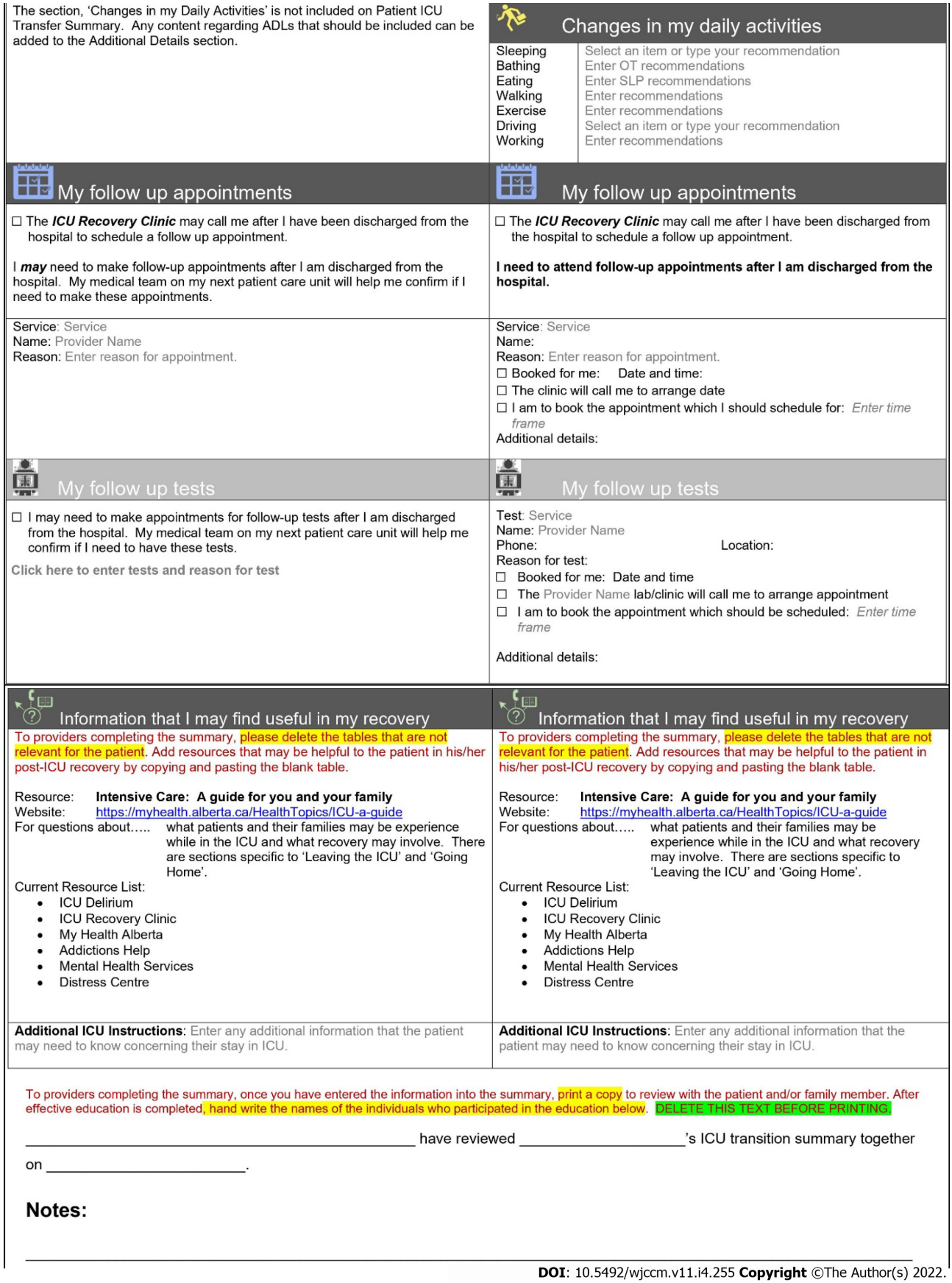
Many patients and families can find the transition out of the ICU stressful. My ICU team has carefully evaluated my health condition and determined that I am now well enough to safely transition directly home. All the details of my ICU stay are available in my electronic medical record which is available 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.

