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MINIREVIEWS

Rationale for integration of palliative care in the medical intensive care: A narrative literature review

Nishkarsh Gupta, Raghav Gupta, Anju Gupta

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Abstract

Despite the remarkable technological advancement in the arena of critical care expertise, the mortality of critically ill patients remains high. When the organ functions de-teriorate, goals of care are not fulfilled and life-sustaining treatment becomes a burden on the patient and caregivers, then it is the responsibility of the physician to provide a dignified end to life, control the symptoms of the patient and provide psychological support to the family members. Palliative care is the best way forward for these patients. It is a multidimensional specialty which emphasizes patient and family-based care and aims to improve the quality of life of patients and their caregivers. Although intensive care and palliative care may seem to be at two opposite ends of the spectrum, it is necessary to amalgamate the postulates of palliative care in intensive care units to provide holistic care and best benefit patients admitted to intensive care units. This review aims to highlight the need for an alliance of palliative care with intensive care in the present era, the barriers to it, and models proposed for their integration and various ethical issues.

Key Words: Intensive care; Palliative care; Support; Barriers; Holistic care; End of life

Core Tip: Critical care and palliative care may seem to be mutually exclusive, but the amalgamation of the two provides the best combination of care to the patients needing intensive care. Palliative care has several beneficial roles in intensive care, such as symptom control, end-of-life discussions, and providing psychological support to patients' caregivers. However, there are several barriers to its implementation. These can be overcome by education and awareness improvement, capacity building, and developing a national-level framework policy for incorporating palliative care with intensive care.

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INTRODUCTION

The aim of admitting patients to the intensive care unit (ICU) is to maintain the homeostasis of the body and to reduce overall morbidity and mortality. Despite the technological advancement and critical care expertise available, the death rate in ICU is still as high as 18.1%[1]. When the organ functions deteriorate, goals of care are not fulfilled and life-sustaining treatment becomes a burden on both the patient and caregivers, then it is the responsibility of the physician to provide a dignified end to life, control the symptoms of the patient and provide psychological support to the family members. Also, it has been observed that patients who survive the ICU stay suffer from 'post-intensive care syndrome' in which they face anxiety, stress and depression for a long period even after discharge. The same syndrome has also been identified in caregivers[2]. The possible solution to this conundrum is palliative care. It is a multidimensional specialty which emphasizes patient and family-based care. It has been defined by International Association for Hospice & Palliative Care (IAHPC) in 2018 as "The active holistic care of individuals across all ages with serious health-related suffering due to severe illness, and especially of those near the end of life. It aims to improve the quality of life of patients and their caregivers"[3]. It states that dying is a natural process and the aim is neither to quicken the death nor delay the inevitable.

Although intensive care and palliative care may seem to be at two opposite ends of the spectrum, it is necessary to amalgamate the postulates of palliative care in ICU to provide holistic care and best benefit ICU patients. This review aims to highlight the need for a coalition of palliative care with intensive care.

MATERIALS AND METHODS

Literature search strategy

Search strategy and selection criteria were developed to identify relevant articles, and key questions were formulated to construct an analytic framework. Using PubMed, Embase, and Google Scholar and a systematic review method, a comprehensive literature search was conducted with the inclusion criteria related to the role of palliative care in intensive care management, specifically studies and reports on the present status, applications, benefits, roadblocks, various models to provide palliative care in critical care setup and ethical issues related to this topic. Studies published prior to 2012 were excluded. Keywords searched included "palliative care," "intensive care," "critical care," "intensive therapy unit," "intensive care unit", "integration", "application", "barriers", "models", "benefits", "ethical issues", "pain assessment" and "capacity building initiative". The various keywords were joined using Boolean operators "And" "Or" and "Not" in various combinations to obtain the relevant articles, which were then carefully screened for eligibility for inclusion in the review. The references of relevant articles were further hand searched. This information was extracted and organized in text and tabular form. The search mainly focused on identifying studies on palliative care in relation to critical care and was then narrowed to relevant literature.

Inclusion criteria

Studies that were included had to meet the following criteria: (1) Having a publication date of on or after 2012 and in the English language; (2) studies related to palliative care and intensive care; (3) all ages, genders and ethnicities; and (4) study designs being case-control studies, case studies, case reviews, guidelines, systematic reviews, and meta-analysis.

Exclusion criteria

Studies that were published prior to 2012; articles in languages other than English; literature that did not

have a full text available; and articles reporting on interventions without evidence of integration or insufficient information to support their approach, were excluded from the review.

Data analysis

This literature review is presented as a qualitative non-meta-analysis narrative review. The data extracted is established on the grounds of previously reviewed articles. The first step in extracting the data was to decide which type of study designs were to be included in this review. Then any publication prior to 2012 was excluded. The next step was to focus on extracting those articles that were related to and supported the core concept of this review while minimizing bias and maintaining the reliability and validity of the data.

DISCUSSION

Key components of palliative care in ICU

Identifying patients who are terminally ill. Inviting patients and caregivers in the decision-making process through effective communication. Inviting a primary physician in the combined decision-making process. Ensuring appropriate ICU admission which benefits the patient. Implementing effective symptom control and management. Providing psychological support to caregivers. Using a step-down approach from ICU to ward after family meeting[4]. Providing bereavement care.

Indications for palliative care in ICU

In case of an acute catastrophic event, patients need to be admitted to ICU for intensive monitoring and better symptom control; and for conducting end-of-life care discussions with the family[5].

Indications for palliative care referral in ICU

Indications for palliative care referral in ICU included: Age > 80 years, chronic critical illness with ICU stay > 14 d; patients with multiple comorbid conditions (e.g., advanced malignancy, chronic liver/kidney disease, *etc*.); advanced medical directive from the patient requesting for minimal interventions; and conditions where life-sustaining treatments are deemed medically futile by primary physicians[6-9]. These indications for the requirement of palliative care in ICU are present in 14%-20% of admitted patients[10]. Identification of triggering factors will lead to better and effective mobilization of ICU resources and help in identifying patients' unmet palliative care needs[11]. Also, according to the recently conducted 'Cross Country Comparison of Expert Assessments of the Quality of Death and Dying' which attempted to assess the standard of end-of-life care given by various countries - India ranked 59th out of 80 countries[12]. This highlights the fact that awareness in India regarding end-of-life care is poor especially due to the reluctance to discuss openly death. Dying in ICU is considered to be impersonal and invasive. A good death is a peaceful end occurring in the presence of loved ones[13]. Thus it is imperative to provide dignified death to a terminally sick patient based on the principle of right attitude, appropriate behavior, compassion and honest communication[14].

Barriers to providing palliative care in ICU

Barriers are at two levels: (1) The level of patient and caregivers. There is an inability to accept the poor outcome, and an inability to accept that there is an endpoint to life-sustaining treatment. There are differences in opinion among caregivers. In many cases, patients are not in a physical condition to make a decision for themselves; (2) the level of the physician[15,16]. There is a misconception that palliative care is only for patients who are actively dying, a concept that if palliative care is provided, it would accelerate the death of the patient, misunderstanding that palliative care is totally different from critical care, rather than being two aspects of the holistic treatment process, challenge to assess and screen the patients for whom palliative care referral should be administered, lack of knowledge and awareness at the level of patients and the physicians are the biggest hurdle. Also, there is a lack of training at the undergraduate level which leads to this lack of knowledge related to palliative care among physicians. There are a few factors at various levels which preclude the integration of palliative care in ICU[17].

Other barriers involve the followings. There is a lack of management resources, training and knowledge among the healthcare workers to provide palliative care in ICU. Also, there is a lack of uniform guidelines and policies.

There is an absence of appropriate infrastructure to facilitate the involvement of family members in providing palliative care. Also, healthcare workers have to face a lot of moral and emotional distress while providing palliative care in ICU.

In many cases, there is disagreement among the family members regarding providing palliative care. Also, patients are unable to participate in the decision-making process during terminal illness.

Lack of communication and interaction among the members of the multidisciplinary team impedes the integration of palliative care in the ICU.

Benefits of integrating palliative care in ICU

The benefits include increased patient and caregiver satisfaction; better patient assessment and symptomatic management; decreased length of ICU and hospital stay; decreased duration of ventilation; decreased anxiety and depression among family members.

Models to provide palliative care in critical care setup

There can be various models: (1) Integration model - Palliative care principles are understood and implemented by ICU physicians without involving any palliative care specialist. The emphasis is to improve the internal system and enhance the skills and knowledge of ICU physicians in providing appropriate palliative care where required. To enhance their knowledge and skills, critical care specialists can attend various programs, *e.g.*, End of Life Nursing Education Consortium (ELNEC)–Critical Care training program and Critical Care Communication skills program ("C-3"); (2) Consultation model - The ICU clinicians request Palliative consultations from Palliative care specialists. This model is superior as it improves overall outcomes. It caters to patients with a higher risk of poor outcomes rather than all the cases in the ICU. Initially, the consultations may be for a specific group of patients, but after the benefits are shown the number of referrals will increase for other patients in ICU as well. Sometimes psychologists, social workers and spiritual workers can also be involved to provide holistic care. This model has a disadvantage in that patients and relatives may feel that there are too many physicians involved and there is no single point of contact for them. Also, ICU clinicians may not develop the interest to enhance their skills pertaining to palliative care if they feel that they already have specialists available; and (3) Mixed model - The primary physician manages basic palliative care problems themselves and consultation with a palliative care specialist is required if they feel that they are unable to resolve the problem. The need for consultation from a palliative care specialist is identified by the factors, *e.g.*, pre-existing functional dependence, age > 80 years, advanced malignancy, multi-organ dysfunction, severe traumatic brain injury and extreme prematurity in pediatric patients. This model incorporates advantages from both the integrative and consultation model (Table 1)[18,19].

Ethical issues in providing palliative care in ICU

End-of-life care discussions: These discussions are always a challenge for both caregivers and physicians in ICU. The acceptance takes time and the cycle of discussion often begins with denial, where a 'cafeteria approach' should be followed. Caregivers must be explained the advantages and disadvantages of aggressive ICU treatment. Caregivers must always be given an assurance that comfort and symptom management of their patients will always be ensured in all circumstances. If the patient has given advanced directive regarding what they would want for themselves if they are critically ill, then it becomes easy for both the physician and caregivers as it reduces the burden on family members to take that difficult decision[20,21]. However, in many countries, the concept of an advanced directive is still in a nascent phase. In Europe, end-of-life care discussions are being carried out by intensive care physicians rather than palliative care specialists[22].

Assessment of the decision capacity of the patient and caregivers: It is important to assess the decision capacity of patients which may be difficult sometimes in the critically ill because of their poor general condition, age, and cognitive and hearing impairment. In such cases, the decision capacity of caregivers should be assessed. But in many cases, there are many family members involved. Thus, it becomes imperative to identify who are the family members available and who among them will take a concrete decision for their patient.

The decision to withhold or withdraw the treatment: This is a very sensitive decision and discussions should be done along with family members and the primary physician before coming to any conclusion. The futility of any further treatment should be established, the consensus among all the decision makers should be reached and the process should be documented before withholding or withdrawing further active treatment measures.

Pain assessment in ICU patients

Pain is the fifth vital sign and is often overlooked in the hospital setting. Pain assessment and management in critically ill patients in ICU is an integral component of providing holistic palliative care [23,24]. Assessment of pain becomes even more difficult in patients who are intubated and unable to communicate. Thus, we must know about various assessment scales.

Scales to assess pain in patients who can communicate: Visual analog scale: The patient marks their pain level on a 10 cm line; Numeric rating scale: patients rate their pain level, zero means no pain and 10 means the worst possible pain they are bearing; Verbal rating scale: Patients can choose a word like mild, moderate and severe which describes their pain level intensity[25].

Scales to assess pain in patients who cannot communicate: Behavioral Pain Scale (BPS): it computes the pain based upon facial expressions, compliance with the mechanical ventilator and upper limb movements. Critical Care Pain Observation Tool (CPOT): Apart from three parameters involved in behavioural pain score, muscle tension should also be considered[26].

Table 1 Steps to choose an appropriate model to provide palliative care in critical care setup

Assess the capacity of staff, availability of resources and level of skills and knowledge among the clinicians
Assess the understanding of ICU clinicians regarding the need for palliative care in ICU and their receptivity to the same
Assess the interest level of ICU clinicians to strengthen their knowledge and skills related to palliative care
Form a multidisciplinary committee including a critical care specialist, palliative care physician, hospital administrator, nursing staff, psychologist and a social worker to decide upon the best model for providing palliative care in the ICU of their institute.
Try to use the 'mixed model' for providing palliative care in ICU as it incorporates advantages of both the integration and consultation model

ICU: Intensive care unit.

Palliative sedation in ICU

Another key component of palliative care is to provide palliative sedation to relieve the patient from unbearable symptoms at the end of life. This is done most commonly with the help of sedatives like opioids and benzodiazepines. The drugs chosen should be easily available and must have good efficacy with minimal side effects. Before initiating palliative sedation, one must ensure that alternative methods to provide relief were not effective or led to major side effects. Palliative sedation should not be considered the same as euthanasia, as it only intends to relieve a patient's suffering and not hasten the process of death[27]. It is based upon the principle of informed consent and autonomy[28].

Capacity building initiative of developing palliative care in ICU

Adding MD and Ph.D. programs in palliative medicine: Palliative care should be included in the academic curricula of all medical colleges. Increasing public awareness and organizing camps with help of non-governmental organizations: Developing national level framework policy for developing palliative care in ICU. Initiating the workshops in which trainers are trained themselves first, which will help in developing local expertise. Teleconsultation should be utilized to gain knowledge from experts. Keyholders from different areas - like ICU care physicians, hospital administrators and palliative care physicians should come together and form a team to implement palliative care in the ICU. Leaders from ICU, palliative care consultation service and hospital administration: conducting a needs assessment and evaluating the resources. There should be a sufficient number of trained personnel. Educational resources such as libraries should be available for physicians to strengthen their knowledge related to palliative care. Legal documents should be there for surrogate decision-making. An alternate place to provide care to the patient should be decided on who no longer needs ICU care. Developing an action plan: According to the availability of resources, goals of care to address the unmet need should be established. Targets should be set that are easy and plausible. Changes that are required in the system should be identified to achieve the set target. The documentation process should be valid. Regular audits should be conducted to evaluate the changes and progress made[29,30].

CONCLUSION

The role of palliative care in critically ill patients admitted to ICU is important and the principles of palliative care should be integrated at the earliest. Integration of palliative care in the ICU improves the overall quality of life and decreases the hospital and ICU stay without affecting the overall mortality. Ensuring a dignified end to life is an art that every physician should learn. ICU doctors should be given palliative care training and they must consult palliative care specialists when required. Training and education starting from the undergraduate level is the way to ensure that all patients who are admitted to ICU along with their caregivers get access to palliative care services.

FOOTNOTES

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MINIREVIEWS

Current role of high dose vitamin C in sepsis management: A concise review

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Abstract

Sepsis and septic shock are common diagnoses for patients requiring intensive care unit admission and associated with high morbidity and mortality. In addition to aggressive fluid resuscitation and antibiotic therapy, several other drugs have been tried as adjuvant therapies to reduce the inflammatory response and improve outcomes. Vitamin C has been shown to have several biological actions, including anti-inflammatory and immunomodulatory effects, which may prove beneficial in sepsis management. Initial trials showed improved patient outcomes when high dose vitamin C was used in combination with thiamine and hydrocortisone. These results, along with relative safety of high-dose (supra-physiological) vitamin C, encouraged physicians across the globe to add vitamin C as an adjuvant therapy in the management of sepsis. However, subsequent large-scale randomised control trials could not replicate these results, leaving the world divided regarding the role of vitamin C in sepsis management. Here, we discuss the rationale, safety profile, and the current clinical evidence for the use of high-dose vitamin C in the management of sepsis and septic shock.

