ISSN 2220-3141 (online)

World Journal of

Critical Care Medicine

World J Crit Care Med 2023 September 9; 12(4): 188-235

Published by Baishideng Publishing Group Inc

World Journal of Critical Care Medicine

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

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL

World Journal of Critical Care Medicine

ISSN

ISSN 2220-3141 (online)

LAUNCH DATE

February 4, 2012

FREQUENCY

Quarterly

EDITORS-IN-CHIEF

Hua-Dong Wang

EDITORIAL BOARD MEMBERS

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

PUBLICATION DATE

September 9, 2023

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https://www.wjgnet.com/bpg/gerinfo/204

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https://www.wjgnet.com/bpg/gerinfo/242

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https://www.wjgnet.com/bpg/GerInfo/239

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World Journal of Critical Care Medicine

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World J Crit Care Med 2023 September 9; 12(4): 188-203

DOI: 10.5492/wjccm.v12.i4.188

ISSN 2220-3141 (online)

MINIREVIEWS

Biomarkers in sepsis-looking for the Holy Grail or chasing a mirage!

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Specialty type: Critical care medicine

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Xie Q, China; Zaninotto M, Italy

Received: March 13, 2023
Peer-review started: March 13, 2023
First decision: April 28, 2023
Revised: May 12, 2023
Accepted: June 12, 2023
Article in press: June 12, 2023
Published online: September 9, 2023

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Abstract

Sepsis is defined as a life-threatening organ dysfunction caused by the dysregulated host response to infection. It is a complex syndrome and is characterized by physiologic, pathologic and biochemical abnormalities in response to an infection. Diagnosis of sepsis is based on history, physical examination and other investigations (including biomarkers) which may help to increase the certainty of diagnosis. Biomarkers have been evaluated in the past for many diseases and have been evaluated for sepsis as well. Biomarkers may find a possible role in diagnosis, prognostication, therapeutic monitoring and anti-microbial stewardship in sepsis. Since the pathophysiology of sepsis is quite complex and is incompletely understood, a single biomarker that may be robust enough to provide all information has not been found as of yet. However, many biomarkers have been studied and some of them have applications at the bedside and guide clinical decision-making. We evaluated the PubMed database to search for sepsis biomarkers for diagnosis, prognosis and possible role in antibiotic escalation and de-escalation. Clinical trials, meta-analyses, systematic reviews and randomized controlled trials were included. Commonly studied biomarkers such as procalcitonin, Soluble urokinase-type plasminogen activator (Supar), presepsin, soluble triggering receptor expressed on myeloid cells 1, interleukin 6, C-reactive protein, *etc*., have been described for their possible applications as biomarkers in septic patients. The sepsis biomarkers are still an area of active research with newer evidence adding to the knowledge base continuously. For patients presenting with sepsis, early diagnosis and prompt resuscitation and early administration of anti-microbials (preferably within 1 h) and source control are desired goals. Biomarkers may help us in the diagnosis, prognosis and therapeutic monitoring of septic patients. The marker redefining our view on sepsis is yet a mirage that clinicians and researchers continue to chase.

Key Words: Sepsis; Sepsis biomarkers; Procalcitonin; Presepsin; Omics

Core Tip: Sepsis is defined as life threatening organ dysfunction caused by a dysregulated host response to infection. Early diagnosis of sepsis and prompt initiation of antimicrobials is essential. Biomarkers may be helpful in early diagnosis, prognostication and monitoring of response to therapy in septic patients. We review commonly used biomarkers such as procalcitonin, presepsin, soluble urokinase plasminogen activator, *etc*., and their utility in clinical practice.

Citation: Ahuja N, Mishra A, Gupta R, Ray S. Biomarkers in sepsis-looking for the Holy Grail or chasing a mirage! *World J Crit Care Med* 2023; 12(4): 188-203
URL: https://www.wjgnet.com/2220-3141/full/v12/i4/188.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i4.188