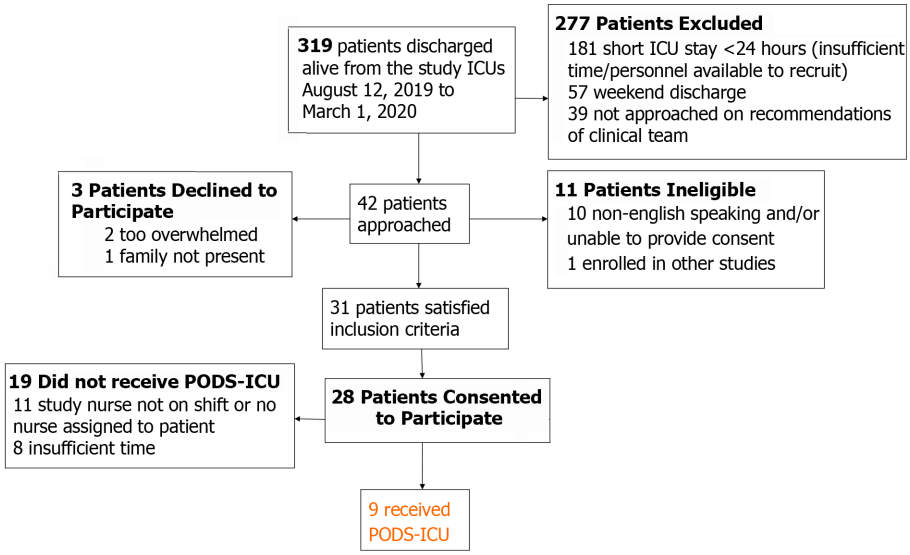
Medications I need to take

☐ 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



DOI: 10.5492/wjccm.v11.i4.255

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).



DOI: 10.5492/wjccm.v11.i4.255 **Copyright** ©The Author(s) 2022.

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)

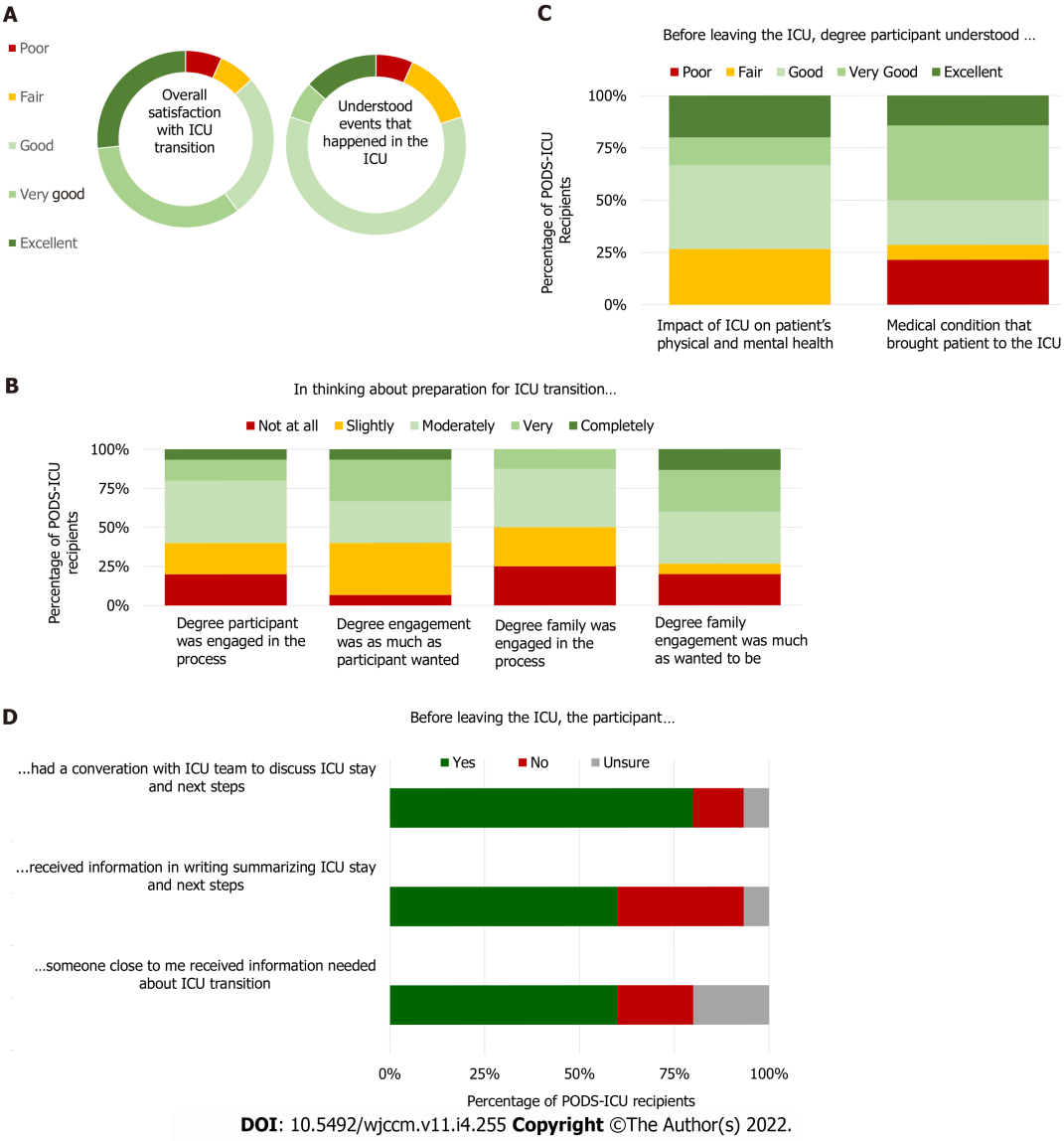
		Total responses, *n* = 10
Respondents	Nurse practitioner	3 (30.0%)
	Registered nurse	4 (40.0%)
	Unknown/response missing	3 (30.0%)
Role in PODS-ICU implementation	Completed and delivered[1]	9 (90.0%)
	Completed only	1 (10.0%)
Main PODS-ICU delivery recipient	Patient only	4 (40.0%)
	Friend/family only	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