Key Words: Ascorbic acid; Critical care; Infection; Sepsis; Septic shock; Vitamin C

Core Tip: High-dose vitamin C is increasingly used in varied clinical conditions including sepsis and septic shock. Even though a few initial studies showed remarkable improvements in outcomes, later studies failed to replicate these effects. Through this article, we wish to review the rationale and current clinical evidence for use of vitamin C in the management of patients with sepsis and septic shock.

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INTRODUCTION

Vitamin C, or ascorbic acid, is a water-soluble vitamin that acts as an anti-oxidant and as a co-factor for multiple enzymes. For a long time, vitamin C deficiency has been associated with the occurrence of Scurvy disease. However, in recent years, vitamin C has been established to have different biochemical effects and has been increasingly used in varied clinical conditions that include severe acute pancreatitis, sepsis, and cancer[1-3]. Being a water-soluble vitamin, vitamin C is generally considered to be safe even at high dosages. Although no clear guidelines or recommendations exist for the administration of vitamin C, it is still being used to manage these diseases, even in critically-ill patients. Mortality associated with sepsis and septic shock remains high though the disease, its prognosis, and management procedures are well established earlier. Intravenous fluid resuscitation and hemodynamic support, early administration of appropriate antibiotics, source control, and organ support form the mainstay of therapy[4]. Over the years, various therapeutic methods that include activated protein C, ulinastatin, and vitamin C have been tested as adjuvant therapies to improve the outcomes[2,5,6]. However, these therapies failed to achieve any significant and meaningful outcome and their role in sepsis management remains ambiguous[4]. In this background, the aim of the current review is to discuss the scientific rationale behind the usage of high-dose vitamin C (HDVC) in patients with sepsis and septic shock and evaluate its clinical evidence.

RATIONALE

In general, normal serum contains more than 50 μmol/L vitamin C[7]. However, acutely-ill patients exhibit a rapid reduction in their vitamin C levels, while critically-ill patients, especially those with sepsis, show extremely low vitamin C levels (below 11 μmol/L), in spite of the recommended enteral and parenteral nutritional intakes[8]. Moreover, commonly-employed organ-support intensive care unit (ICU) interventions like continuous renal replacement therapy (CRRT) also reduce the levels of water-soluble vitamins like vitamin C[9].

Vitamin C exhibits several biochemical effects that may potentially benefit the management of patients with sepsis and septic shock (Table 1)[10,11]. Sepsis results in the release of several reactive oxygen species (ROS) which are capable of causing severe injury to lipids, proteins, and nucleic acid that in turn results in endothelial and mitochondrial dysfunction, cell death, and ultimately multiple organ dysfunction syndrome (MODS). Vitamin C exerts its anti-oxidant effects by scavenging these ROS. Further, it also helps in recycling other anti-oxidants like vitamin E and tetrahydrobioptrin (BH4). Thus, it plays a major role in preventing oxidative damage and cell death[12,13].

Sepsis tends to reduce the functions of adenosine triphosphate (ATP) and causes bioenergetic failure of mitochondria, secondary to oxidative damage caused by mitochondrial ROS and alterations in fatty acid metabolism[14]. Vitamin C exhibits anti-oxidant effect and prevents the oxidative damage, and it also helps in carnitine production that improves fatty acid metabolism in mitochondria[15]. These actions may be helpful in the prevention of cell death, leading to septic cardiomyopathy and MODS.

Sepsis causes microvascular dysfunction which reduces the arteriolar reactivity to vasoconstrictors. This phenomenon results in vasodilation and shock. Vitamin C acts as a co-factor for the enzymes that are required for the synthesis of catecholamines and vasopressors. Thus, it enhances the synthesis of these enzymes and improves arteriolar sensitivity to vasopressors by inhibiting endothelial expression of inducible nitric oxide synthase (iNOS). In addition, vitamin C also has several immuno-modulatory and anti-inflammatory effects that help in abating cytokine storm associated with sepsis-induced MODS [10,11,16].

Table 1 Biological effects of vitamin C

Biological effects of vitamin C	Mechanisms of action
Antioxidant properties	Reduced production of reactive oxygen species; Reduced production of endothelial nitric oxide
Prevention of mitochondrial dysfunction	Reduction of oxidation injury; Reduces apoptosis
Prevention of septic cardiomyopathy	Reduction of oxidation injury; Increased carnitine synthesis; Reduces apoptosis
Prevention of micro and macro vascular dysfunction	Acts as a co-factor for synthesis of catecholamines (epinephrine, norepinephrine) and vasopressin; Inhibition of iNOS expression
Anti-inflammatory effects	Supresses activation of nuclear factor kappa-B (NF-κB); Inhibits tumor necrosis factor-α; Reduces pro-inflammatory cytokines like high mobility group box-1; Lowers histamine levels
Immune enhancing effects	T-cell maturation and modulation; Improves neutrophil chemotaxis and phagocytosis; Enhances oxidative killing; Promotes proliferation of lymphocytes; Stimulates interferon production; Increased antibody production

CLINICAL STUDIES

Several randomised controlled trials (RCTs) have been conducted in recent years to explore the plausibility of clinical benefits, achieved from the antioxidative effect of vitamin C, in reducing sepsis-induced tissue injury (Table 2). The authors conducted a systematic search using keywords such as 'Vitamin C' OR 'Ascorbic acid' AND Sepsis OR "Septic Shock" in PubMed and Google Scholar and found a total of 17 RCTs suitable for the current analysis. Out of the 17, five were about the application of vitamin C alone in patients with sepsis[17-21]. The current study followed a heterogeneous design with different doses of vitamin C monotherapy *vs* combination therapy with thiamine and hydrocortisone and the timing of administration.

Isolated vitamin C therapy

Out of the RCTs considered, five compared vitamin C with placebo in patients with sepsis. Different doses were used in the studies under consideration[17-21]. All the studies, except one, failed to infer any clinically meaningful difference with the usage of vitamin C[18]. The CITRIS-ALI trial compared vitamin C (at a dose of 50 mg/kg q6h) with a placebo in patients with sepsis and acute respiratory distress syndrome. No significant difference was found in the mean change of sequential organ failure assessment (SOFA) scores between the groups considered, from baseline to 96 h. The changes in C-reactive protein (CRP) and thrombomodulin levels, at 168 h, were also statistically non-significant. In terms of subgroup analysis, the 28-d mortality rate (without adjustment for multiple comparisons) was found to be significantly lower in the vitamin C group (29.8% *vs* 46.3%; $P = 0.03$)[17].

The largest and the most recently published LOVIT study was a phase III, multicentre RCT that involved 35 medical-surgical ICUs which spanned across Canada, France, and New Zealand. The study included patients with suspected or proven infection and those who were on vasopressor support. Vitamin C was intravenously administered once for 6 h, at a dosage of 50 mg/kg, up to 96 h to 429 patients in the intervention group. On the other hand, a placebo was administered to 434 patients who belonged to the control group. The administration of thiamine and glucocorticoids was left to the clinical discretion of the treating physician. The primary outcome, *i.e.*, a composite of death or persistent organ dysfunction at 28 d, was significantly higher in the intervention (vitamin C) group *vs* the control group [44.5% *vs* 38.5%; risk ratio: 1.21; 95% confidence interval (CI): 1.04-1.40; $P = 0.01$]. However, no significant difference was found in the individual components of composite primary outcome: Mortality or persistent organ dysfunction, organ dysfunction-free days at 28 d, SOFA scores at pre-defined time intervals from days 1-8, 6-mo survival, and health-related quality of life. The study outcomes not only inferred the lack of benefit but also provided insights on possible harm caused by high dosage administration of vitamin C in patients with sepsis and septic shock[20].

Vitamin C as a part of combination therapy

Marik *et al*[22] conducted a single-centre retrospective study involving 47 patients. This study compared cocktail therapy that included hydrocortisone, ascorbic acid, and thiamine (HAT) with a control group (standard care) among patients with severe sepsis and septic shock. The authors recorded a low hospital mortality rate in the treatment group (8.5% *vs* 40.4%, $P < 0.001$). The dosage regimen was as follows: Vitamin C at 1.5 g/h q6h, hydrocortisone at 50 mg q6h, and thiamine at 200 mg/12 h. Moreover, the mean duration of the vasopressors, used for shock, was also significantly shorter in the intervention arm (18.3 h *vs* 54.9 h, $P = 0.001$)[22]. This observational study started a debate on the suggested possible benefits of cocktail therapy among patients with septic shock. Subsequently, multiple RCTs were conducted to validate the findings of this study.

Table 2 Randomized Trials of vitamin C in sepsis

No.	Title	Ref.	Acronym	Country of origin	Study design	Sample size in control arm	Sample size in intervention arm	Intervention summary	Results in brief
Studies using isolated vitamin C									
1	Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit	Lamontagne *et al*[20], 2022	**LOVIT Trial**	Canada	RCT	437	435	Intravenous vitamin C (at a dose of 50 mg/kg body weight) 6 hourly for 96 h	This trial reported significantly higher composite primary outcome (risk of mortality OR persistent organ dysfunction at 28 d) in vitamin C group. One patient had a severe hypoglycemic episode and another had a serious anaphylaxis event.
2	Intravenous vitamin C administration to patients with septic shock: a pilot randomised controlled trial	Rosengrave *et al*[19], 2022		New Zealand	RCT	20	20	Intravenous vitamin C (at a dose of 25 mg/kg of body weight every 6 h) for up to 96 h, or until death or discharge	Treatment with intravenous vitamin C did not result in reduction of mean dose and duration of vasopressor infusion. Both the groups were comparable for rise in inflammatory markers, length of ICU stay, length of hospital stay, and mortality.
3	Early use of high-dose vitamin C is beneficial in treatment of sepsis	Lv *et al*[18], 2020		China	RCT	56	61	Intravenous vitamin C 3.0 g in 5% dextrose (100 ml/time, 2 times/d)	Treatment with vitamin C resulted in a significant reduction in the 28-d mortality. There was a significant reduction in SOFA score at 72 h and duration of vasopressor use, also there was increased clearance of procalcitonin.
4	Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial	Fowler *et al* [17], 2019	**CITRIS-ALI RCT**	United States	RCT	83	84	Intravenous infusion of vitamin C (50 mg/kg in dextrose 5% in water, n = 84) every 6 h for 96 h	There was no significant difference in SOFA score at 96 h, and levels of marker of inflammation (CRP) and vascular injury (thrombomodulin) at 168 h.
5	Effect of vitamin C administration on neutrophil apoptosis in septic patients after abdominal surgery	Ferrón-Celma *et al*[21], 2008		Spain	PD interventions RCT study	10	10	The vitamin C group received 450 mg/d of the vitamin in 3 doses	Vitamin C treatment in postoperative septic abdominal surgery patients have an antiapoptotic effect on peripheral blood neutrophils, reducing caspase-3 and PARP levels, and increasing BCL-2 levels. However this effect is not maintained all the time.
Studies using vitamin C in combination therapy									
6	Effect of Supplementation of Vitamin C and Thiamine on the Outcome in Sepsis: South East Asian Region	Ap *et al*[27], 2022		India	RCT	20	20 + 20 + 20	Intervention group received vitamin C, thiamine, both, and neither, respectively. Vitamin C (2 g 8 hourly) and thiamine (200 mg 12 hourly) were given intravenously for 5 d	Intervention with vitamin C and thiamine did not reduce mortality. The vitamin C level and thiamine level were significantly lower than those in healthy controls.
7	Biomarker Analysis for Combination Therapy of Vitamin C and Thiamine	Park *et al*[34], 2022	**Post hoc ATESS**	South Korea	RCT (post hoc analysis)	52	45	Intravenous vitamin C (50 mg/kg, maximum single dose 3 g) and thiamine	Baseline biomarker levels (IL-6, IL-10, AP2, and S100β) at 72 h were not significantly different

	in Septic Shock: A Post-Hoc Study of the ATESS Trial							(200 mg) administration every 12 h for a total of 48 h	between the treatment and the placebo groups, also the rate of reduction was not significantly different between the two groups.
8	Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis: The VICTAS Randomized Clinical Trial	Sevransky JE *et al*[25], 2021	**VICTAS Trial**	United States	RCT	252	249	Vitamin C (1.5 G), thiamine (100 mg), and hydrocortisone (50 mg) every 6 h	In patients with sepsis and septic shock, treatment with combination therapy did not reduce ventilator days and vasopressor use. Mortality at 30 d was also comparable between the groups.
9	Vitamin C Therapy for Routine Care in Septic Shock (ViCTOR) Trial: Effect of Intravenous Vitamin C, Thiamine, and Hydrocortisone Administration on Inpatient Mortality among Patients with Septic Shock	Mohamed *et al*[33], 2020	**ViCTOR Trial**	India	RCT	43	45	Intravenous combination of vitamin C (1.5 g every 6 h), thiamine (200 mg every 12 h), and hydrocortisone (50 mg every 6 h) within 6 h of onset of septic shock admission	This trial found no difference in all-cause mortality in the two groups. The data reported earlier reversal of septic shock but no difference in improvement of SOFA score at 72 h, use of vasoactive substances, or use of mechanical ventilation.
10	Combined Treatment with Hydrocortisone, Vitamin C, and Thiamine for Sepsis and Septic Shock: A Randomized Controlled Trial	Chang *et al*[32], 2020	**HYVCTTSSS**	China	RCT	40	40	Combination therapy with hydrocortisone (50 mg every 6 h for 7 d), vitamin C (1.5 g every 6 h for 4 d), and thiamine (200 mg every 12 h for 4 d)	Combination therapy did not reduce 28 d all-cause mortality in sepsis and septic shock patients. However, it was associated with 72-h change in Sequential Organ Failure Assessment score improvement. The treatment group exhibited more incidents of hypernatremia.
11	Usefulness of Antioxidants as Adjuvant Therapy for Septic Shock: A Randomized Clinical Trial	Aisa-Alvarez *et al*[28], 2020		Mexico	RCT	18	18 + 18 + 18 + 18	Enterally administered tablets of NAC 600 mg every 12 hourly. Further, 50 mg of MT in capsules of 5 mg were given to patients once a day, and 1 mg vitamin C tablets were administered every 6 h. Vitamin E capsules of 400 units were given every 8 h for 5 d	Antioxidant therapy helps to regulate inflammation in septic patients with shock. Vitamin C therapy in pulmonary sepsis increases vitamin C serum levels and decreases levels of inflammatory marker like CRP, PCT, and NO^{3-}/NO^{2-}.
12	Effect of Ascorbic Acid, Corticosteroids, and Thiamine on Organ Injury in Septic Shock: The ACTS Randomized Clinical Trial	Moskowitz *et al*[24], 2020	**ACTS RCT**	United States	RCT	102	103	Parenteral vitamin C (1500 mg), hydrocortisone (50 mg), and thiamine (100 mg) every 6 h for 4 d	Combination therapy with ascorbic acid, corticosteroids, and thiamine did not lead to a significant reduction of SOFA score in septic shock patients during the first 72 h after enrolment. Data from this trial do not support routine use of combination therapy in septic shock.
13	Combination therapy of vitamin C and thiamine for septic shock: a multicentre, double-blinded randomized, controlled study	Hwang *et al*[26], 2020	**ATESS Trial**	South Korea	RCT	58	53	Vitamin C (50 mg/kg, maximum single dose 3 g) and thiamine (200 mg) administration every 12 h for a total of 48 h intravenously	Vitamin C therapy and thiamine administration did not improve organ function and need for organ support despite improvement in levels of these vitamins in early phase of septic shock.
14	Outcomes of Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in the Early Treatment of Sepsis: The ORANGES Trial	Iglesias *et al*[29], 2020	**ORANGES trial**	United States	RCT	69	68	Ascorbic acid 1500 mg q6h, thiamine 200 mg every 12 h, and hydrocortisone 50 mg q6h for a maximum of 4 d	Combination therapy resulted in quicker reversal of shock; however, no difference was found in reversal of organ dysfunction or other secondary outcomes.
15	Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients	Fujii *et al*[23], 2020	**VITMAINS RCT**	Japan	RCT	107	109	Intravenous vitamin C (1.5 g every 6 h), hydrocortisone (50 mg every 6 h), and thiamine (200 mg every 12 h), given in intervention group and intravenous	Findings from this trial suggest that combination therapy does not lead to rapid resolution of septic shock in comparison to hydrocortisone alone with no significant improvement in overall mortality

	With Septic Shock: The VITAMINS Randomized Clinical Trial						hydrocortisone (50 mg every 6 h) alone in comparison group until shock resolution or up to 10 d	with intervention. No serious adverse events were reported.
16	Combination of vitamin C, thiamine and hydrocortisone added to standard treatment in the management of sepsis: results from an open label randomised controlled clinical trial and a review of the literature	Wani *et al* [30], 2020	India	RCT	50	50	Combination of vitamin C (1.5 g q6h for 4 d), thiamine (200 mg q12h for 4 d), and hydrocortisone (50 mg q6h for 7 d/ICU discharge, taper over 3 d)	Combination therapy does not improve in hospital mortality and mortality at 30 d. However, lactate clearance was faster and vasopressor use was lower in intervention group.
17	The effects of intravenous antioxidants in patients with septic shock	Galley HF *al* [31], 1997	United Kindom	RCT	14	16	Antioxidants (n-acetylcysteine 150 mg/kg for 30 min then 20 mg/kg/h plus bolus doses of 1 g ascorbic acid and 400 mg α-tocopherol)	Basal vitamin C was low and redox-reactive iron was elevated in all patients. Levels of vitamin C were increased but overall antioxidant capacity was unaffected after supplementation. Heart rate cardiac index increased and systemic vascular resistance index decreased in patients treated with antioxidants.