INTRODUCTION

Sepsis is defined as a life-threatening organ dysfunction caused by the dysregulated host response to infection. It is a complex syndrome and is characterized by physiologic, pathologic and biochemical abnormalities in response to an infection. It is a leading cause of mortality across the world and is a major healthcare concern[1]. Septic shock is a subset of sepsis in which the underlying cellular/metabolic abnormalities are profound enough to increase mortality. These patients are identified with the help of clinical criteria of hypotension requiring vasopressors to maintain a mean blood pressure of more than 65 mmHg and a serum lactate level of more than 2 mmol/L despite adequate fluid resuscitation. Initially, sepsis was defined in 1991 as infection or suspected infection leading to the onset of systemic inflammatory response syndrome (SIRS) where SIRS was defined as the presence of any two out of four criteria-tachycardia (heart rate > 90/min), tachypnoea (respiratory rate > 20 breaths per min), fever or hypothermia (temperature > 38 C or < 36 C), leukocytosis or leukopenia (Total Leukocyte Count > 12000/mm^3 or < 4000/mm^3 or immature forms or bands > 10%. Rudd *et al*[2] have attempted to estimate the global, regional and national incidence of sepsis and associated mortality using the Global Burden of Diseases, Injuries and Risk Factor Study estimates. They estimated an incidence of 48.9 million cases [95% uncertainty interval (UI): 38.9-62.9] of sepsis recorded worldwide in 2017. Almost 11 million (10.1-12) deaths were recorded as related to sepsis which is approximately 19.7% (18.2-21.4%) of all global deaths. In comparison from 1990 to 2017, age-standardized sepsis incidence decreased by 37% (95%UI: 11.8-54.5) and mortality decreased by 52.8% (47.7-57.5). The highest burden of sepsis was estimated to be in sub-Saharan Africa, Oceania, south Asia, East Asia, and Southeast Asia. Markwart *et al*[3] in their study have estimated that around 23.6 % of cases (95%CI: 17%-31.8%, range 16%-36.4%). Among the patients with sepsis associated with organ dysfunction in intensive care unit (ICU), 24.4% (95%CI: 16.7%-34.2%, range 10.3%-42.5%) were acquired during ICU stay while 48.7% (95%CI: 38.3%-59.3%, range 18.7%-69.4%) had a hospital origin. In ICU patients, with hospital-acquired sepsis associated with organ dysfunction, a mortality of 52.3% (95%CI: 43.4%-61.1%, range 30.1%-64.6%). With this huge burden of sepsis worldwide, there is a pressing need for early and accurate diagnosis of sepsis to allow early initiation of therapy.

The pathophysiology of sepsis is complex and is poorly understood. It involves the activation of various pro-inflammatory and anti-inflammatory pathways in response to a pathogen and its effects on the host. These pathways tend to disrupt the metabolomic profile and the identification of these metabolites can be helpful in diagnosis, therapy modification, and prognostication in sepsis patients.

Early recognition of sepsis and prompt management is essential and can help to reduce mortality in such patients. Differentiation of septic patients from other patients with a systemic inflammatory response due to non-infectious causes is difficult. Diagnosis of sepsis is based on history, physical examination and other investigations (including biomarkers) may help to increase the certainty of diagnosis. Early initiation of antibiotics is one of the cornerstones of the management of septic patients. However prudent antimicrobial therapy is required to prevent the emergence of drug-resistant organisms and hence an increased certainty in the diagnosis of sepsis will help to rationalize initiation of anti-microbials and also might help to de-escalate or discontinue them in critically ill patients, thereby reducing the chances of resistance. Biomarkers may serve as an aid for diagnosis, prognosis and therapy modification in septic patients. In the plethora of biomarkers, only a few have been recognized for their diagnostic abilities, but none have marked their presence as the absolute indicator of sepsis diagnosis.

A biological marker or a biomarker is defined as a character that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention. They may be used for diagnosis, staging of disease, prognostication, and for prediction and monitoring of clinical response to therapy. An ideal biomarker for sepsis should have the following characteristics: (1) Early identification of sepsis to initiate timely antibiotics; (2) High specificity to differentiate from noninfective causes of SIRS; (3) Identify bacterial sepsis from other causes of infection; (4) Prognostication of the patient's condition; and (5) Guide antibiotic therapy-escalation and de-escalation of antibiotics

A few biomarkers for sepsis have been described in Table 1. Our review aims to assess the role of biomarkers in diagnosis, prognosis and antibiotic stewardship in septic patients.

Table 1 Biomarkers in sepsis

Biomarker	Description
Procalcitonin	Precursor of hormone calcitonin secreted by C cells of thyroid gland
C-reactive protein	Acute phase protein secreted by hepatocytes in response to pathogen or tissue damage
IL6	A cytokine, mainly produced by macrophages and lymphocytes in response to infection and it can affect the activation of B and T lymphocytes
suPAR	A protein derived from cleavage and release of cell membrane bound urokinase plasminogen activator receptor
sTREM1	Mainly expressed on the surface of polymorphonuclear cells and mature monocytes
Presepsin (sCD14-ST)	sCD14 is cleaved by proteases during inflammation, to form an N terminal fragment-the sCD14 subtype (sCD14-ST)
Adrenomedullin	A 52 amino acid peptide initially isolated from phaeochromocytomas. It is secreted by mammalian tissues and endothelial cells in response to various stimuli such as hypoxia, angiotensin 2, inflammatory cytokine such as TNF-α, IL-1β, *etc.*
Mid regional Proadrenomedullin (MR-proADM)	A peptide secreted by multiple tissues in order to stabilize the microcirculation and protect against endothelial permeability

IL: Interleukin; sTREM1: Soluble triggering receptor expressed on myeloid cells 1; suPAR: Soluble urokinase plasminogen activator receptor; TNF: Tumor necrosis factor.

BIOMARKERS FOR DIAGNOSIS OF SEPSIS

In our review for biomarkers for the diagnosis of sepsis, we searched the PubMed database for sepsis biomarkers for diagnosis and narrowed the search by selecting biomarkers which have been studied in at least 300 patients or had a meta-analysis done with at least 1000 patients. Biomarkers with an area under the receiver operator characteristic curve (AUC) of at least 0.80 were then individually researched and included (Table 2). Few of the biomarkers and their utility in diagnosing sepsis, have been explained in our review.