DOI: 10.5492/wjccm.v11.i4.255 **Copyright** ©The Author(s) 2022.

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

We would like to thank the working group for their role in developing the patient-oriented discharge summary tool (PODS-ICU), the individuals involved in PODS-ICU testing, and the patient partners involved in participant recruitment for all their hard work on this project.

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.

S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

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]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2022 July 9; 11(4): 269-297

DOI: 10.5492/wjccm.v11.i4.269

ISSN 2220-3141 (online)

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

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

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Samadder S, India
A-Editor: Yao QG

Received: July 22, 2021
Peer-review started: July 22, 2021
First decision: November 11, 2021
Revised: December 1, 2021
Accepted: May 16, 2022
Article in press: May 16, 2022
Published online: July 9, 2022

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.

Citation: Andaluz-Ojeda D, Vidal-Cortes P, Aparisi Sanz Á, Suberviola B, Del Río Carbajo L, Nogales Martín L, Prol Silva E, Nieto del Olmo J, Barberán J, Cusacovich I. Immunomodulatory therapy for the management of critically ill patients with COVID-19: A narrative review. *World J Crit Care Med* 2022; 11(4): 269-297
URL: https://www.wjgnet.com/2220-3141/full/v11/i4/269.htm
DOI: https://dx.doi.org/10.5492/wjccm.v11.i4.269

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.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and confirm that the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

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]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2022 July 9; 11(4): 298-310

DOI: 10.5492/wjccm.v11.i4.298

ISSN 2220-3141 (online)

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

Specialty type: Respiratory system

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Alberca RW, Brazil

Received: November 30, 2021
Peer-review started: November 30, 2021
First decision: April 19, 2022
Revised: April 25, 2022
Accepted: June 16, 2022
Article in press: June 16, 2022
Published online: July 9, 2022

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.

Citation: 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, Mbaga DS, Bowo-Ngandji A, Kengne-Ndé C, Esemu SN, Njouom R, Ndip L. Association between early viral lower respiratory tract infections and subsequent asthma development. *World J Crit Care Med* 2022; 11(4): 298-310

URL: https://www.wjgnet.com/2220-3141/full/v11/i4/298.htm

DOI: https://dx.doi.org/10.5492/wjccm.v11.i4.298

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

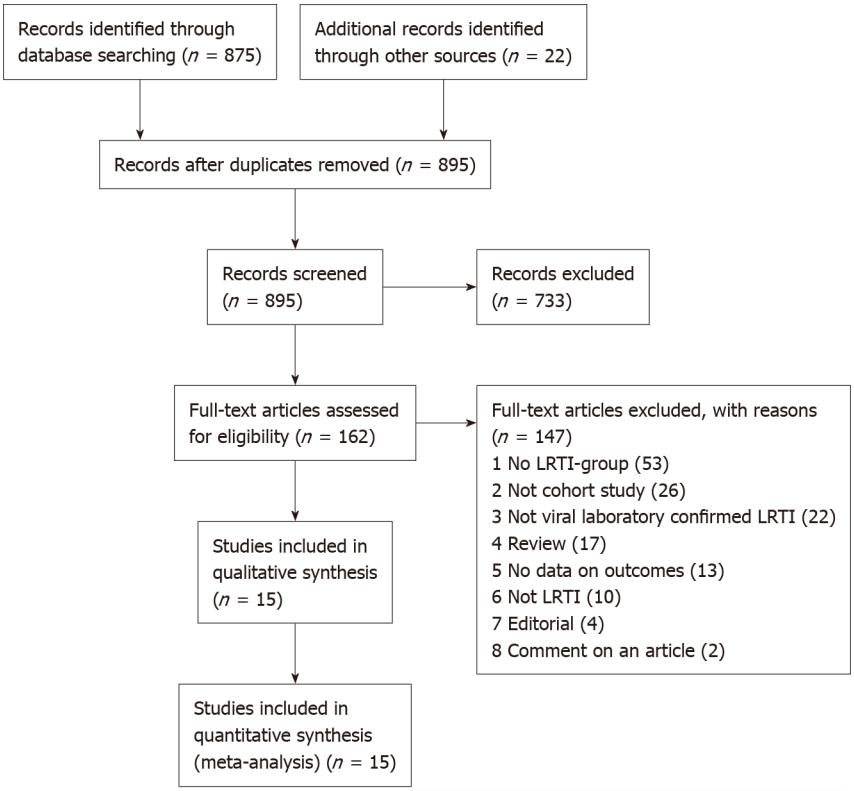
LRTI: Lower respiratory tract infection; OR: Odds ratio; NA: Not applicable.