AP2: Angiopoietin-2; CRP: C-reactive Protein; DOI: Digital object identifier; ICU: Intensive care unit; IL-10: Interleukin-10; IL-6: Interleukin-6; MT: Melatonin; NAC: N-acetyl cysteine; NO2: Nitrite; NO3: Nitrate; PARP: Poly (ADP-ribose) polymerase; PCT: Procalcitonin; PMID: PubMed unique identifier; S100β: S100 calcium-binding protein B; SOFA: Sequential organ failure assessment score.

The VITAMINS trial, a multicentric RCT involving 211 patients, evaluated the effectiveness of a combination of vitamin C (1.5 g q6h), thiamine (200 mg q12h), and hydrocortisone (50 mg q6h) in patients suffering from septic shock. To conduct primary analysis, 107 patients were recruited for the intervention arm and 104 patients under the control arm. The eligibility criteria for this study were as follows: A primary diagnosis of septic shock with an acute increase in SOFA score by two points or more, a lactate level > 2 mmol/L, and the requirement for vasopressor support for at least 2 h, prior to enrolment. The study found no significant difference between the groups in terms of primary outcome, duration of time alive, and vasopressor-free days until day 7 [122.1 (76.3–145.4 h) *vs* 124.6 (82.1–147.0 h), $P = 0.83$)]. Among the secondary outcomes too, no significant difference was found in 28 d, 90 d, ICU-, or hospital-mortality between the groups. Further, the two groups also exhibited similar secondary outcomes like vasopressor-free days, mechanical ventilation-free days, and renal replacement-free days. While SOFA scores got reduced by day 3 in both the groups, the decline was marginally higher in the intervention group. In this study, two patients had adverse events (fluid overload and hyperglycemia, one each) in the intervention group[23].

A multicentre RCT (ACTS trial) was conducted among 205 septic shock patients randomised into either a placebo ($n = 102$) or an intervention arm ($n = 103$) with intravenous vitamin C (1500 mg q6h), hydrocortisone (50 mg q6h), and thiamine (100 mg q6h) for 4 d. No significant change was observed in SOFA score (difference between baseline and SOFA score at 72 h) between intervention *vs* placebo (-0.8; 95%CI: -1.7 to 0.2; $P = 0.12$). Further, no significant difference was found in the secondary outcomes too, such as incidence of acute kidney injury (AKI) and ventilator-free days. Shock-free days were found to be higher in the intervention group (median difference of 1 d; 95%CI: 0.2-1.8 d; $P < 0.01$)[24].

In another multicentric RCT (VICTAS trial) conducted among patients with sepsis and septic shock ($n = 252$), a cocktail of vitamin C (1.5 g q6h), thiamine (100 mg q6h), and hydrocortisone (50 mg q6h) was used, commencing within 4 h of randomization for 4 d. On the other hand, a matching placebo was

administered in the control group (n = 249). The trial was prematurely terminated due to the lack of funding though the actual plan was to recruit 2000 patients. No significant difference was found in terms of primary outcomes such as ventilator- and vasopressor-free days for the first 30 d [25 d (0-29 d) *vs* 26 d (0-28 d), P = 0.85]. Further, no significant difference was found between 30-d mortality between the groups (22% *vs* 24%). In addition to these, no serious adverse events were reported during the study. This study, although terminated early, did not reveal any difference with vitamin C cocktail in patients with sepsis, including respiratory or cardiovascular dysfunction[25].

Similar findings were reported in another multi-center RCT (ATESS trial) conducted in South Korea. Patients with septic shock in emergency department were randomized to receive either vitamin C (50 mg/kg) and thiamine (200 mg q6h for 48 h) in the intervention arm (n = 53) or placebo (n = 58) in the control group. Hydrocortisone (200 mg/d) and intravenous vasopressin infusion were administered in both the arms of patients who required high dosage norepinephrine. No statistically significant difference was found in the primary outcome whereas the SOFA score (difference between the baseline and 72-h score) significantly changed between the intervention and placebo groups [3, (- 1 to 5) *vs* 3, (0–4), P = 0.96]. Further, there was no significant difference between the intervention arm and placebo in baseline vitamin C or thiamine levels. After the treatment, vitamin C and thiamine levels were found to have increased in the intervention group. However, there was no significant difference observed in any of the secondary outcomes, including mortality at day 7, 28, or 90, shock reversal, ventilator-free days, incidence of AKI, and reduction of CRP or procalcitonin[26].

Several non-randomized trials have also been conducted earlier to evaluate the role of vitamin C, either as a single entity or as a part of combination therapy, in the management of sepsis (Table 3).

Meta-analysis of vitamin C in sepsis

Various systematic reviews and meta-analyses have been published on vitamin C in sepsis, with conflicting results on the short-term mortality (Table 4). However, no effect was found in the trials with long-term mortality. A recent metanalysis by Agarwal *et al*[44], with 41 RCTs and 4915 patients (including recently published LOVIT trial), explored the effect of intravenous vitamin C as monotherapy or combination therapy among hospitalized patients with severe infection. With low-certainty evidence, there was a trend towards reduced in-hospital mortality [21 RCTs, 2762 patients, risk ratio (RR) = 0.88 (95%CI, 0.73-1.06)], 30-d mortality [24 RCTs, 3436 patients, RR = 0.83 (0.71-0.98)], and early mortality [34 RCTs, 4366 patients, RR = 0.80 (0.68-0.93)] with vitamin C. However, on sensitivity analysis involving published trials which were blinded and with a low risk of bias, the impact of vitamin C was attenuated with no statistical significance. The RR of hospital mortality (6 RCTs, 1371 patients) was 1.07 (0.92-1.24), with moderate certainty evidence; that of 30-day mortality (9 RCTs, 2057 patients) was 0.88 (0.71-1.10), with low certainty evidence; and that of early mortality (11 RCTs, 2214 patients) was 0.88 (0.73-1.06), with low certainty evidence. With moderate certainty evidence, increased 90-d mortality was suggested in five RCTs, including 1722 patients (RR = 1.07, 0.94-1.21). The reason for heterogeneity was that few trials with large treatment effects were either single centre, or had small sample size. The RR of early mortality in trials reporting 90-d mortality was 1.05 (0.91-1.21). Among the adverse events, there were no major adverse events, except an increased risk of hypoglycemia (1 RCT, 862 patients, RR = 1.20 [0.69-2.08]), with moderate certainty of evidence. The result of other secondary outcomes was mixed with reduction of duration and use of mechanical ventilation and increased risk of AKI or need of RRT, based on low-certainty evidence. No credible subgroup effects were observed related to cointerventions (monotherapy *vs* combined therapy), dose of vitamin C, or the type of infection (SARS-CoV-2 *vs* others) [44].

DOSING

Different authors have tried several different dosing regimens. Higher doses of intravenous vitamin C are also being prescribed regularly, with doses up to 100 g/d used to manage patients with sepsis[50]. Even "high-dose" is not clearly defined and is arbitrarily considered a dose of more than 2-10 g/d in adults, by different authors[57,58].

The current literature suggests using six-hourly dosage for vitamin C in order to alleviate the deficiency, achieve steady plasma levels rapidly, and maintain normal serum levels. This dosing schedule may also be able to rapidly normalize the neutrophil ascorbic acid levels[36,39]. Even though intravenous formulations are generally preferred in critically ill patients, especially those in shock, and may rapidly increase the serum vitamin C levels, no difference in clinical efficacy has been reported between intravenous and oral formulations of vitamin C[59,60].

ADVERSE EFFECTS

As a water-soluble vitamin, vitamin C is generally considered safe, even when used at high doses. Most

Table 3 Non randomized studies of vitamin C in sepsis

No.	Title	Ref.	Country of origin	Study design	Sample size in control arm	Sample size in intervention arm	Intervention summary	Results in brief
Studies using isolated vitamin C								
1	High dose intravenous vitamin C treatment in Sepsis: associations with acute kidney injury and mortality	McCune *et al*[35], 2021	United States	Cohort study (retrospective cohort)	1178	212	Cohort of patients who have received at least one dose of 1.5 g IV vitamin C	Vitamin C therapy was associated with significant chances of AKI and death.
2	Effect of high-dose intravenous vitamin C on point-of-care blood glucose level in septic patients: a retrospective, single-center, observational case series	He *et al* [38], 2020	China	Observational case series		82	Patients with septic shock on admission received 100 mg/kg/d, while other patients received < 100 mg/kg/d	High-dose vitamin C therapy may interfere with point-of-care glucose testing results.
3	Pharmacokinetic data support 6-hourly dosing of intravenous vitamin C to critically ill patients with septic shock	Hudson EP *et al* [36], 2019	Australia	Observational PK study		11	Patients received 1.5 g intravenous vitamin C every 6 h	Injectable vitamin C 1.5 g every 6 h helps in correction of vitamin C deficiency and hypovit-aminosis C, and it also provides appropriate dosing schedule for vitamin C supplementation in septic shock.
4	Accuracy of Point-of-Care Blood Glucose Level Measurements in Critically Ill Patients with Sepsis Receiving High-Dose Intravenous Vitamin C	Smith *et al* [37], 2018	United States	Observational PK study		5	Patients who have received vitamin C 1500 mg intravenously two or more doses and had point of care blood glucose checked and laboratory venous BG levels measured within 1 h of each other during vitamin C therapy	The accuracy and agreement of POC BG did not have significant interreference during vitamin C treatment in sepsis.
5	Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis	Fowler *et al*[39], 2014	United States	Phase I safety trial		24 total in 1:1:1 ratio	Patients with severe sepsis in the medical intensive care unit were randomized 1:1:1 to receive intravenous infusions every 6 h for 4 d of ascorbic acid: Lo-AscA (50 mg/kg/24 h, *n* = 8), or Hi-AscA (200 mg/kg/24 h, *n* = 8), or placebo (5% dextrose/water, *n* = 8)	Intravenous vitamin C infusion is safe and tolerated well and may have a positive impact on endothelial injury, the extent of multiple organ failure, and levels of inflammatory biomarkers.
Studies using combination therapies including vitamin C								
6	Adding vitamin C to hydrocortisone lacks benefit in septic shock: a historical cohort study	Chang *et al* [40], 2020	Canada	Cohort study (retrospective cohort)	88	52	Retrospective cohorts of vitamin C with hydrocortisone and hydrocortisone therapies for 72 h were compared in patients with sepsis or septic shock	Outcomes for hospital mortality, ICU mortality, ventilator free days, vasopressor free days, dialysis use, and duration of ICU admission were comparable between the groups.
7	Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study	Marik *et al* [22], 2017	United States	Cohort study (before and after study)	47	47	Intravenous vitamin C (1.5 g q6h for 4 d or until ICU discharge), hydrocortisone (50 mg q6h for 7 d or until ICU discharge followed by a taper over 3 d) as well as intravenous thiamine (200 mg q12h for 4 d or until ICU discharge)	Results of this study suggest that the early use of intravenous vitamin C, together with corticosteroids and thiamine, prevents progressive organ dysfunction, including acute kidney injury, and reduces the mortality of patients with severe sepsis and septic shock.
Other studies								

9	Plasma Cortisol, Aldosterone, and Ascorbic Acid Concentrations in Patients with Septic Shock Do Not Predict Treatment Effect of Hydrocortisone on Mortality. A Nested Cohort Study	Cohen *et al* [42], 2020	Australia and NZ	Cohort Study (nested cohort study)			Levels of total and free plasma cortisol and aldosterone were measured along with quantitatively measured vitamin C levels	In patients with septic shock, plasma aldosterone and ascorbic acid concentrations are not associated with outcome.
10	Vitamin C levels amongst initial survivors of out of hospital cardiac arrest	Gardner *et al*[43], 2020	United States	Observational study	34	25 post arrest, 25 post sepsis	Observational	Vitamin C levels are lower in cardiac arrest patients in comparison to healthy patients.
11	Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes	Carr *et al* [8], 2017	New Zealand	Observational study	20	24	Patients with septic shock and non-septic aetiology	Critically sick patients have low levels of vitamin C, and septic shock patients have significantly depleted levels.
12	Colistin-associated Acute Kidney Injury in Severely Ill Patients: A Step Toward a Better Renal Care? A Prospective Cohort Study	Dalfino *et al*[41], 2015	Italy	Cohort (prospective cohort)	39 non AKI	31 AKI	Intervention cohort patients have received colistin at a median daily dose of 9 million IU	Independent renal-protective role emerged for ascorbic acid among other factors responsible for higher chances of AKI.

AKI: Acute kidney injury; Hi-AscA: High dose ascorbic acid; ICU: Intensive care unit; Lo-AscA: Low dose ascorbic acid; POC BG: Point of care blood glucose.

of the large trials evaluating the efficacy of vitamin C have not assessed adverse effects as a primary objective. Hence, the data regarding adverse events has largely come from case reports, case series, and meta-summary of case reports[61]. Most commonly reported side effects are mild and include interference with laboratory tests, lethargy, fatigue, phlebitis, glycemic disturbances (hypo- or hyperglycemia), hypernatremia, muscle cramps, nausea, vomiting, headache, altered mental status, syncope, methemoglobinemia, oxalosis, and renal stones. However, rarely patients may develop life-threatening complications like haemolysis, AKI, and disseminated intravascular coagulation[62,63]. The probability of developing complications is reported to be higher in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and in those with underlying renal dysfunction[61]. Even though vitamin C has anti-oxidant properties, when used at higher doses, it may deplete the intra-erythrocyte glutathione stores and cause oxidative stress. Patients with G6PD deficiency are unable to replenish these glutathione stores and develop haemolysis secondary to oxidative damage[64,65].

DISCUSSION

Despite a pathophysiological rationale, the current clinical evidence does not support the use of vitamin C in sepsis. Indeed, there was a trend towards harm observed in the LOVIT trial. However, the primary outcome was composite, and its components did not reach statistical significance. The harm was not seen in other RCTs. In the LOVIT trial, the intervention arm had more patients in shock and on invasive mechanical ventilation at the baseline compared to the control arm. This imbalance in baseline characteristics between the groups may explain the higher incidence of organ dysfunction. Furthermore, despite excluding patients staying > 24 h in ICU, the time gap between the actual onset of sepsis and administration of vitamin C is unclear[20].