C-REACTIVE PROTEIN

C-reactive protein (CRP) is an acute phase reactant which rises early in any inflammatory response including sepsis. Though its specificity has been challenged repeatedly, it is still among the most frequently included parameter in clinical studies[4].

PROCALCITONIN

Procalcitonin (PCT) demonstrated better diagnostic accuracy and specificity compared to CRP[5,6]. Alongside CRP, it is the most extensively studied marker and the most common marker against which most other markers have been compared for their diagnostic and prognostic role in sepsis. It is now well established that its levels rise in sepsis. However, the increase in PCT levels is significantly influenced by the type of infection, the site of infection, the severity of the patient's illness and post-operative status and the type of surgery. It increases within 4 h of injection of endotoxin, so it has the potential to recognize Gram-negative sepsis early. Higher procalcitonin levels are seen in Gram-negative bloodstream infections compared to Gram-positive infections and candidemia[7,8].

Patients with Gram-negative bacteremia had higher procalcitonin levels than Gram-positive bacteremia or candidemia [9]. However, Goodlet *et al*[10] found that PCT failed to rule out bacteremia.

In burn patients, PCT has been shown to be effective for early diagnosis of sepsis (AUC: 0.92)[11].

PCT like many other sepsis biomarkers [CRP, interleukin 6 (IL6)] increases in response to surgery in the first 24 h. Major cardiac and abdominal surgeries have been found to have higher PCT values. Unlike CRP, PCT levels rapidly fall and any subsequent rise has been shown to corroborate with post-operative sepsis.

Dong *et al*[12] found in post-cardiac surgery that PCT was able to identify infective SIRS compared to CRP and white blood cell count (WBC) ($P < 0.0001$)[12].

Procalcitonin-based antibiotic initiation failed to show any short-term mortality benefit rather than a delay in antibiotic initiation in sepsis. Procalcitonin-based antibiotic protocol, though, has shown its role in the de-escalation of antibiotics [13]. Hence it is imperative to use procalcitonin within a clinical context rather than as a sole marker for the diagnosis of sepsis.