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

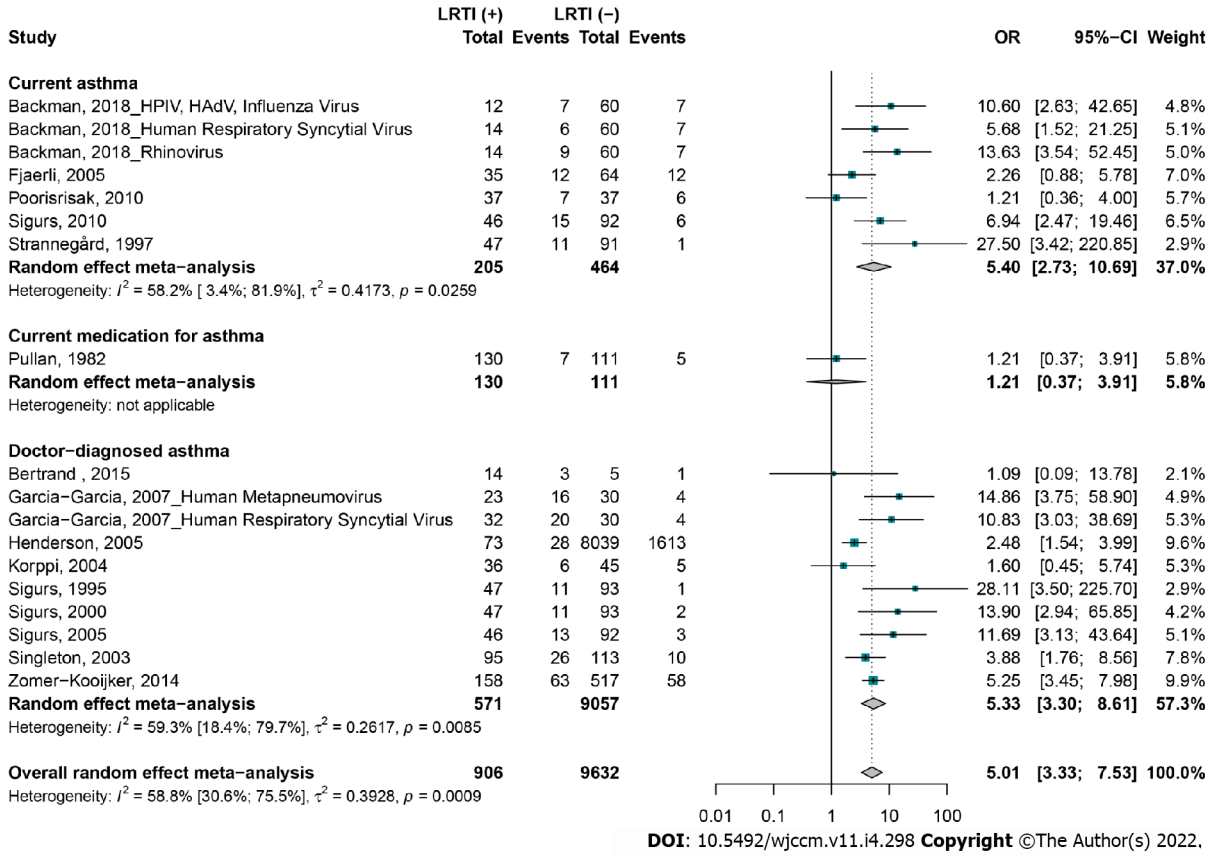


Figure 2 Forest plot of asthma in children with and without viral lower respiratory tract infections in infancy. LRTI: Lower respiratory tract infection; OR: Odds ratio.

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.

Supported by the European Union (EDCTP2 Programme), No. TMA2019PF-2705.

Conflict-of-interest statement: The authors deny any conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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.

S-Editor: Zhang H
L-Editor: Filipodia CL
P-Editor: Zhang H

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]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com