Table 4 Meta-analyses of trials on vitamin C in sepsis

No.	Title	Ref.	Country of origin	Study design	Included studies	Included sample size	Intervention summary	Results in brief
Studies with isolated vitamin C therapy								
1	IV Vitamin C in Critically Ill Patients: A Systematic Review and Meta-Analysis	Patel *et al* [45], 2022	United States	Meta-analysis	15 RCTs	2490 participants	Compared intravenous vitamin C at high and low doses with placebo among pooled study participants	Intravenous vitamin C therapy is associated with a trend toward reduced overall mortality. Data further reveals that High-dose IV vitamin C was associated with a significant reduction in overall mortality. None of the included trials reported an increase in adverse events related to IV vitamin C therapy.
2	Efficacy of intravenous vitamin C intervention for septic patients: A systematic review and meta-analysis based on randomized controlled trials	Li *et al*[47], 2021	China	Meta-analysis of RCTs	10 RCTs	1400 patients	Studies that have intravenous vitamin C supplementation were included	Data from this meta-analysis reports improved SOFA score within 72 h but no significant improvement in short term (28-30 d) mortality, long term mortality (90 d), hospital stay, ventilator-free days, ICU-stay in sepsis or septic shock patients.
3	Effect of vitamin C in critically ill patients with sepsis and septic shock: A meta-analysis	Feng *et al* [48], 2021	China	Meta-analysis of RCTs	9 RCTs	584 patients	Studies with vitamin C treatment in critically sick sepsis and septic shock patients were included	Data from this study finds significant differences in 28-d mortality and dose of vasopressors. However, the ICU length of stay was the same between the two groups.
4	Efficacy of vitamin C in patients with sepsis: An updated meta-analysis	Wei *et al* [46], 2020	China	Meta-analysis	6 RCTs and 6 observational studies	1176 in control group	This analysis included data from RCTs and observational studies that evaluated the effect of vitamin C in patients with sepsis	This study reports no significant improvement in 28-d or in-hospital mortality. There was also no difference in vasopressor duration and ICU or hospital stay.
Vitamin C as a combination therapy								
5	Thiamine, Ascorbic Acid, and Hydrocortisone As a Metabolic Resuscitation Cocktail in Sepsis: A Meta-Analysis of Randomized Controlled Trials With Trial Sequential Analysis	Assouline B *et al*[49], 2021	Switzerland	Meta-analysis	8 RCTs	1335 patients	Combination of thiamine, ascorbic acid, and hydrocortisone compared to in patients with sepsis or septic shock	Data in this study was homogenous and intervention led to improved change in SOFA score at 72 h; however, there was no difference in ICU mortality and renal composite outcome (incidence of AKI 3 or need for Renal replacement therapy).
6	The Efficacy of vitamin C, thiamine, and corticosteroid therapy in adult sepsis patients: a systematic review and meta-analysis	Somagutta *et al*[50], 2021	United States	Meta-analysis	15 studies (8 RCTs and 7 cohort studies)	67349 patients	Combination of HAT treatment in patients with sepsis	Meta-analysis from RCTs concluded that hospital mortality, ICU stay, hospital stay, and renal replacement therapy was not significant. Results from cohort studies have also concluded that hospital mortality, ICU mortality, ICU length of stay, length of hospital stay, change in SOFA score, the use of renal replacement therapy, or vasopressor duration was not significant.
7	Vitamin C, Thiamine, and Hydrocortisone in the Treatment of Sepsis: A Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials	Zayed *et al* [51], 2021	United States	Meta-analysis	6 RCTs	839 patients	Vitamin C, thiamine, and steroid in combination for sepsis and septic shock	Data from this study concluded that there is no significant difference in long term mortality, ICU mortality, incidence of acute kidney injury, hospital length of stay, ICU length of stay, and ICU free days on day 28 between the intervention and control groups. However, there was a significant reduction in SOFA score on 3rd day.

8	Mortality in septic patients treated with vitamin C: a systematic meta-analysis	Scholz *et al* [52], 2021	Germany	Meta-analysis	17 studies (randomized and non-randomized, blinded and unblinded, prospective and retrospective, and single- and multi-centre studies)	3133 patients	Vitamin C 1.5 g every 6 h, 100 mg thiamine every 6 h, and 50 mg hydrocortisone every 6 h. However, initiation and duration of the intervention differed considerably within the studies	Pooled analysis in this study indicated no mortality benefit; however, a subgroup analyses revealed an improved survival, if vitamin C treatment was applied for 3-4 d.
9	Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer-term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis	Fujii *et al* [53], 2021	Japan	Meta-analysis (network meta-analysis)	43 RCTs	10257 patients	Compared networked interventions of very high dose vitamin C, high dose vitamin C, vitamin C, vitamin B1, and glucocorticoids	This study found that metabolic resuscitation with vitamin C, glucocorticoids, vitamin B1, or combinations of these drugs have no difference in long term mortality. Also they did not find effect of vitamin C or B1 on organ dysfunction or ICU length of stay. However, adding glucocorticoid to the combination therapies reduces the duration of vasopressor therapy and ICU stay.
10	Steroid, ascorbic acid, and thiamine in adults with sepsis and septic shock: a systematic review and component network meta-analysis	Fong *et al* [54], 2021	Hong Kong	Meta-analysis (component network meta-analysis)	33 RCTs	9898 patients	Additive network meta -analysis was performed, adding vitamin C, glucose corticoid, and thiamine sequentially	Data from this study reveals that combination of glucocorticoid and fludrocortisone improved short-term and longer-term mortality in sepsis and septic shock patients. Steroids shortened the time to resolution of shock and duration of mechanical ventilation. However, there was no evidence to support use of thiamine and vitamin C in sepsis and septic shock.
11	Effect of Combined Hydrocortisone, Ascorbic Acid and Thiamine for Patients with Sepsis and Septic Shock: A Systematic Review and Meta-Analysis	Wu *et al* [55], 2021	China	Meta-analysis of RCT and observational studies	6 RCTs and 7 observational studies	1559 participants.	This study compared hydrocortisone, thiamine, and ascorbic acid use to usual care or hydrocortisone	Combination therapy associated with significant reductions in duration of vasopressor in RCTs, but not in observational studies. It was associated with lower SOFA score at 72 h both in RCTs and observational studies. Combination therapy associated with lower hospital mortality and higher PCT clearance in observational studies.
12	Thiamine combined with vitamin C in sepsis or septic shock: a systematic review and meta-analysis	Ge *et al*[56], 2021	China	Systematic review and meta-analysis	7 RCTs	868 patients	Thiamine combined with vitamin C in patients with sepsis or septic shock	Data from this study found no significant differences for in hospital mortality, but have shorter duration of vasopressor use and reduced SOFA score during 72 h.

HAT: Hydrocortisone; ascorbic acid and thiamine combination; ICU: Intensive care unit; IV: Intravenous; RCT: Randomized control trial; SOFA: Sequential organ failure assessment score.

We know that sepsis is a syndrome and has proven to be a graveyard of various therapies modulating inflammation. The role of vitamin C, if there is, may be in the initial phase of hyperinflammation or cytokine storm associated with release of ROS. Besides, these RCTs used the heterogeneous cohort and failed to consider the sepsis phenotypes based on the level of inflammation. Finally, baseline vitamin C levels were not measured in all the trials, and a fixed dose therapy without measuring therapeutic levels may have caused inconsistent results.

In the absence of current evidence showing any clinical benefits, the recent surviving sepsis guidelines suggest against using vitamin C for managing patients with sepsis and septic shock[4]. The clinical practice at our institute is also in accordance to these latest recommendations and we refrain from making vitamin C a part of our routine sepsis management regimen. The future may be the individualization of these therapies using different disease models based on the aetiology of sepsis, illness severity, and degree of inflammation.

FURTHER TRIALS

Presently, there are more than 30 ongoing clinical trials to evaluate the effect of vitamin C in the management of sepsis and septic shock, in different parts of the world. These trials are evaluating the role of different doses (up to 12 g/d), different patient populations (alcoholic hepatitis, acute lung injury, and patients on invasive mechanical ventilation), and different combinations (along with steroids, thiamine, pyridoxine, or cyanocobalamine). Many of these are randomized multi-center trials (CEMVIS, REVISTA-DOSE, and C-EASIE) which may shed light on many of the unanswered questions regarding the utility of vitamin C in sepsis management. Ongoing studies in different cohorts, like patients with COVID-19 (LOVIT-COVID and REMAP-CAP), burn (VICTORY), post-cardiac arrest (VITaCCA), and/or cardiac surgery patients (advanceCSX) may answer the question of whether vitamin C can produce clinically meaningful outcomes in more specific patient populations.

CONCLUSION

Theoretically, vitamin C has been established to protect cells from oxidative damage, reduce inflammatory response, maintain immune functions, and increase the hemodynamic reserve. All these biological actions may be beneficial in the management of sepsis and septic shock. However, in the aftermath of recent interests and several multi-center trials, it can be concluded that there is still a lack of strong evidence to prove its clinical benefits. Contrary to popular belief, use of intravenous HDVC may rarely be associated with adverse effects like haemolysis, especially in vulnerable patients like those with G6PD deficiency or underlying renal dysfunction. Hence, routine use of HDVC is presently not recommended in the management of sepsis or septic shock.

FOOTNOTES

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ORIGINAL ARTICLE

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Scoring systems in critically ill: Which one to use in cancer patients?

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Abstract

BACKGROUND

Scoring systems have not been evaluated in oncology patients. We aimed to assess the performance of Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE III, APACHE IV, Simplified Acute Physiology Score (SAPS) II, SAPS III, Mortality Probability Model (MPM) II_0 and Sequential Organ Failure Assessment (SOFA) score in critically ill oncology patients.

AIM

To compare the efficacy of seven commonly employed scoring systems to predict outcomes of critically ill cancer patients.

METHODS

We conducted a retrospective analysis of 400 consecutive cancer patients admitted in the medical intensive care unit over a two-year period. Primary outcome was hospital mortality and the secondary outcome measure was comparison of various scoring systems in predicting hospital mortality.

RESULTS

In our study, the overall intensive care unit and hospital mortality was 43.5% and 57.8%, respectively. All of the seven tested scores underestimated mortality. The mortality as predicted by MPM II_0 predicted death rate (PDR) was nearest to the actual mortality followed by that predicted by APACHE II, with a standardized mortality rate (SMR) of 1.305 and 1.547, respectively. The best calibration was shown by the APACHE III score ($\chi^2 = 4.704$, $P = 0.788$). On the other hand, SOFA score ($\chi^2 = 15.966$, $P = 0.025$) had the worst calibration, although the difference was not statistically significant. All of the seven scores had acceptable discrimination with good efficacy however, SAPS III PDR and MPM II_0 PDR (AUROC = 0.762),

had a better performance as compared to others. The correlation between the different scoring systems was significant ($P < 0.001$).

CONCLUSION

All the severity scores were tested under-predicted mortality in the present study. As the difference in efficacy and performance was not statistically significant, the choice of scoring system used may depend on the ease of use and local preferences.

Key Words: APACHE score; Intensive care unit; Medical oncology; SOFA score; Scoring systems; Severity of illness index

Core Tip: Scoring systems are important for patient triaging, benchmarking intensive care unit (ICU) performance, comparing different ICUs and may also help in patient prognostication, selecting treatment options and resource utilization. However, validity and utility of these scores may be questionable in the patient population apart from where they were developed. Hence, these scores need to be tested and validated in different patient populations, in different geographical areas and over different time periods. There is a lack of an ideal score for prognostication of critically ill cancer patients. In our retrospective study, analyzing data from 400 patients and comparing seven commonly employed critical illness scores, we observed that all the scores had similar efficacy and under-predicted mortality. Therefore, the selection of severity of illness score should depend on the ease of use and local preferences.

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INTRODUCTION

The application of prognosticating scoring systems is considered as an important phase in intensive care units (ICUs) since these severity scoring systems estimate the probability of mortality for patients. These scores help the physicians to facilitate resource utilization or continuous quality improvement and to stratify the patients for clinical research[1,2]. ICU scoring systems can help both patients as well as their attendants to select from further treatment options. Further, the scores calculated by these scoring systems help in evaluating the impact of newer treatment modalities and organizational changes which in turn contributes towards the development of treatment standards. In addition to the above, the scoring systems' outcomes also help in benchmarking ICU performance and comparing the scores secured by different ICU patient populations so as to find out the differences in mortality. However, these systems are unreliable in predicting the clinical outcomes of an individual though it has proven efficacy in predicting mortality for a particular patient cohort[3].

Acute Physiology and Chronic Health Evaluation (APACHE) II and Simplified Acute Physiology Score (SAPS) II are arguably the two most-commonly used and validated tools used in the prediction of ICU patient outcomes[4,5]. These scoring systems were developed in the 1980s and have become outdated due to technological and clinical advancements in critical care management of patients in recent years. Hence, there is a need to develop new scoring systems that include APACHE IV, SAPS III and Mortality Probability Model (MPM) II0[6-9]. Such newly-created systems encompass a large number of variables and are highly complicated to compute.

In addition, both validity and utility of the existing scoring systems may be questionable in terms of current patient population compared to the patient population during which they were developed. These scores are widely used and the scoring systems have been validated for a notable time to predict the outcome in general medical or surgical procedures conducted upon critically ill patients. However, whether these systems can predict the mortality accurately among cancer patients remains unknown [10]. There is a dearth of studies that compare different generations of scoring systems and especially the ones used upon cancer patients admitted in medical oncology ICUs. Only a few studies have assessed their usefulness in cancer patients with conflicting results. Moreover, geographic variations in patient populations and the types of cancer necessitate that these scores should be evaluated for different populations[11]. Therefore, the current study is aimed at analyzing the efficacy of seven commonly-used scoring systems to predict the mortality amongst patients admitted in oncology ICUs.

MATERIALS AND METHODS

A retrospective observational cohort study was carried out at a multi-disciplinary onco-medical ICU of a tertiary care center in India. We have an advanced ICU setup and 24-h intensivist coverage with state-of-the-art facilities. Approval for the study and a consent waiver from the institutional ethics committee was obtained.

The data from the records of adult patients who were admitted between January 2018 and February 2020, *i.e.*, 2 years, was collected and analyzed. If the patient was readmitted to the ICU more than once during his/her hospital stay, only the first admission was included in the study. Patients who had ICU stays of less than 12 h, post-operative patients and those admitted from or discharged to another ICU were excluded from the study. Patients fulfilling inclusion criteria were serially recruited. The researchers collected the following data; baseline patient characteristics, indication for ICU admission, type of malignancy, presence of metastasis, need for vasopressor, renal and mechanical ventilation (MV), length of ICU and hospital stay, and ICU and hospital mortality. The data, required to compute various scores, was collected and calculated specified by the procedures.

Statistical analysis

The collected data was then transformed into variables, coded and entered in Microsoft Excel. Then, it was statistically analyzed using SPSS software (version. PC-25). Quantitative data was expressed in mean ± SD or median with an interquartile range. Normality distribution difference between two comparable groups was measured using student's *t*-test or Mann Whitney '*U*' test. Qualitative data was expressed in percentage whereas the statistical differences between the proportions were tested using chi square or Fisher's exact test, as appropriate.

Standardized Mortality Ratio (SMR) was computed by dividing the observed 28 d' mortality by predicted hospital mortality based on different scores. Further, 95% confidence interval (CI) was calculated for SMR by considering the observed mortality as a Poisson variable and then dividing its 95%CI by predicted mortality.