Table 2 Biomarkers for diagnosis of sepsis

Ref.	Study characteristics		Results and inference			
	Study type	Patient characteristics	Variables	AUC/95%CI	Sensitivity/specificity/PPV/NPV	Inference
Tan *et al* [5], 2019	Meta-Analysis; 9 studies	Pooled data. Total: 1368 patients. Sepsis: 495. Non sepsis: 873	CRP; PCT	0.73 (95%CI: 0.69-0.77), 0.85 (95% CI: 0.82-0.88)	Sensitivity 0.80 (95%CI: 0.63-0.90); spec: 0.61 (95%CI: 0.50-0.72) DOR: 6.89 (95%CI: 3.86-12.31); sensitivity 0.80 (95%CI: 0.69-0.87); specificity: 0.77 (95%CI: 0.60-0.88) DOR: 12.50 (95%CI: 3.65-42.80)	Diagnosis accuracy and specificity of PCT are higher than those of CRP
Thomas-Rüddel *et al*[9], 2018	Randomised control trial, Prospective, Secondary analysis	Gram negative *vs* Gram positive bacteremia and candidemia	PCT (Gram negative bacteremia)	0.72 (95%CI: 0.71-0.74)	Value was 10 ng/mL sensitivity 69%, specificity 35% for Gram negative bacteraemia	Streptococci, *E. coli* and other Enterobacteriaceae detected from BC were associated with three times higher PCT values. Urogenital or abdominal foci of infection were associated with twofold increased PCT
Lai *et al* [7], 2020	Meta-Analysis; 25 studies	GNBSI	CRP	0.85 (0.81–0.87)	Sens: 0.75 (0.56–0.87); Spec: 0.80 (0.68–0.88)	PCT was helpful in recognizing GNBSI, but the test results should be interpreted carefully with knowledge of patients' medical condition and should not serve as the only criterion for GNBSI
			PCT	0.87 (0.84–0.90)	Sens: 0.80 (0.60–0.91); Spec: 0.82 (0.72–0.89)	
			IL6	0.83 (0.80-0.86)	Sens: 0.76 (0.58–0.88); Spec: 0.79 (0.71-0.85)	
Zhao *et al* [29], 2014	Prospective; Observational, single centre	Total: 652; Sepsis: 452; Non sepsis SIRS: 200	PCT	0.803	Sens: 75.2%, Spec: 80.0%, PPV: 89.5%, NPV: 58.8%	Combination of PCT, IL6 and D-dimer enhances the diagnostic ability for sepsis and severe sepsis
			IL6	0.770	Sens: 81.0%, Spec: 61.0%, PPV: 82.4%, NPV: 58.7%	
			D-Dimer	(0.737)	Sens: 79.9%, Spec: 59.0%, PPV: 81.5%, NPV: 56.5%	
			PCT + IL6 + D-Dimer	0.866	Sens: 81.6%, Spec: 73.6%, PPV: 56.0%, NPV: 90.6%	
Kondo *et al*[14], 2019	Meta-Analysis; 19 studies	Adult. Tot: 3012	Presepsin	0.87	Sens: 0.84 (95% 0.80-0.88); Spec: 0.73 (0.61-0.82)	Diagnostic accuracy of procalcitonin and presepsin in detecting infection was similar
			PCT	0.84	Sens: 0.80 (0.75-0.84); spec 0.75 (0.67-0.81)	
Kang *et al* [16], 2019	Adult	Infected trauma: 89; Non infected trauma: 68; Healthy controls: 60	Presepsin	0.853 (0.784-0.922)	321.5 pg/mL; Sens: 67.2%; Spec: 91.9; PPV: 87.5; NPV: 78.2; LR+: 4.89; LR-: 0.39	Presepsin might be a superior biomarker for early differentiation of infection in trauma patients
			PCT	0.771 (0.682-0.859)	0.923 ng/mL; Sens: 61.1%; Spec: 88.2%; PPV: 79.1; NPV: 74.7; LR+: 5.21; LR-: 0.47	
			Presepsin + ISS	0.939 (0.9-0.977)		
Liu *et al* [15], 2013	Prospective, adult consecutive, emergency department	Total: 859; Control: 100; SIRS: 372; Sepsis: 372; Severe sepsis: 210; Septic shock: 98	Presepsin	0.820 (0.784-0.856)	317 pg/mL; Sens: 70.8%; Spec: 85.8%; PPV: 93.2%; NPV: 51.6%; LR+: 4.99; LR-: 0.34	Presepsin is a valuable biomarker for early diagnosis of sepsis. trauma stress elevates PCT, CRP, and WBCs even in the absence of infection
			PCT	0.724 (0.680 to 0.769)	0.25 ng/mL; Sens: 60%; Spec: 77.7%; PPV: 93.2%; NPV: 28.4%; LR+: 2.69; LR-: 0.51	
Cong *et al* [20], 2021	Meta-Analysis	Adult 20 studies	CD 64	0.94 (0.91-0.96)	Sens: 0.88 (0.81-0.92); Spec: 0.88 (0.83-0.91); LR+: 7.2; LR-: 0.14; DOR-51 (25-101)	Neutrophil CD64 test has a high sensitivity and specificity in adult sepsis patients, and was superior to the traditional biomarkers PCT and IL6
			PCT	0.87 (0.83-0.89)	Sens: 0.82 (0.78-0.85); Spec-: 0.78 (0.74-0.82); LR+: 3.7; LR-: 0.23; DOR-16 (11-23)	
			IL6	0.77 (0.73-0.80)	Sens: 0.72 (0.65-0.78); Spec: 0.70 (0.62-0.76); LR+: 2.4; LR-: 0.40; DOR-6 (4-9)	
Gámez-Díaz *et al*	Prospective, cohort	Emergency, total 631 pts; based on	nCD-64	NA	Sens: 65.8% (95%CI: 61.1%-70.3%); Spec: 64.6% (95%CI: 57.8%-70.8%); LR+: 1.85	Patients suspected of having any infection in the ED, the