The calibration of the scores was executed using Hosmer-Lemeshow goodness-of-fit statistics which divides the subjects into deciles based on the predicted probabilities of death. Afterwards, it computes a Chi-square value from the observed and expected frequencies. Low Chi-square values and high *P* values ($P > 0.5$) correspond to a better fit. The ability of the scores to predict ICU mortality was explored and discrimination was tested using Area Under Receiver Operating Characteristic (AUROC) curves. If the AUROC curves are more than 0.8, it denotes excellent outcome while 0.6-0.8 are considered to be acceptable. The cut-off values were calculated for different scores using Youden's index based on which sensitivity and specificity of the scores were calculated.

Clinically-relevant variables that produced $P < 0.05$ during univariate analyses and are easily accessible on admission were also entered into multiple logistic regression models as the outcome variable of interest. Odds ratio (OR) was calculated along with 95%CI. A *P* value < 0.05 was considered to be statistically significant.

Sample size calculation

The sample size calculation was done for the estimation of the AUROC curve for APACHE 2 score, using the following formula:

$n \geq Z^2_{\alpha/2} V(AUC) \div d^2$

Where, $V(AUC) = 0.0099 \times e^{-a2/2} \times (6a^2 + 16)$, $a = \phi^{-1}(AUC) \times 1.414$ and ϕ^{-1} is the inverse of standard cumulative normal distribution for AUC.

For a 95% level of confidence $Z_{\alpha/2=1.96}$; d = 0.05 which is the margin of error in estimation and AUC was obtained from a similar study conducted by Schellongowski *et al*[12] who reported an AUC of 0.776 for the APACHE II score.

Substituting these values in the above formula gives $n \geq 196$. As our study was retrospective in nature, we included 400 patients.

RESULTS

During the study period, the data from 400 patients who fulfilled the inclusion criteria were included in the final analysis. Thirty-eight patients were excluded because 31 were admitted from or discharged to another ICU, five were post-operative patients and two had ICU stays less than 12 h. Their baseline characteristics are given in Table 1 and the comparison between various scores is given in Table 2.

Predicted mortality

All of the scoring systems tested in the current study underestimated the mortality (Table 3). The mortality, predicted by MPM II_0 PDR, was nearest to the actual mortality with an SMR of 1.305, followed by APACHE II (1.547) and SAPS II (1.74).

Table 1 Comparison of baseline variables among survivors and non-survivors

Parameters	Survivors, *n* = 169	Non-survivors, *n* = 231	Total, *n* = 400	*P* value
Age in yr	62.85 ± 12.49	61.45 ± 14.82	62.04 ± 13.88	0.527
Male	98 (58.0%)	142 (61.5%)	240 (60.0%)	0.48
Female	71 (42.0%)	89 (38.5%)	160 (40.0%)	
DM	56 (33.1%)	62 (26.8%)	118 (29.5%)	0.17
Hypertension	61 (36.1%)	63 (27.3%)	124 (31.0%)	0.06
Reason for ICU admission				
Sepsis	42 (24.9%)	68 (29.4%)	110 (27.5%)	0.31
Respiratory distress/failure	76 (45.0%)	93 (40.3%)	169 (42.2%)	0.34
Cardiac arrest	1 (0.6%)	8 (3.5%)	9 (2.2%)	0.08
Gastrointestinal bleed	15 (8.9%)	14 (6.1%)	29 (7.2%)	0.33
Altered sensorium	33 (19.5%)	45 (19.5%)	78 (19.5%)	1
Acute kidney injury	2 (1.2%)	3 (1.3%)	5 (1.2%)	1
Type of malignancy				
Solid organ	135 (79.9%)	187 (81.0%)	322 (80.5%)	0.78
Hematological	34 (20.1%)	44 (19.0%)	78 (19.5%)	
Metastasis	80 (59.3%)	145 (77.5%)	225 (69.9%)	0.001
Previous history of surgery for CA				
Yes	72 (42.6%)	74 (32.0%)	146 (36.5%)	0.03
No	97 (57.4%)	157 (68.0%)	254 (63.5%)	
ICU stay	5 (3-8)	4 (2-10)	5 (3-9)	0.58
Hospital stay	14 (8-21)	11 (5-22)	12 (7-21)	0.006
Use of MV	24 (14.2%)	130 (56.3%)	154 (38.5%)	< 0.001
Days of MV	5 (3-7.75)	3 (2-6)	3 (2-7)	0.002
Use of renal support	7 (4.1%)	29 (12.6%)	36 (9.0%)	0.004
Days of renal support	2.14 ± 0.90	2.48 ± 2.06	2.42 ± 1.88	0.786
Use of vasopressor support	26 (15.4%)	174 (75.3%)	200 (50.0%)	< 0.001
Days of vasopressor support	3 (2-4)	2 (1.75-4.0)	2 (2-4)	0.276

ICU: Intensive care unit; MV: Mechanical ventilation.

Calibration

Using the Lemeshow-Hosmer goodness-of fit test, APACHE III (4.704) achieved the best calibration with $P = 0.788$ whereas SOFA score (15.966) was the worst with $P = 0.025$ (Table 4). The least statistically significant discrepancy between the predicted and observed mortality was shown by the APACHE III score.

Discrimination

The efficacy of various scores is given in Figure 1. All the scores tested in the current study exhibited good efficacy, even though there was no statistically significant difference between AUROCs and SAPS III PDR. On the other hand, MPM II_0 PDR (AUROC = 0.762) yielded the best performance (Table 5).

Correlation between various scoring systems

As shown in Table 6, there was a significant correlation found among various scoring systems ($P <$ 0.001) as assessed by linear regression analysis.

Factors associated with hospital mortality

Five factors that showed significance in univariate analysis such as hypertension, surgery for cancer, use

Table 2 Comparison between survivors and non-survivors for various scores

Scoring system	Survivors, *n* = 169	Non-survivors, *n* = 231	Total, *n* = 400	*P* value
APACHE II	17.66 ± 4.96	22.82 ± 8.34	20.64 ± 7.55	< 0.001
APACHE II PDR	28.10 ± 17.74	44.04 ± 25.88	37.30 ± 24.10	< 0.001
APACHE III	59.01 ± 16.95	81.36 ± 31.37	71.92 ± 28.46	< 0.001
APACHE III PDR	17.59 ± 15.80	37.59 ± 28.51	29.14 ± 25.91	< 0.001
APACHE IV	58.80 ± 16.98	80.45 ± 31.70	71.30 ± 28.55	< 0.001
APACHE IV PDR	20.45 ± 14.99	40.45 ± 27.91	32.00 ± 25.33	< 0.001
SAPS II	34.67 ± 11.83	49.20 ± 19.87	43.06 ± 18.39	< 0.001
SAPS II PDR	19.81 ± 16.97	42.83 ± 30.51	33.10 ± 28.06	< 0.001
SAPS III PDR	18.12 ± 16.95	34.66 ± 24.12	27.67 ± 22.88	< 0.001
SOFA Score	5.76 ± 2.80	9.02 ± 4.58	7.64 ± 4.24	< 0.001
MPM II_0 PDR	33.39 ± 15.08	52.16 ± 26.63	44.23 ± 24.31	< 0.001

APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; MPM: Mortality Probability Model; PDR: Predicted death rate.

Table 3 Comparison of the actual and predicted mortality rates for the various scoring systems

Scoring system	Actual mortality	Predicted mortality	SMR	95%CI
APACHE II	0.577	0.373	1.547	1.423-1.678
APACHE III	0.577	0.291	1.982	1.824-2.151
APACHE IV	0.577	0.320	1.803	1.659-1.956
SAPS II	0.577	0.331	1.743	1.604-1.891
SAPS III	0.577	0.277	2.083	1.917-2.26
MPM II_0 PDR	0.577	0.442	1.305	1.201-1.416

SMR: Standardized mortality rate; CI: Confidence interval; APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; MPM: Mortality Probability Model; PDR: Predicted death rate.

of MV, vasopressors and renal support were used in multivariate analysis as well. Out of the five factors, two factors, *i.e.* need for MV (OR 2.437, 95%CI = 1.315-4.515, *P* = 0.005) and vasopressor support (OR 10.465, 95%CI = 5.901-18.557, *P* = 0.000) were statistically associated with hospital mortality.

DISCUSSION

The current study compared various mortality prediction scoring systems and found that all the scores under-predicted the mortality in critically-ill cancer patients. Amongst the scoring systems considered, mortality predicted by MPM PDR was the closest to that of the actual mortality with an SMR of 1.305. AUROC values showed that all of the seven scoring systems had good efficacy and acceptable discrimination. MPM PDR and SAPS III PDR achieved the best discrimination. We found the best sensitivity in SAPS II score (76.2%) and best specificity in SAPS III PDR score (92%). The Lemeshow-Hosmer goodness-of fit tests showed that the APACHE III score had the best calibration although there was no statistically significant difference.

In the current study, all of the scores were significantly higher among non-survivors (*P* value < 0.001) as reported in the literature[13-18]. However, all the scores tested in this study underestimated the mortality (SMR > 1), like previous studies[14,15,19,20].

Discrimination is the ability to determine the patients who may die and who will survive. Measures of discrimination include sensitivity, specificity and AUROC curve. But no single scoring system excelled in all of the three areas. SAPS III PDR and MPM II_0 PDR (AUROC = 0.762) had the best AUROC values whereas sensitivity was at its best for SAPS II and specificity was at its best for SAPS III PDR.

Table 4 Lemeshow-Hosmer goodness-of-fit tests for evaluating the calibration of the scoring systems

Scoring system	Chi square value	*P* value
APACHE II	9.366	0.312
APACHE II PDR	12.159	0.144
APACHE III	4.707	0.788
APACHE III PDR	6.471	0.595
APACHE IV	9.331	0.315
APACHE IV PDR	10.763	0.216
SAPS II	9.479	0.304
SAPS II PDR	10.410	0.237
SAPS III PDR	10.787	0.214
SOFA Score	15.966	0.025
MPM II_0 PDR	11.265	0.187

APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; MPM: Mortality Probability Model; PDR: Predicted death rate.

Table 5 Area under curve for predicting hospital mortality for various scoring system

Scoring system	AUC	*P* value	95%CI	Cut off	Sensitivity	Specificity
APACHE II	0.688	< 0.001	0.637-0.739	> 18.5	67.5%	62.7%
APACHE III	0.720	< 0.001	0.672-0.769	> 78.5	46.8%	87.6%
APACHE IV	0.708	< 0.001	0.659-0.758	> 72.5	53.7%	79.3%
SAPS II	0.734	< 0.001	0.685-0.782	> 34.5	76.2%	60.4%
SAPS III PDR	0.762	< 0.001	0.715-0.808	39.0	44.3%	92.0%
SOFA Score	0.715	< 0.001	0.665-0.764	> 7.5	58.0%	79.3%
MPM II_0 PDR	0.762	< 0.001	0.714-0.810	36.45	71.3%	69.9%

AUC: Area under the curve; CI: Confidence interval; APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; MPM: Mortality Probability Model; PDR: Predicted death rate.

However, these differences were not statistically significant. In the current study, AUROC outcomes showed that discrimination is acceptable in all the scoring systems tested as reported in the literature [14-16,20-22]. All the severity illness scores showed good efficacy with no statistically significant difference in AUROCs.

Calibration evaluates the accuracy of the degree of correspondence between the estimated probability of mortality and the observed actual mortality. Calibration is good if the predicted mortality is close to the observed mortality. APACHE III (4.704) had the best calibration with $P = 0.788$. This infers that it had the least statistically significant discrepancy between the predicted and observed mortality. Good calibration of these scores have also been reported by other authors[14-16,20].

A significant correlation was found among various scoring systems ($P < 0.001$) as per linear regression analysis. This correlation may be attributed to the overlap of multiple variables, considered for calculating the scores. Sculier *et al*[21] also reported an excellent correlation between APACHE II and SAPS II in their study on oncology patients. ICU mortality rate among cancer patients was reportedly high and in the range of 30% to 77%[23-26]. The overall ICU mortality rate in the current study was 43.5%. Even though it is higher, the ICU mortality of the current cohort does not differ from the mortality reported in similar studies conducted earlier[23,24]. The hospital mortality rate in the current study was 57.8% which is again similar as reported earlier[27,28].

Use of MV and vasopressor support have a direct association with hospital mortality. Similar studies conducted earlier have also reported the need for organ support in the form of MV. At times, vasopressor use is directly associated with increased mortality among cancer patients[29]. An ideal scoring system is the need of the hour. This system should be well calibrated, easy to compute, able to have high

Table 6 Correlation of different scoring system with each other

Scoring system		APACHE II Score	A2 PDR	APACHE III Score	A3 PDR	APACHE IV Score	A4 PDR	SAPS II Score	SAPS2 PDR	SAPS 3 PDR	SOFA score
APACHE II Score	*r* value		0.898	0.892	0.836	0.883	0.826	0.820	0.812	0.748	0.679
	P value		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
A2 PDR	*r* value	0.898		0.824	0.832	0.814	0.805	0.751	0.752	0.716	0.635
	P value	0.000		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
APACHE III Score	*r* value	0.892	0.824		0.929	0.966	0.895	0.910	0.902	0.820	0.753
	P value	0.000	0.000		0.000	0.000	0.000	0.000	0.000	0.000	0.000
A3 PDR	*r* value	0.836	0.832	0.929		0.897	0.895	0.851	0.852	0.763	0.711
	P value	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000	0.000
APACHE IV Score	*r* value	0.883	0.814	0.966	0.897		0.915	0.890	0.877	0.821	0.762
	P value	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000
A4 PDR	*r* value	0.826	0.805	0.895	0.895	0.915		0.836	0.839	0.782	0.727
	P value	0.000	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000
SAPS II Score	*r* value	0.820	0.751	0.910	0.851	0.890	0.836		0.972	0.814	0.756
	P value	0.000	0.000	0.000	0.000	0.000	0.000		0.000	0.000	0.000
SAPS 2 PDR	*r* value	0.812	0.752	0.902	0.852	0.877	0.839	0.972		0.813	0.773
	P value	0.000	0.000	0.000	0.000	0.000	0.000	0.000		0.000	0.000
SAPS 3 PDR	*r* value	0.748	0.716	0.820	0.763	0.821	0.782	0.814	0.813		0.684
	P value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000		0.000
SOFA score	*r* value	0.679	0.635	0.753	0.711	0.762	0.727	0.756	0.773	0.684	
	P value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	
MPM II_0 PDR	*r* value	0.704	0.653	0.777	0.729	0.759	0.734	0.790	0.805	0.714	0.700
	P value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; MPM: Mortality Probability Model; PDR: Predicted death rate.

levels of discrimination and predict mortality rates with high accuracy based on the easily-available patient parameters. Additionally, an ideal score also needs to be dynamic, reflecting the change in management and case mix over time. In this search for an ideal scoring system, newer scoring systems have been developed. However, these systems are highly complex in nature, demand huge sets of patient data and need computer assistance to calculate the scores. Hence, the development of an ideal scoring system has a long way to go.

The accuracy of scoring systems may differ over a period of time and may produce varied results in different countries due to differences in ethnicity, patient population, healthcare systems, ICU structure and organization. So, its accuracy cannot be generalized and all such models need external validation in independent patient populations to prove its reproducibility. Therefore, it becomes imperative to compare and test the validity of scoring systems under different geographical areas and upon different patient populations. The current study is one of the few studies conducted on the Indian subcontinent and the researchers have compared a huge number of scoring systems developed for cancer patients in a significantly large cohort of patients.