[25], 2011		expert consensus, Sepsis- 416			(95%CI: 1.52-2.26); LR-: 0.52 (95%CI: 0.44-0.62)	accuracy of nCD64, sTREM1, and HMGB-1 was not significantly sensitive or specific for diagnosis of sepsis
			HMGB-1		Sens: 57.5% (95%CI: 52.7%-62.3%); Spec: 57.8% (95%CI: 51.1%-64.3%); LR+: 1.36 (95%CI: 1.14-1.63); LR-: 0.73 (95%CI: 0.62-0.86)	
			s-TREM-1		Sens: 60% (95%CI: 55.2%-64.7%). Spec: 59.2% (95%CI: 52.5%-65.6%). LR+: 1.47 (95%CI: 1.22-1.76). LR-: 0.67 (95%CI: 0.57-0.79)	
Yeh *et al* [19], 2019	Metaanalysis. 14 studies	Adult, pooled data: Total: 2471; Control: 1167; Sepsis: 1304	Neutrophilic CD 64	0.89 (0.87–0.92)	Sens: 0.87 (0.80-0.92); spec 0.89 (0.82-0.93)	Neutrophil CD64 levels are an excellent biomarker with moderate accuracy outperforming both CRP and PCT determinations
			PCT	0.84 (0.79–0.89)	Sens: 0.76 (0.61-0.86); spec 0.79 (0.70-0.86)	
			CRP	0.84 (0.80–0.88)	Sens: 0.83 (0.78-0.86); spec 0.71 (0.56-0.85)	
Dimoula *et al*[22], 2014	Prospective observational study	548 adult ICU patients. Sepsis: 103; Non sepsis: 445	nCD64	NR	230 MFI. sens: 89% (81%-94%); spec: 87% (83%-90%).	Combining CRP and nCD64 expression, an abnormal result for both was associated with a 92% probability of sepsis, whereas sepsis was ruled out with a probability of 99% if both were normal. In nonseptic patients, an increase in nCD64 expression ≥ 40 MFI predicted ICU-acquired infection (n = 29) with a sensitivity of 88% and specificity of 65%
Wang *et al*[23], 2021	Metaanalysis: 7 articles	Neonatal, paediatric and adults	IL27	0.88 (0.84-0.90)	Sens: 0.85 (95%CI: 0.72-0.93); Spec: 0.72 (95%CI: 0.42-0.90); DOR-15 (95%CI: 3-72)	IL27 is a reliable diagnostic biomarker for sepsis and should be evaluated with other clinical tests
Wong *et al*[24], 2013	Prospective	Adults, infective (n = 145) and non-infective (n = 125) critically ill	IL27	0.68 (0.62-0.75)		IL27 inferior to PCT in sepsis diagnosis
			PCT	0.84 (0.79-0.89)		
Uusitalo-Seppälä *et al*[27], 2012	Prospective cohort	525 adult patients in emergency. Severe sepsis: 49; Sepsis: 302; SIRS: 58. Sirs with no bacterial infection: 53. Bacterial infection no SIRS: 63	PLA(2)GIIA	NA	OR: 1.48 (1.20-1.81, P < 0.001)	Differences in AUC between these parameters were not significant. On multivariate logistic regression analysis only PLA(2)GIIA could differentiate patients with severe sepsis from others (OR: 1.37, 95%CI: 1.05-1.78, P = 0.019
			BPI		OR: 2.66 (1.54-4.60, P = 0.001)	
			CRP		OR: 1.35 (1.02-1.77, P = 0.036)	
			WBC		OR: 2.81 (1.48-5.34, P = 0.002)	
Aksaray *et al*[26], 2016	Prospective	ICU, Adult, Sepsis (52), SIRS (38)	STREM1	0.78 (0.69–0.86)	sTREM1 cut-off value ≥ 133 pg/mL. Sens: 71.1%; Spec: 67.33%; PPV: 80.43; NPV: 65.91	sTREM1, APACHES II higher in patients with positive culture than negative cultures. sTREM1, PCT and CRP levels, or WBC count performed equally to differentiate
			PCT	0.65 (95%CI: 0.53–0.76)	PCT cut-off value of 1.57 ng/mL. Sens: 67.31; Spec: 65.79%; PPV: 72.92; NPV: 70	

AUC: Area under the receiver operator characteristic curve; BPI: Bactericidal/permeability-increasing protein; CRP: C-reactive protein; GNBSI: Gram negative blood stream infection; HMGB: High mobility group box 1; IL: ICU: Intensive care unit; Interleukin; NA: Data not available; NPV: Negative predictive value; NR: Data not reported; OR: Odds ratio; PCT: Procalcitonin; PPV: Positive predictive value; sens: Sensitivity, specificity.

PRESEPSIN (SCD14-ST)

Presepsin is released from monocytes following infection and in a recent meta-analysis, it is as good as procalcitonin for diagnosis of sepsis with an AUC of 0.87 and sensitivity and specificity of 0.84 and 0.73, respectively. The major limitation was the inclusion of only observational studies and no randomized controlled trials (RCTs)[14].

Liu *et al*[15] evaluated 859 patients in a single center presenting in emergency and found that compared to SIRS, patients with sepsis had significantly presepsin values (P < 0.0001). The value increased with the severity of sepsis. Presepsin had significantly higher AUC than PCT in diagnosing sepsis (P < 0.01).

Following trauma; PCT, CRP, and total blood count[15] increase irrespective of infective status, unlike presepsin which was found to be significantly increased in infected trauma cases only[16].

Halıcı *et al*[17] found presepsin to be effective in differentiating chronic obstructive pulmonary disease exacerbation with and without pneumonia[17].

Thus, presepsin has the potential to diagnose sepsis early and also to differentiate sepsis from non-infective SIRS, thereby optimising antibiotic initiation. Further randomised control trials are needed.

SOLUBLE UROKINASE-TYPE PLASMINOGEN ACTIVATOR RECEPTOR

Soluble urokinase-type plasminogen activator receptor (SuPAR) is normally present in blood and various other body fluids and is increased in states of inflammation. In the recent meta-analysis by Huang *et al*[18] SuPAR had a moderate diagnostic ability for sepsis similar to procalcitonin, but was inferior to PCT in differentiating from non-infective SIRS[18].

NEUTROPHILIC CD 64

Neutrophilic CD 64 (NCD64) is a surface receptor on the antigen-presenting cells which increases in response to infections and exposure to endotoxins.

In adult patients, Yeh *et al*[19] and Cong *et al*[20] found NCD64 outperformed procalcitonin, CRP and IL6 for sepsis diagnosis[19,20].

Liu *et al*[21] in their observational study found NCD64 to be significantly increased in bacterial and viral infections compared to fungal infections ($P < 0.0005$), and in DNA virus infections compared to RNA virus infections($P < 0.0071$) [21]. Further studies may be needed to establish its role to distinguish bacteremia.

In critically ill patients, NCD64 when combined with other markers like CRP is useful for diagnosing sepsis, especially when combined with CRP. A normal CRP and NCD64 [cut off 230 mean fluorescence intensity (MFI)] ruled out sepsis with a 99% probability. An increase of ≥ 40 MFI may indicate ICU-acquired infection in a previously non-infected patient as per their results[22].

OTHER BIOMARKERS

Various markers like IL27, Soluble triggering receptor expressed on myeloid cells 1 (sTREM1), and high mobility group box 1 (HMGB-1) failed to perform as diagnostic markers in larger trials[23-26].

Group IIA secretory phospholipase A2 (sPLA2-IIA) in a prospective cohort analysis could differentiate severe sepsis but needs further studies. Bactericidal/permeability-increasing protein in the same study did not show a significant benefit[27].

COMBINATION OF BIOMARKERS

Recent researchers are now also focusing on using a combination of markers with promising results[28]. Novel markers when used with traditional/time-tested clinical tools like neutrophil count, CRP, *etc*. increases the probability of differentiating sepsis from non-infective SIRS and initiates timely management.

PCT when combined with CRP and IL6 significantly increased its diagnostic accuracy for sepsis[29]. NCD64 combined with CRP have shown similar results[22,30].

Timely antibiotic initiation remains the most important factor determining patient survival. At present, most biomarkers act as an aid to clinical judgement and not its replacement in the diagnosis of sepsis and antibiotics administration (Table 3).

BIOMARKERS FOR SEPSIS PROGNOSIS

Apart from diagnosis, biomarkers may also be used for prognostication in septic patients. We searched the PubMed database for biomarkers that have been previously described commonly in the literature. We searched for the biomarker in question in the context of prognosis in septic patients. Only clinical trials, meta-analyses, systematic reviews and randomized controlled trials were included. Some of the biomarkers studied in sepsis patients have been evaluated for prognostication in such patients and results have been promising.

Table 3 Biomarkers for diagnosis of sepsis-current understanding in diagnosis of sepsis

Biomarker	Diagnosis of sepsis	Differentiating sepsis and SIRS	Guiding antibiotic initiation	Organism identification
Procalcitonin	Better than CRP; cannot be used independently; diagnosis based on clinical context	Better than CRP; cannot be used independently; diagnosis based on clinical context	Delays antibiotic administration; No short term mortality benefit	Higher in Gram negative bacteremia than Gram positive. Higher in bacteremia than in candidemia. No defined cutoffs. Treatment to be based on clinical judgement
Presepsin	Possible role	Possible role	No significant data	No significant data
nCD64	Possible role; when combined with CRP, higher diagnostic accuracy and high negative predictive value	No significant data	No significant data	Increased in bacterial and viral infection more than fungal
suPAR	Possible role	Performed poorly	No significant data	No significant data
IL6	Inferior to PCT, CRP	Inferior to PCT, CRP	No significant data	No significant data

CRP: C-reactive protein; IL6: Interleukin 6; PCT: Procalcitonin; SIRS: Systemic inflammatory response syndrome; suPAR: Soluble urokinase plasminogen activator receptor.

PROCALCITONIN

In a meta-analysis conducted by Arora *et al*[31], procalcitonin levels were found to be significantly lower in survivors of sepsis than non-survivors. Another meta-analysis by Patnaik *et al*[32] that had 1974 patients evaluated for procalcitonin clearance had an overall mortality of 37.54%. They concluded that procalcitonin non-clearance can be used as a marker for mortality. However, optimal cutoff points for the same for septic patients in the ICU are unknown. An overall AUC of 0.708 (95%CI: 0.648-0.769) was observed for the same under the random effect model as a result of moderate variation (50.80%) in the studies included. So, procalcitonin clearance could be used as a predictor for mortality and prognostication in septic patients with non-clearance suggesting a higher risk of death (Table 4).

PRESEPSIN

Masson *et al*[33] evaluated presepsin (a soluble CD 14 subtype) and its relation with mortality in patients with septic shock enrolled in the multicenter ALBIOS trial. 997 patients were evaluated and their results showed that baseline presepsin concentrations increased with SOFA score, the number of prevalent organ dysfunction failures, and the incidence of new failures of respiratory, coagulation, liver and kidney systems. A rise in the concentration of presepsin from day 1 to day 2 predicted a significantly higher ICU and 90-d mortality. They concluded that presepsin is an early predictor of host response and mortality in septic patients (Table 5).

ADRENOMEDULLIN (ADM) AND PRO ADRENOMEDULLIN

Adrenomedullin (ADM) and Pro adrenomedullin (proADM) are other markers that could be used for prognostication in septic patients and it is one of the biomarkers that has been evaluated for prognostication in community acquired pneumonia (CAP) patients (apart from IL6). Christ-Crain *et al*[34] have described its prognostic significance in CAP patients and concluded that proADM could be used as a risk stratification marker in patients with CAP. Ortqvist *et al*[35] in their observational trial found that higher IL6 levels were associated with higher mortality and bacterial pneumonia patients had the highest IL6 levels as compared to pneumonia of other aetiologies. Li *et al*[36] evaluated the ability of Adm and proADM for prognosis in septic patients in a meta-analysis and their results showed that increased AM or Pro ADM levels are associated with increased mortality (pooled RR: 3.31; 95%CI: 2.31-4.75) (Table 6).