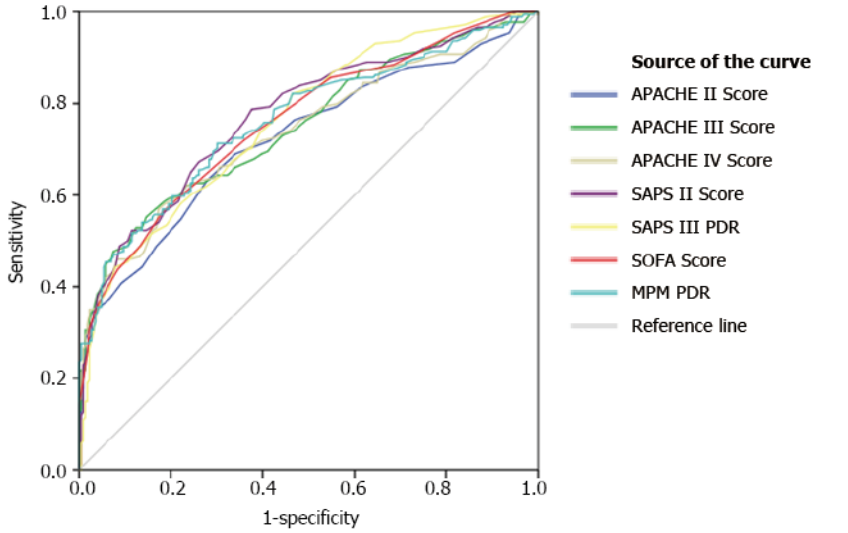

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Figure 1 Comparison between the area under the receiver operating characteristic curves of APACHE II, APACHE III, APACHE IV SAPS-II, SAPS-III, SOFA score and MPM II_0-PDR in discriminating survivors from non-survivors. APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; MPM: Mortality Probability Model.

The current study has a limitation to address, *i.e.* being a single center retrospective study where concerns may arise in terms of generalizing the conclusions arrived in this study. The missing data may have also led to information bias. Nonetheless, the study has several salient features such as the comparison of seven scoring systems, fairly large sample size, well-defined study protocol and the inclusion of only medical oncology patients.

CONCLUSION

The current study concludes that all of the scoring systems considered for this study cohort underpredicted the mortality. However, the APACHE III score had the least discrepancy between the predicted and observed mortality. There was no statistically significant difference in efficacy and all the scores tested had good calibration and acceptable discrimination. Hence, the choice of scoring system in critically-ill oncology patients should not only be based on the performance of the score, but also on other factors such as ease of use and local preferences.

ARTICLE HIGHLIGHTS

Research background

The application of prognosticating scoring systems is considered as an important phase in intensive care units (ICUs) since these severity scoring systems estimate the probability of mortality for patients. These scores help the physicians to facilitate resource utilization or continuous quality improvement and to stratify the patients for clinical research. ICU scoring systems can help both patients as well as their attendants to select from further treatment options. Further, the scores calculated by these scoring systems help in evaluating the impact of newer treatment modalities and organizational changes which in turn contributes towards the development of treatment standards. In addition to the above, the scoring systems' outcomes also help in benchmarking ICU performance and comparing the scores secured by different ICU patient populations so as to find out the differences in mortality.

Research motivation

There is a dearth of studies that compare different generations of scoring systems especially the ones used upon cancer patients admitted in medical oncology ICUs. Only a few studies have assessed their usefulness in cancer patients with conflicting results.

Research objectives

To compare the efficacy of seven commonly employed scoring systems to predict outcomes of critically ill cancer patients.

Research methods

We conducted a retrospective analysis of 400 consecutive cancer patients admitted in the medical intensive care unit over a 2-year period. The primary outcome was hospital mortality and the secondary outcome measure was comparison of various scoring systems in predicting hospital mortality.

Research results

Overall ICU mortality in our study was 43.5% whereas hospital mortality was 57.8%. All scoring systems tested underestimated the mortality. Mortality predicted by MPM II_0 predicted death rate (PDR), was closest to that of the actual mortality followed by that of APACHE II, with a standardized mortality rate (SMR) of 1.305 and 1.547, respectively. APACHE III (χ^2 = 4.704, P = 0.788) had the best calibration and SOFA score (χ^2 = 15.966, P = 0.025) had the worst calibration, but the difference was not statistically significant. All the scores tested had good efficacy and acceptable discrimination, however SAPS III PDR and MPM II_0 PDR (AUROC = 0.762), performed better than others. There was a significant correlation between the various scoring systems (P < 0.001).

Research conclusions

Overall, all the scores in our study cohort under-predicted the mortality. The difference in efficacy was not statistically significant in all scores. The choice of scoring system should depend on the ease of use and local preferences as all the scores tested had similar performance.

Research perspectives

There is a lack of an ideal score for prognostication of critically ill cancer patients. In our retrospective study, analyzing data from 400 patients and comparing seven commonly employed critical illness scores, we observed that all the scores had similar efficacy but under-predicted mortality. Therefore, the choice of scoring system should depend on the ease of use and local preferences.

FOOTNOTES

Author contributions: Beniwal A and Juneja D designed the study; Beniwal A, Juneja D and Beniwal HK collected the data, analyzed the results, performed the majority of the writing and prepared the tables; Singh O, Goel A and Singh A provided critical input in writing the paper and reviewed the manuscript.

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SYSTEMATIC REVIEWS

Postoperative complications and critical care management after cytoreduction surgery and hyperthermic intraperitoneal chemotherapy: A systematic review of the literature

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Abstract

BACKGROUND

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a comprehensive treatment option performed for peritoneal surface malignancies. Postoperatively almost all patients are transferred to the intensive care unit electively.

AIM

To describe the common and rare postoperative complications, postoperative mortality and their critical care management after CRS-HIPEC.

METHODS

The authors assessed 54 articles for eligibility. Full text assessment identified 14 original articles regarding postoperative complications and critical care management for inclusion into the final review article.

RESULTS

There is an exaggerated metabolic and inflammatory response after surgery which may be termed as physiological in view of the nature of surgery combined with the use of heated intraperitoneal chemotherapy with/out early postoperative intravenous chemotherapy. The expected postoperative course is further discussed. CRS-HIPEC is a complex procedure with some life-threatening complications in the immediate postoperative period, reported morbidity rates between 12%-60% and a mortality rate of 0.9%-5.8%. Over the years, since its inception in the 1980s, postoperative morbidity and survival have significantly improved. The commonest postoperative surgical complications and systemic toxicity due to chemotherapy as reported in the last decade are discussed.

CONCLUSION
CRS-HIPEC is associated with a varying rate of postoperative complications including postoperative deaths and needs early suspicion and intensive care monitoring.

Key Words: Intensive care units; Hyperthermic intraperitoneal chemotherapy; Morbidity; Peritoneal neoplasms; Postoperative period

Core Tip: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is a complex procedure with some life-threatening complications in the immediate postoperative period, reported morbidity rates between 12%-60% and a mortality rate of 0.9%-5.8%. There is an exaggerated metabolic and inflammatory response after surgery which may be termed as physiological in view of the nature of surgery combined with use of heated intraperitoneal chemotherapy.

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INTRODUCTION

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a comprehensive treatment option performed for peritoneal surface malignancies (PSM), both primary peritoneal cancers and peritoneal metastasis secondary to colorectal, appendiceal, ovarian, gastric and other malignancies. CRS comprises the surgical removal of visible tumour from peritoneal surfaces as well as abdomino-pelvic organs. CRS includes a wide spectrum which ranges from excision of a single peritoneal nodule to complete peritonectomy along with multi-visceral resections and up to 3-5 anastomoses. It is followed by HIPEC which involves pumping highly concentrated chemotherapy drugs heated to 41°C–43°C into the peritoneal cavity. HIPEC can be performed either with closed or open abdominal techniques. The advantages of a closed abdominal HIPEC are increased intraabdominal pressure leading to increased tissue penetration and prevention of heat loss whereas the advantage of open abdominal HIPEC is better distribution of the chemotherapeutic drugs. The primary disease and institutional protocol dictate the type of HIPEC treatment used in various institutes. The duration of surgery can vary from eight to fifteen hours, with longer duration being the norm rather than an exception.

CRSHIPEC is a complex procedure with some life-threatening complications in the immediate postoperative period, reported morbidity rates between 12%-60% and a mortality rate of 0.9%-5.8%[1-4]. The postsurgical complications have been reported as late as 90 d after surgery[1,5]. Over the years since its introduction in 1980's, better patient selection, improvements in surgical techniques, surgical skills and perioperative management strategies, have further reduced the morbidity and improved the survival after CRS-HIPEC. Additionally, disease progression even after comprehensive treatment, necessitating a repeat CRS-HIPEC procedure has been reported to be useful in selected patients with recurrent peritoneal malignancies[6].

The present article reviews the early postoperative management and common complications after CRS-HIPEC, reported in the last decade.

MATERIALS AND METHODS

Literature search strategy

An electronic literature search was conducted using the databases of 'PubMed' and 'Google Scholar'. The 'Reference Citation Analysis', an artificial intelligence technology-based open citation analysis database was employed. The period of the search was from 2010 to 2021. The search terms included, "Peritoneal Cancer", "Hyperthermic", "Intraperitoneal", "HIPEC", Critical Care, Intensive Care, Postoperative Care, Perioperative Care, Postoperative Complications and their synonyms in various combinations. The extracted articles were further reviewed in a step-wise manner for identification of relevant studies. The titles and abstracts were inspected independently by two authors.

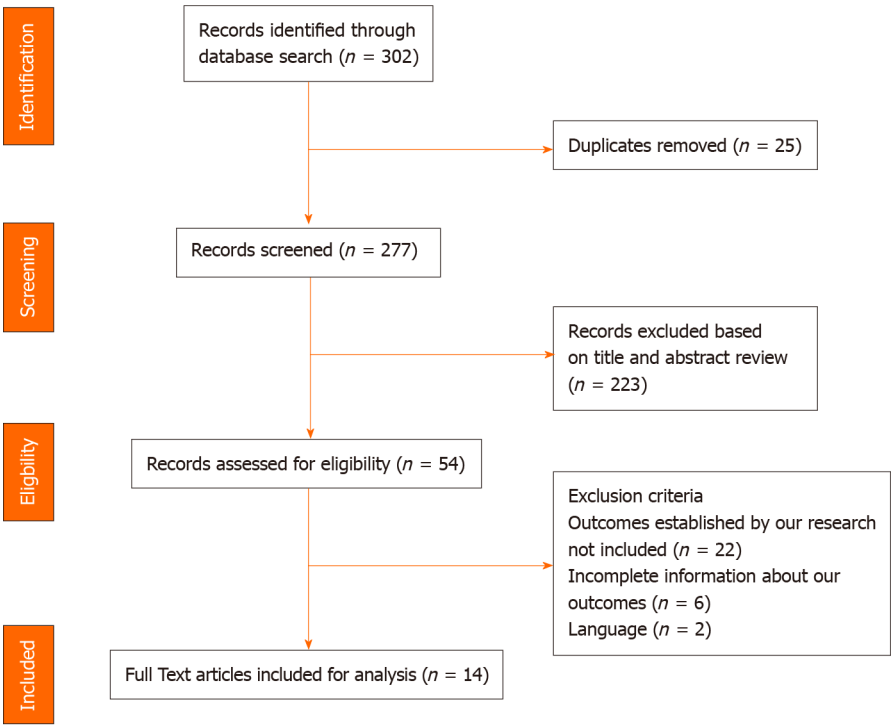

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Figure 1 PRISMA flow diagram.

Study selection criteria

Only full text articles published in English were included for review. Only articles which reported postoperative critical care management and complications were included. Articles regarding only preoperative and intraoperative management were excluded. Only original research articles were included for analysis. Meta-analyses and review articles were excluded.

RESULTS

Literature search results

A total of 277 articles were identified after the initial literature search. Initial review included screening of article titles for relevance and identifying duplicates. A further screening of abstracts identified articles for full text review. Full text assessment identified 14 original articles regarding postoperative complications and critical care management for inclusion into the final review article (Table 1, Figure 1).

DISCUSSION

Critical care management

Postoperatively almost all the patients were transferred to the intensive care unit (ICU) electively. Only a few selected patients with limited CRS and short duration HIPEC may be amenable for high dependency unit (HDU) management. There is an exaggerated metabolic and inflammatory response after surgery which may be termed as physiological in view of the nature of surgery combined with use of heated intraperitoneal chemotherapy with/out early postoperative intravenous chemotherapy.

At the end of surgery, the decision to extubate or electively ventilate depends upon patient comorbidities, duration of surgery, degree of cytoreduction, haemodynamic instability, vasopressor use, blood loss and the need for massive blood transfusion, and metabolic derangement. Even in the ICU, it is quite common to extubate the patients to a high flow nasal cannula or non-invasive ventilation depending upon the extent of diaphragmatic peritonectomy, breathing efforts of the patients and site of gastrointestinal anastomosis. Preoperative malnutrition and anaemia, long duration of surgery, fluid overload, poorly controlled pain leading to diaphragmatic splinting, lithotomy with steep Trendelenburg positioning, preoperative pleural effusion, ascites or presence of preoperative compromised pulmonary functions predispose a patient to postoperative pulmonary complications. Adherence to enhanced recovery after surgery (ERAS) protocols including preoperative incentive

Table 1 Demographic details and disease load

Ref.	Data duration	Type of Cohort/Study	No of Institutes (Country)	PSM	No of procedures	Age		PCI	
Cavaliere *et al* [35], 2011	1995-2007	Prospective	Five (Italy)	Colorectal	146	56 (19-76)	median (range)	< 11-48, 11-20-72, > 20-26	Range
Glehen *et al*[36], 2010	1989-2007	Retrospective	Twenty-five (Europe and Canada)	Non-ovarian	1154, 190(EPIC)	52 (12)	mean (SD)	13.1 (8.9)	mean (SD)
Cooksley *et al*[7], 2011	2009-2010	Retrospective	Single (England)	Mixed	69	53.3 (30-73)	mean (range)	10.5	Mean
Mizumoto *et al* [37], 2012	2007-2011	Retrospective	Single (Japan)	Mixed	284	57 (13) (23–88)	mean (SD) (range)	20 (13) (0–39)	mean (SD) (range)
Bakrin *et al*[1], 2012	1991-2008	Retrospective	Two (France)	Ovarian	246	57.5 (28.6-77.6)	Mean (range)	10.8 (1-31)	Mean (range)
Baratti *et al*[17], 2012	1995-2011	Prospective	Single (Italy)	Mixed	426	53.4 (12.7)	mean (SD)	18.7 (10.8)	mean (SD)
Bakrin *et al*[16], 2013	1991-2010	Retrospective	Thirteen (France)	Ovarian	566	57.89 (22-77)	Median (range)	8.5 (0-31)	Median (range)
Canda *et al*[27], 2013	2007-2012	Retrospective	Single (Turkey)	Mixed	118	53.4 (20-82)	Mean (range)	14.7 (3-28)	Mean (range)
Jafari *et al*[15], 2014	2005-2011	Retrospective	> 500 (USA)	Mixed	694	55 (10)	mean (SD)	NA	
Levine *et al*[30], 2014	1991-2013	Prospective	Single (USA)	Mixed	1000	52.9 (12.4)	mean (SD)	12	Mean
Cascales-Campos *et al* [24], 2016	2008-2014	Prospective	Single (Spain)	Mixed	156	57 (33-79)	Median (range)	8 (0-13)	Median (range)
Martin *et al*[25], 2016	1991-2014	Retrospective	Single (USA)	Mixed	302	54% (40-60)	Percent (range)	13 (6-18)	Median (IQR)
Elekonawo *et al* [38], 2019	2010-2015	Case matched RCT	Two centres in Netherlands	Colorectal	223	61.4(10.7)	mean (SD)	9.0 (0–24)	Median (range)
Kelly *et al*[39], 2018	2007-2014	Retrospective	Single (USA)	Mixed	226	53 (20-66)	Median (range)	14 (0-27)	Median (range)

RCT: Randomised controlled trial; PCI: Peritoneal carcinomatosis index; EPIC: Early postoperative intravenous chemotherapy; SD: Standard Deviation; PSM: Peritoneal surface malignancies; NA: Not available.

spirometry and respiratory muscle training and its continuation in the postoperative period have been proven to reduce pulmonary complications. Cooksley *et al*[7] extubated all their HIPEC patients at the end of surgery with the use of good epidural analgesia and goal-directed fluid therapy.