SuPAR

suPAR has been evaluated in multiple trials and systematic reviews[18] to assess for prognostication in septic patients and has been validated to be a useful prognostic marker in adult septic patients (Table 7).

sTREM1 could also be useful in predicting mortality in septic patients at an initial stage of infection and has also been used for prognostication in neonatal septic patients[37] (Table 8).

Various biomarkers as described above and, in the table, have been evaluated for prognostication in septic patients. Sepsis biomarkers by themselves can provide valuable information for prognostication and in conjunction with organ dysfunction scores and severity scoring systems for critically ill patients, can provide an improved assessment for mortality and prognosticating in such patients. However, costs associated with their use, limited availability and limited knowledge about them are a hindrance in the clinical application of these markers. The optimal cut-off for prediction for

Table 4 Procalcitonin for prognosis of sepsis

Ref.	Type of study	Patient population	Aim	No. of patients/studies	Results	Conclusion of study
Ryu *et al* [52], 2015	Observational	Adults	To compare changes in PCT and CRP concentration in critically ill septic patients to determine which marker better predicts outcome	157 patients; 171 episodes	CPCTc and CRPc are significantly associated with treatment failure (P = 0.027 and P = 0.03 respectively) and marginally significant with 28 d mortality (P = 0.064 and 0.062 respectively). AUC for prediction of treatment success-PCTc-0.71 (95%CI: 0.61-0.81); CRPc-0.71 (95%CI: 0.61-0.81); AUC for survival prediction-PCTc-0.77 (95%CI: 0.66-0.88); CRPc-0.77 (95%CI: 0.67-0.88)	Changes in PCT and CRP concentrations were associated with outcomes of critically ill septic patients. CRP may not be inferior to PCT in predicting outcomes in these patients
Patnaik *et al*[32], 2020	Meta-Analysis	Adults	To evaluate the results of all non-clearance of serial PCT as a mortality predictor	10 studies, 1974 patients	AUC varied between the studies between 0.52 and 0.86. Overall AUC-0.711 (95%CI: 0.662-0.760) under fixed effect model and 0.708 (95%CI: 0.648-0.769) under random effect model. Overall proportion of mortality-37.54%	PCT non clearance is a marker for increased mortality. Optimal cut off points for PCT non clearance in septic patients admitted to ICU are not known
Park *et al* [53], 2013	Observational	Adults	To evaluate the value of PCT in women with APN at ED	240	AUC for predicting 28 d mortality for PCT-0.68. For predicting mortality, a cut off value of 0.42 ng/mL, sensitivity was 80% and specificity was 50%. Disease classification systems were predicted to be superior to PCT in predicting 28 d mortality	By distinguishing the severity of sepsis related to APN mortality, PCT levels help clinicians in disease severity classification and treatment decisions at ED
Oberhoffer *et al*[54], 1999	Observational	Adults	To predict outcome with traditional and new inflammatory markers in septic patients	242	AUC for PCT was 0.878 which was highest as compared to other markers	PCT may be a better marker than other inflammatory markers, CRP, leukocyte count, body temperature to identify patients endangered by severe infection or sepsis
Arora *et al* [31], 2015	Meta-Analysis	Adults	To study the procalcitonin levels in survivors and non survivors of sepsis	25 studies; 2353 patients	Mean difference in procalcitonin levels between survivors and non survivors on day 1 (P = 0.02) and day 3 (P = 0.03) was statistically significant	Significantly lower levels of procalcitonin were observed in survivors as compared to non survivors in early stages of sepsis

APN: Acute pyelonephritis; AUC: Area under the receiver operator characteristic curve; CRP: C-reactive protein; CRPc: Clearance of CRP; PCT: Procalcitonin; PCTc: Clearance of PCT.

prognosis has not been well defined and there is considerable heterogeneity in the literature. Site-specific values of these biomarkers (such as urine, cerebrospinal fluid, *etc*.) have not been adequately studied. Procalcitonin is a biomarker that has been used relatively more frequently in many countries and its non-clearance is associated with a higher mortality. The domain of biomarkers for sepsis prognosis is a promising field and many new biomarkers are expected to be discovered with the use of omics technologies.

ROLE OF BIOMARKERS IN ANTIBIOTIC STEWARDSHIP/DE-ESCALATION

Longer and injudicious use of broad-spectrum antibiotics has been associated with a higher frequency of adverse effects and interference with the microbiome, more treatment costs and the emergence of antibiotic resistance. Ruling out sepsis with certainty and withholding antibiotics, especially in critically ill patients is a challenging task even for a highly experienced physician. Although a shorter treatment course instead of longer has been recommended by the current Surviving Sepsis guidelines, a definitive duration of treatment for different sites and severity of infection has not been clearly defined[38]. CRP and PCT have been studied extensively in the biomarker-based algorithmic approach including antibiotic initiation and discontinuation.