Massive fluid shifts, third spacing and blood loss are quite common in the CRS phase of the surgery whereas the HIPEC phase can lead to extensive vasodilatation necessitating use of vasopressors. The fluid losses, both external and internal (third space), continue in the immediate postoperative period. The abdominal drain losses can be as high as 40% of the total output, in the first 72 h after surgery[3,8]. Continuous monitoring and assessment of fluid status guided by various static and dynamic parameters such as cardiac output monitoring, central venous pressure, serum lactate, urine output, abdominal drain and nasogastric losses need to be conducted. Adequate and timely resuscitation with crystalloids, colloids, blood and blood products helps reduce postoperative morbidity and mortality. In view of the increased risk of postoperative sepsis, acute kidney injury and coagulopathy, it is advisable to avoid use of hydroxylethyl starches in the perioperative period. There is a significant protein loss secondary to the exudating ascitic fluid and extensive surgical dissection. Postoperative decline in albumin levels is common, which starts intraoperatively and continues postoperatively, with the need for exogenous replacement. The routine use of furosemide, mannitol or low doses of dopamine to prevent renal injury is no longer recommended.

Malfroy *et al*[8] found that abdominal drain output more than 1500 mL, postoperative fluid resuscitation > 70 mL/kg or the need for vasopressors in the first 24 h after surgery are predictors of increased 30-d morbidity and mortality. Earlier concerns regarding chemotherapy-induced nephropathy, replacement of large volume ascites and dehydration due to preoperative bowel preparations, led to liberal fluid replacement during the intraoperative period with resultant postoperative

fluid overload leading to tissue and bowel edema and increased abdominal, respiratory and cardiac complications. In CRSHIPEC procedures, Colantonio *et al*[9] found that patients in the protocolised goal-directed therapy (GDT) group received significantly less fluids in the intraoperative period, had lower abdominal and other systemic morbidity and postoperative length of stay but with no significant difference in mortality. They reported that GDT with individualised therapeutic end points can be achieved using a combination of colloids, crystalloids and vasopressors.

Coagulopathy during the perioperative period is multifactorial which includes the length of surgery, extent of resection, both hypothermia and hyperthermia, blood loss and massive blood transfusion. There may be prolongation of prothrombin time, activated partial thromboplastin time and/or reduction in platelet count. Monitoring viscoelastic properties of clots with the use of thromboelastography both intra- and postoperatively can help with management. The coagulation profile generally normalises by the third to sixth postoperative day. Platelet transfusion is rarely required and should only be considered when platelet levels fall below 50000 with associated bleeding or additional surgical procedures become imminent.

Electrolyte abnormalities may be common due to perioperative massive fluid shifts. Sodium, chloride, potassium, calcium, magnesium and phosphate should be measured periodically and replacement should be done in the ICU.

Extensive CRS and HIPEC can cause wide fluctuations in temperature. The hyperdynamic alterations secondary to hyperthermia generally reverse once the temperature normalises. Hyperthermia can also cause coagulopathies, renal tubulopathy, liver dysfunction, neuropathies and seizures. Delta temperature (difference between lowest and highest temperatures) during CRSHIPEC was found to be a significant predictor of ICU stay > 5 d[3]. This is highest in patients with a high peritoneal carcinomatosis index (PCI) necessitating longer, aggressive resection. Hypothermia during the CRS phase is associated with cardiac morbidity, decreased humoral and cellmediated immunity and worsen metabolic acidosis and may be responsible for increased ICU stay. The lactate levels after HIPEC should be interpreted with caution and along with other markers of perfusion as the inflammatory state itself can be responsible for hyperlactatemia.

Perioperative fluid shifts and hypoperfusion combined with nephrotoxic chemotherapy especially cisplatin predisposes to acute kidney injury. The critical time for renal perfusion is generally the first 2 postoperative days. Transient severe hypophosphatemia may be observed on the first two-three postoperative days due to hyperthermia-related renal tubulopathy. It can lead to decreased diaphragm mobility leading to atelectasis and increased insulin requirements. Transaminitis (2to 3fold rise) is common during the first four postoperative days. Diarrhoea can occur in the first week due to digestive hypersecretion secondary to the hyper inflammatory status.

Initiation of enteral feed should depend on the extent of bowel resection, presence or absence of inflammation and haemodynamic stability. Parenteral nutrition should be initiated early and switched to enteral nutrition as soon as possible. The decisions regarding nutrition should consider patients baseline nutritional status, and surgical and medical concerns. Dieticians should be actively involved from the preoperative phase. Preoperative nutritional status may predict length of stay, risk of infectious complications and possibly long-term survival.

The anticipated postoperative course includes lowgrade fever up to 38°C, even in the absence of infection, during the first 7-10 postoperative days. Leukocyte counts and platelet counts progressively decrease in the first two weeks followed by a progressive increase. Inflammatory markers such as Creactive protein, interleukins and elastase increase during surgery and return to normal within 12-24 h. Hyperglycaemia can be a common finding due to surgical stress and hypercatabolic state, necessitating insulin infusions. The glycaemic targets are set at blood sugar levels between 140 to 180 mg/dL. Routine postsurgical antibiotic prophylaxis is recommended. An escalation after appropriate cultures may be required in the event of infections.

Moderate to severe pain is quite common. Use of thoracic epidural anaesthesia (TEA) is desirable in these patients for management of postoperative analgesia, prevention of respiratory complications and reduction in rates of paralytic ileus. Thoracic epidural analgesia with local anaesthetics and short acting opioids up to 72-96 h after surgery have been found to be useful. Owusu-Agyemang *et al*[10] in their study of 215 patients reported that intraoperative initiation of continuous epidural infusions pre-HIPEC was associated with significantly less blood loss and decreased intraoperative fluid requirements. Despite common postoperative coagulation abnormalities and an increased incidence of sepsis, no epidural hematomas or abscesses were reported in their study. A single centre retrospective analysis reported improved survival and reduced grade III/IV postoperative morbidity after HIPEC when TEA was used compared to patient-controlled opioid analgesia[11]. Along with thoracic epidural analgesia, adjuncts such as paracetamol as a component of multimodal analgesia are recommended. Opioid usage needs to be minimised. The use of truncal blocks such as transversus abdominis block or quadratus lumborum blocks in the absence of epidurals are encouraged.

Adherence to ERAS protocols in the perioperative period have helped to considerably decrease the grade III/IV complications and associated morbidity, length of ICU and hospital stays and improve the survival rates[3,12-14]. Mechanical and pharmacological deep vein thrombosis prophylaxis should be considered as appropriate during the entire perioperative period if not contraindicated. The first dose of low molecular weight heparin is generally given the previous night as part of ERAS and continued

postoperatively. Implementation of ERAS protocols in the postoperative period such as early extubation, early removal of drains and urinary catheter, and early mobilisation are recommended. Stress ulcer prophylaxis can be followed as per institutional protocols.

Compliance to ERAS protocols have been found to reduce the major postoperative complication rate from 33% to 21% due to early detection and reversal of the pathophysiological cascade after this major surgery, consequently reducing the length of stay from 13.1 ± 9.5 d to 8.6 ± 4.9 d[12]. A more recent National Surgical Quality Improvement Program review reported an average length of stay of 13 d[15].

Complications in the postoperative period

The extent of peritoneal disease as scored by the PCI, the completeness of the cytoreduction (CC) score and dose of intraperitoneal platinum chemotherapy are important prognostic factors of both morbidity and survival[1,8,16]. PCI > 8-10 and CC-1/CC-2 have been found to have an increased incidence of postoperative grade III/IV complications. The risk of complications increased by 3.5% for every single point increase in PCI[17]. Additionally, initial indication of surgery, ECOG score, number of organ resections *etc* may help further prognostication[1,17]. Tao *et al*[18] in their meta-analysis, reported a similar incidence of anastomotic leaks and duration of hospital stay between younger (< 65 years) and elderly (> 65 years) patients but the morbidity outcomes and mortality were higher in elderly patients. Cooksley *et al*[7] found that the higher the vasopressor requirement intra- and postoperatively, the higher the risk of postoperative complications.

In recent years, a gamut of studies investigated the utility of inflammatory markers to predict the postoperative course as well as survival. Inflammation plays an important role not only in carcinogenesis but also during CRS-HIPEC surgery. Some inflammatory biomarkers have been found to have an increased association with postoperative infective complications. Kim *et al*[19] reported that higher values of preoperative neutrophil to lymphocyte ratio (NLR) and mean platelet volume (MPV), platelet to lymphocyte ratio (PLR), and MPV on postoperative days 2, 3, and 5 were associated with decreased 1-year survival after CRS-HIPEC. C-reactive protein (CRP), an acute phase inflammation protein, is a highly sensitive but nonspecific biomarker of systemic inflammatory response. van Kooten *et al*[20] reported an increasing value of CRP after postoperative day (POD) 2 or CRP > 166 mg/L at POD3 or > 116 mg/L at POD4, had a predictive value for early detection of severe adverse events. Saeed *et al*[21] studied the dynamics of precalcitonin (PCT) pre and postoperative in CRS-HIPEC patients and compared them to CRP and white cell counts (WCC) in patients who developed infective complications postoperatively. They found a trend for faster rise in serum PCT on POD1 as compared to CRP and WCC, along with a faster PCT decline following appropriate therapy on POD3 and 6 when infected cases were clinically resolving while WCC and CRP continued to rise, particularly in non-splenectomised patients. Splenectomised patients had an increase in PCT postoperatively even in the absence of infection. Although all three, namely PCT, WCC and CRP showed an increase postoperatively consequent to systemic inflammatory response syndrome (SIRS) post CRS-HIPEC surgery, PCT had the highest negative predictive value to rule out bacterial infectious complications. Finally, they cautioned the interpretation of postoperative PCT in predicting infectious complications only in association with other clinical, biochemical, microbiological and radiological findings. Viyuela García *et al*[22] reported that CRP on POD7 and 8 had best accuracy, with an optimal cut-off value of 88 mg/L and 130 mg/L, respectively, to predict postoperative infective complications in ovarian cancer patients who underwent CRS-HIPEC.

The complications are commonly graded on two main classification systems – Clavien Dindo classification and National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCICTCAE). Major surgical complications generally include those requiring interventional endoscopy or CT-scan/ultrasound-guided procedures (grade 3), return to the operating room or ICU (grade 4), and death (grade 5). It has been found that conventional 30-d mortality underestimates post-operative mortality by 50% in CRS-HIPEC patients[5]. In their study, Alyami *et al*[5] found that most major complications occurred within 30 d, but more than 50% of deaths related to postoperative complications occurred after 30 d. Various studies have suggested evaluating morbidity and mortality related to complex surgical procedures such as CRS-HIPEC, using a 90-d time period for its definition[5,17,23].

CRS-HIPEC, being a major abdominal surgery, is associated with a gamut of postoperative complications. Grade III/IV complications are most common in the first 2 wk after surgery (Table 2). Malfroy *et al*[8] reported a median time to complications post-surgery of 2.5 d.

Gastrointestinal complications

CRS with HIPEC involves extensive abdominal surgery with major handling of small bowel, several visceral resections, anastomosis and peritonectomy. The major complications include anastomotic leaks, gastrointestinal perforations distant from the suture line, abdominal abscess, sepsis, haemorrhage, biliary, pancreatic or ureteral leakage, pancreatitis, paralytic ileus, diarrhoea *etc.* An important consideration is the timing of the anastomosis vis-à-vis HIPEC. There is no evidence in the literature to suggest an increased risk of anastomotic leaks or isolated disease recurrence on suture lines if anastomosis is performed at the completion of the cytoreduction and prior to HIPEC[6]. Some authors prefer bowel anastomoses to be performed before HIPEC in closed procedures to avoid reopening the patient but after HIPEC in cases of open procedure[16]. Malfroy *et al*[8] found that septic shock was the commonest

Table 2 Surgical complications

Ref.	N	Mortality (%)	Days	Morbidity (Grade III/IV), %	Complication classification	Commonest complications			Re-operations (%)
						First (%)	Second (%)	Third (%)	
Cavaliere *et al*[35], 2011	146	2.7	30	27.4	WHO	GI perforation/anastomotic leak (7.4)	Sepsis (4.1)	Pancreatitis/pancreatic fistula (1.4)	NA
Glehen *et al*[36], 2010	1154, 190 (EPIC)	4.1	30	33.6	NCICTCAE	GI perforation/anastomotic leak (9.7)	Pneumonia (9.1)	Intraabdominal bleeding (7.7)	14
Cooksley *et al*[7], 2011	69	0	30	5.79	NA	Pneumonia (2.9)	Central line infection (1.5)	Uncontrolled hypertension (1.5)	NA
Mizumoto *et al*[37], 2012	284	3.5	30	17	NCICTCAE	GI perforation/anastomotic leak (6.7)	Sepsis (4.6)	Intraabdominal bleeding (2.1)	11
Bakrin *et al* [1], 2012	246	0.37	30	11.6	NCICTCAE	GI perforation/anastomotic leak (4.9)	Intraabdominal bleeding (2.4)		4.9
Baratti *et al* [17], 2012	426	2.6	90	25.3	NCICTCAE	GI perforation/anastomotic leak (11.03)	Sepsis (3.76)	Intraabdominal bleeding (3.3)	10.7
Bakrin *et al* [16], 2013	566	0.8	30	31.3	NCICTCAE	Intraabdominal bleeding (8)	GI perforation/anastomotic leak (3)		8
Canda *et al* [27], 2013	118	7.6	30	31.35	NCICTCAE	Sepsis (7.6)	Pneumonia (2.5)	Ileus (2.5)	5.08
Jafari *et al* [15], 2014	694	2.3	30	32.9	NA	Intraabdominal bleeding (17)	Sepsis (15.9)	Pneumonia (4.8)	9.8
Levine *et al*[30], 2014	1000	3.8	30	42	NA	Sepsis	GI perforation/anastomotic leak	Pneumonia	NA
Cascales-Campos *et al*[24], 2016	156	0.6	30	11.5	NCICTCAE	Pleural effusion (4.49)	Sepsis (3.8)	GI perforation/anastomotic leak (1.9)	NA
Martin *et al*[25], 2016	302	3	30		NA	Pleural effusion (10.8)	Thrombosis (6.8)	Sepsis (5.4)	NA
Elekonawo *et al*[38], 2019	223	1.5	30	17.6	Clavien Dindo	Sepsis (14.7)	GI perforation/anastomotic leak		NA
Kelly *et al* [39], 2018	226		30	NA	NA	Ileus (31)	Sepsis (21)	Thrombosis (15)	16

EPIC: Early postoperative intravenous chemotherapy; GI: Gastrointestinal; NA: Not available; NCICTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCICTCAE).

factor for postoperative ICU re-admission (28.1%) with gastrointestinal origin of sepsis to be the highest (64.3%). Paralytic ileus is the commonest morbidity observed postoperatively, classified as Grade I-III morbidity[24]. One meta-analysis showed an incidence of prolonged postoperative ileus of 10.2% following elective colonic surgery, with potential higher rates with added effects of the hyperthermic bath, chemotherapy and peritoneal carcinomatosis[14]. The use of thoracic epidural analgesia, postoperative use of prokinetics, laxatives and adjuncts such as coffee or chewing gum, and early mobilisation have all been recommended to hasten gut recovery after such major surgery. ICU readmissions occur in 11%-25% of patients and in one study, ileus/dehydration was responsible for one third of readmissions[14]. The rate of re-operations increases in patients with postoperative complications due to sepsis, anastomotic leaks, *etc*.

Sepsis both abdominal and unrelated to the surgical site is the commonest complication post-surgery. It is also the commonest cause of mortality. Infections with resistant organisms are also common[8].

Martin *et al*[25] reported 30- and 90-d readmission rates after CRS-HIPEC to be 14.9% (n = 32), and 21.4% (n = 46), respectively. The main factor implicated in re-admissions was the presence of enterocutaneous fistula. They did not find any association between factors such as age, sex, race, intraoperative

blood loss, pancreatic or hepatic resection at the index operation, and postoperative complications of surgical site infection, line infection, and thromboembolic events with higher re-admission rates.

Respiratory complications

Common postoperative grade III/IV respiratory complications include pneumonia, pleural effusions, respiratory failure, and pulmonary embolism[8,23,26]. These can prolong the ICU stay or cause ICU re-admissions. Respiratory sepsis is the second most common cause of septic shock at 28.6%[8]. The massive fluid shifts during CRS-HIPEC are most commonly responsible for the increased incidence of unplanned intubations, prolonged ventilations and pulmonary interventions. Preti *et al*[26] reported an incidence of pulmonary adverse events of 10% which included 4.6% pleural effusions, 4.2% respiratory distress necessitating oxygen supplementation and intubations and 3.2% pneumonia. Martin *et al*[25] reported pleural effusions in 10.8% of patients postoperatively and mortality in two patients secondary to pulmonary embolism.

Cardiovascular complications

Hypovolemic shock especially in the first 48 h post-surgery secondary to exuding peritoneal surfaces and systemic inflammatory response can lead to higher rates of grade III/IV complications. The incidence of acute myocardial infarction and arrythmias is similar to any major gastrointestinal surgery. Jafari *et al*[15] reported a 0.3% incidence of postoperative myocardial infarction. Martin *et al*[25] reported a 4.4% incidence of cardiac arrythmias (atrial fibrillation, supraventricular tachycardia and pulseless electrical activity) and attributed one patient's mortality to cardiac dysrhythmia.

Miscellaneous

Sepsis (unrelated to abdominal complications), central line infections as well as urinary tract infection are common[6,17,25,27]. Some case reports have mentioned rare complications such as non-cirrhotic, non-total parenteral nutrition hyperammonia *etc*[28]. Prolonged postoperative acidosis has also been observed[8]. Multi-organ failure is common. The risk of pulmonary embolism, deep venous thrombosis and superior mesenteric vein thrombosis is in the range of 5%-10%[29]. The significant risk factors associated with the development of venous thromboembolism include advanced cancer stage at the time of diagnosis, prolonged immobilization, extensive surgical procedures, mucinous tumours of the gastrointestinal tract and the use of central venous catheters.

Systemic toxicity due to hyperthermic chemotherapy

Depending on the cancer histology, high concentrations of different chemotherapeutic agents (20-1000 times greater than plasma levels) are delivered into the abdominal cavity. Drugs which have a synergistic effect with heat, namely, mitomycinC and the platinumbased drugs, cisplatin, carboplatin, and oxaliplatin are used for intraperitoneal (IP) administration. The less commonly used drugs are doxorubicin, 5fluorouracil, docetaxel, paclitaxel and irinotecan.

Intraperitoneal chemotherapy is sometimes combined with concomitant or early postoperative administration of intravenous chemotherapy, aiming to create a bidirectional diffusion gradient through the cancer cells.

Most of the PSM are platinum-sensitive, with cisplatin being the commonest chemotherapeutic agent used for HIPEC. Common toxicities include nephropathy and haematological toxicity (Table 3). A cisplatin dose more than 240 mg was demonstrated to increase both surgical morbidity and systemic toxicity[17]. Some centres have used sodium thiosulphate for the prevention of cisplatininduced nephrotoxicity with promising results[3,14,30]. One of the considerations for patients with a second recurrence is platinum sensitivity. The progression-free interval since the most recent course of platinum chemotherapy may differentiate between platinum sensitive and platinum resistant disease [16]. Few studies have reported an increased rate of systemic complications with the combined use of cisplatin and mitomycin for IP chemotherapy[1,31]. Canda *et al*[27] found that patients with pre-operative renal dysfunction and previous chemotherapy may present with grade III/IV postoperative nephrotoxicity. Despite a 30% dose reduction in the chemotherapeutic agent doses during HIPEC in older patients (age > 70 years), patients with preoperative renal dysfunction or previous systemic/intraperitoneal chemotherapy, they found a high incidence of post-operative renal dysfunction with five patients requiring haemodialysis and two patients continuing with chronic haemodialysis[27]. Bakrin *et al*[16] suggested a 30% dose reduction in patients older than 70 years, with previous chemotherapy and/or extensive surgical cytoreduction as they found a higher incidence of postoperative renal dysfunction with 8% of patients (n = 51) suffering from postoperative renal insufficiency, 2% of patients (n = 15) chronic renal insufficiency and 1% of patients (n = 6) requiring long-term dialysis.

Haematological complications secondary to chemotherapeutic agents are also commonly reported in various studies[1,7,32]. Leukopenia and neutropenia have been frequently reported. Mitomycin-C (MMC), when dosed by body surface area or weight, has been attributed to leukopenia to the tune of 20%-40%[32]. In a study by Feferman *et al*[32], the use of MMC-HIPEC produced an incidence of 7% severe leukopenia and 4.5% neutropenia, with some patients requiring therapeutic granulocyte colony

Table 3 Systemic toxicities due to chemotherapy

Ref.	HIPEC drugs	EPIC	Nephrotoxicity, %	Haematological toxicity, %
Glehen *et al*[36], 2010	MMC + CDDP/Ox + 5FU/leucovorin	MMC+5FU	1	13.3
Bakrin *et al*[1], 2012	CDDP + MMC/DX			3
Baratti *et al*[17], 2012	CDDP + MMC/DX		5.4	5.9
Bakrin *et al*[16], 2013	CDDP/MMC/DX		11	11
Canda *et al*[27], 2013	CDDP + /MMC		25.8	19.8
Jafari *et al*[15], 2014	NA		3.7	0

EPIC: Early postoperative chemotherapy; HIPEC: Hyperthermic intraperitoneal chemotherapy; MMC: Mitomycin-C; CDDP-Cisplatin, 5FU" % flurouracil; Ox: Oxaloplatin; Dx: Adriamycin.

stimulating factor (GCSF). They reported that the risk of myelosuppression was reduced with a fixed 40 mg dose of MMC in HIPEC and routine use of GCSF for prophylaxis is not indicated. Bakrin *et al*[16] reported an 11% incidence of grade III/IV leukopenia in their cohort of 566 epithelial ovarian cancer patients undergoing CRS-HIPEC.

Limitations

The data provided in the included studies in this systematic review lacks standardisation in reporting of methodology, postoperative complications *etc*[33-37]. There is variance in the classification of complications, drugs used in HIPEC, *etc.* Although the first ERAS protocols for major abdominal surgery were developed in 2010, ERAS guidelines for CRS-HIPEC were recently published[14,38,39]. Hence the degree of adherence to ERAS in the studies included in our review and its effect on the rate of complications may vary in the future.

CONCLUSION

CRS-HIPEC for PSM has advantageous survival outcomes, and has become a common surgery in oncological centres all over the world. Being a complex surgery, with proven postoperative systemic inflammatory response, the focus in recent years has shifted to understanding the immediate postoperative pathophysiology and its management, early detection of complications and the institution of appropriate treatment to reduce morbidity and improve survival. The implementation of ERAS guidelines specific to CRS-HIPEC should help to further reduce postoperative complications.

ARTICLE HIGHLIGHTS

Research background

CRS-HIPEC is an aggressive option for the comprehensive management of all peritoneal surface malignancies. It can result in some life-threatening complications in the immediate postoperative period and reported higher morbidity and mortality rates. Postoperative morbidity and survival have significantly improved. The commonest postoperative surgical complications and systemic toxicity due to chemotherapy as reported in the last decade are discussed.

Research motivation

The number of patients undergoing CRS-HIPEC has increased in the last decade as have improvements in surgical techniques, surgical skills and perioperative management strategies. All these have led to improvements in post-surgical outcomes and survival rates. The present article reviews the early postoperative management and common complications after CRS-HIPEC, reported in the last decade.

Research objectives

To review early postoperative management after CRS-HIPEC. To review common im-mediate post-surgical complications, namely gastrointestinal, respiratory, cardiovascular, miscellaneous and systemic toxicity secondary to chemotherapy, in these patients.

Research methods

An electronic literature search was conducted using the databases of 'PubMed' and 'Google Scholar', during the period from 2010 to 2021. Postoperative complications and their synonyms in various combinations were searched. The extracted articles were further reviewed in a step-wise manner for the identification of relevant studies. The full-text assessment identified 14 original articles regarding postoperative complications and critical care management for inclusion in the final review article.

Research results

This article reviewed the early postoperative critical care management of such patients and the immediate post-surgical complications as reported in the gamut of studies included in the final review.

Research conclusions

CRS-HIPEC is a complex surgery, with a proven postoperative systemic inflammatory response. The focus in recent years has shifted to understanding the immediate postoperative pathophysiology and its management, early detection of complications and the institution of appropriate treatment to reduce morbidity and improve survival. The implementation of ERAS guidelines specific to CRS-HIPEC should help to further reduce postoperative complications.

Research perspectives

There are two major avenues for research in this area. One is the early prediction of postoperative complications and early intervention to reduce morbidity and mortality. Although numerous inflammatory markers such as mean platelet volume, CRP, procalcitonin *etc* have been studied, no single test is foolproof and they should be utilized in association with the clinical scenario, microbiological and biochemical investigations. The second avenue is the implementation of ERAS guidelines for CRS-HIPEC and its impact on postoperative outcomes and survival.

FOOTNOTES

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CORRECTION

Correction to "Retrospective analysis of anti-inflammatory therapies during the first wave of COVID-19 at a community hospital"

Jose I Iglesias, Andrew V Vassallo

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Abstract

Correction to: "Iglesias JI *et al*. Retrospective analysis of anti-inflammatory therapies during the first wave of COVID-19 at a community hospital. *World J Crit Care Med* 2021 Sep 9; 10(5): 244-259. DOI: 10.5492/wjccm.v10.i5.244. PMID: 34616660; PMCID: PMC8462025." In this article, corrections were made to Tables.

Key Words: Corrections; COVID-19; Corticosteroids; Intensive care unit; Methylprednisolone; Tociluzimab; Anti-inflammatory

Core Tip: This manuscript is an author's correction for "Retrospective analysis of anti-inflammatory therapies during the first wave of COVID-19 at a community hospital." *World J Crit Care Med* 2021 Sep 9; 10(5): 244-259. DOI: 10.5492/wjccm.v10.i5.244. PMID: 34616660; PMCID: PMC8462025.

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TO THE EDITOR

Correction to: Iglesias JI, Vassallo AV, Sullivan JB, Elbaga Y, Patel VV, Patel N, Ayad

Table 1 Coronavirus disease 2019 patients admitted to intensive care unit characteristics of survivors and non-survivors

	Non-survivor (*n* = 167)	Survivors (*n* = 94)	*P* value	OR	95%CI
Age	72 (63-82)	65.5 (51-74)	< 0.001		
Race (Caucasian)	125 (74.9)	57 (60.6)	0.016	1.9	1.12-3.3
BMI	29 (23.9, 34.7)	28.6 (24, 33)	0.49		
Sex (male)	102 (61)	56 (60)	0.81	1.065	0.63-1.78
Diabetes	60 (35)	24 (26)	0.08	1.63	0.93-2.8
CHF	24 (15)	10 (11)	0.38	1.42	0.64-3.1
CAD	45 (27)	20 (21)	0.30	1.36	0.74-2.48
COPD	38 (23)	23 (25)	0.75	0.9	0.5-1.64
CKD	25 (15)	13 (14)	0.8	1.09	0.53-2.26
HTN	100 (60)	45 (48)	0.061	1.62	0.97-2.70
AKI	87 (52)	30 (32)	0.002	2.3	1.21-2.5
Mechanical ventilation	134 (80)	44 (47)	< 0.001	4.6	2.64-8
Hemodialysis	29(18)	10 (11)	0.13	1.8	0.83-3.8
Neutrophils × 10^9/L	7.4 (5-11.79)	7.8 4.4-12.9	0.92		
Lymphocytes	0.7 (0.5, 1.2)	0.9 (0.6, 1.6)	0.011		
Neutrophil/lymphocyte	10 (6, 18.5)	7.54 4.3-14.2	0.017		
SCr (mg/dL)	1.2 (0.8-1.8)	1.1 (0.8, 0.8)	0.49		
Plts (× 10^9/L)	202 (166-268)	232 (155-301)	0.27		
Tbili (mg/dl)	0.5 (0.4, 0.8)	0.5 (0.4, 0.8)	0.65		
SOFA admit	4 (3-7)	4 (2, 6)	0.095		
PaO2/FIO2	190 (76, 285)	232 (123, 307)	0.039		
PaO2	69 (55-86)	73 (59-96)	0.083		
FIO2	0.44 (0.24-1)	0.36 (0.21-0.97)	0.12		

OR: Odds ratio; CI: Confidence interval; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; CHF: Congestive heart failure; AKI: Acute kidney injury; HD: Hemodialysis; tBili: Total bilirubin; Plts: Platelets INR: International normalized ratio; PaO2/FiO2: Partial pressure of oxygen/inspired concentration of oxygen ratio; SOFA: Sequential Organ Failure Assessment; BMI: Body mass index; SCr: Serum creatinine.

L, Benson P, Pittiglio M, Gobran E, Clark A, Khan W, Damalas K, Mohan R, Singh SP. Retrospective analysis of anti-inflammatory therapies during the first wave of COVID-19 at a community hospital. *World J Crit Care Med* 2021 Sep 9; 10(5): 244-259. DOI: 10.5492/wjccm.v10.i5.244. PMID: 34616660; PMCID: PMC8462025[1].

In the original manuscript, there are some errors in the table data presented, which need to be modified. The corrected tables are shown as Table 1 (original Table 1) and Table 2 (original Table 4). These errors do not change the ultimate results and conclusion of the paper but have been provided for clarification and overall accuracy.

Patient characteristics are described in Table 1. Univariate predictors of decreased survival included the need for mechanical ventilation, acute kidney injury, Caucasian race, older age, lower total lymphocyte count, higher neutrophil/Lymphocyte ratio, and a greater degree of respiratory failure manifested by a lower PaO2/FIO2 ratio. As anticipated non-survivors demonstrated a higher degree of elevated inflammatory and pro-thrombotic markers, D-Dimer at 24 h (Table 2, Original Table 4).

Table 2 Inflammatory markers in coronavirus disease 2019 survivors and non-survivors

	Non-survivors (*n* = 167)	Survivors (*n* = 94)	*P* value
IL-6 day 1 (pg/mL)	116 (33, 410)	72 (45, 210)	0.75
IL-6 day 2	470 (36, 1299)	153 (10, 280)	0.38
D-Dimer day 1 (ng/mL)	855 (522, 2434)	595 (337, 1349)	0.013
D-Dimer day 2	691 (436, 1743)	1040 (550, 3431)	0.11
CRP day 1 (mg/L)	125 (61, 179)	130 (89, 185)	0.55
CRP day 2	116 (82, 185)	119 (47, 175)	0.29
Ferritin day 1 (ng/mL)	869 (406, 1467)	995 (488, 1571)	0.35
Ferritin day 2	822 (447, 1432)	1053 (712, 2057)	0.05

IL-6: Interleukin 6, CRP: C-reactive protein.

FOOTNOTES

Author contributions: Iglesias JI did the formal analysis; Vassallo AV did the original draft editing and project administration; all authors participate in the manuscript conceptualization, methodology and original draft writing.

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