Table 5 Presepsin for prognosis of sepsis

Ref.	Type of study	Patient population	Aim	No. of studies/patients	Results	Conclusion of study
Masson *et al* [33], 2015	Retrospective case control study	Adults	To evaluate the prognostic value of presepsin and comparison with procalcitonin	100	Presepsin levels at day 1 were higher in decedents (2269 pg/mL, median-1171 to 4300 pg/mL) than in survivors (1184 pg/mL, median-875 to 2113 pg/ml); $P = 0.002$) whereas PCT was not different (18.5 mcg/L, median 3.4 to 45.2) and 10.8 mcg/L (2,7 to 41.9 mcg/L) $P = 0.13$). The evolution of presepsin levels over time was significantly different in survivors compared to non survivors (P for time-survival interaction-0.03)	Presepsin showed better prognostic accuracy than procalcitonin in the range of SOFA. (AUC: 0.64-0.75 *vs* AUC: 0.53-0.65)
Behnes *et al* [55], 2014	Prospective cohort study	Adults	Evaluation of diagnostic and prognostic value of presepsin in sepsis and septic shock patients during the 1st wk of ICU treatment	116	AUC- 0.64 TO 0.71; Presepsin cut off values-Sepsis-530 pg/mL; Severe sepsis-600 pg/mL; Septic shock-700 pg/mL	Presepsin has good prognostic value in terms of prognosis for 30 d and 6 mo all cause mortality throughout the 1st wk of ICU stay and its prognostic value for all cause mortality is comparable to that of IL6 and better than that of PCT, CRP or WBC
Yang *et al*[56], 2018	Meta-Analysis	Adults	To evaluate the mortality prediction value of presepsin in septic patients	10 studies; 1617 patients	Initial prespesin levels (within 24 h) were significantly lower in survivors as compared to non survivors. Pooled SMD (standardized mean difference) between survivors and non survivors-0.92 (95%CI: 0.62–1.22)	Some mortality prediction of presepsin; further studies may be needed to define optimal cut off points for presepsin to predict mortality in sepsis
Wang *et al*[57], 2020	Observational	Elderly patients	To investigate the prognostic value of presepsin for elderly septic patients in ICU	142	Presepsin levels were significantly higher in infected patients. Day 3 presepsin levels showed a significant prognostic value for 30 d mortality but was not found to be superior to other biomarkers	Early diagnostic ability comparable to that of PCT; however not a perfect biomarker for prognosis of 30 d mortality in elderly patients
Koh *et al*[58], 2021	Observational	Adults	Estimation of prognostic value of presepsin in septic patients	153	AUC for presepsin- 0.656; Presepsin levels > 1176 pg/mL (odds ratio 3.352, $P < 0.001$) was a risk factor for in hospital mortality	Non survivors had higher presepsin levels; presepsin may have prognostic value
Endo *et al*[59], 2014	Prospective study	Adults	To compare presepsin with other conventional biomarkers (PCT, CRP, IL6) for evaluating the severity of sepsis	103	In patients with unfavorable prognosis: (1) Presepsin levels did not decrease significantly during follow up; (2) Higher duration of antibiotic therapy was used ($P < 0.05$); and (3) Higher 28 day mortality ($P < 0.05$)	Presepsin levels correlated with severity during follow up as compared to other conventional biomarkers
Masson *et al* [33], 2015	Observational	Adults	Evaluating the relationship between presepsin levels and host response, appropriateness of antibiotics, and mortality in severe sepsis patients	997 patients with severe sepsis or septic shock in ALBIOS trial	Baseline Presepsin concentrations increased with SOFA score, number of organ failures, and incidence of new organ failures; An increasing concentration of presepsin from day 1 to day 2 predicted higher ICU ($P < 0.0001$) and 90 d mortality ($P < 0.01$)	Presepsin is an early predictor of host response and mortality in patients with sepsis

AUC: Area under the receiver operator characteristic curve; CRP: C-reactive protein; IL6: Interleukin 6; PCT: Procalcitonin; WBC: White blood cell count.

PROCALCITONIN

Based on the multiple RCTs that evaluated PCT to guide antimicrobial treatment in patients with lower respiratory tract infections (LRTI), the current guidelines by IDSA recommend a shorter treatment course for pneumonia under PCT guidance[39]. The ProHOSP trial conducted at tertiary care hospitals in Switzerland included 1359 patients with severe LRTIs and studied the role of PCT in the initiation and discontinuation of antibiotics. The trial concluded a lower mean duration of antibiotic exposure and less frequent antibiotic-associated adverse effects in the PCT group as compared to the control group [standard of care (SOC)] within 30 d from the time of presentation[40].

Table 6 Adrenomedullin and pro adrenomedullin for prognosis of sepsis

Ref.	Type of study	Patient population	Aim	No. of patients	Results	Conclusion of study
Christ-Crain *et al*[34], 2006	Prospective observational	Adult patients with CAP	To evaluate the value of Pro ADM levels for severity assessment and outcome prediction in CAP	302	Pro ADM levels (as compared to CRP and leukocyte count) increased with increasing severity of CAP (calculated through PSI score). Pro ADM levels at admission significantly higher 2.1 (1.5 to 3) nmol/L compared to survivors 1 (0.6 to 1.6) nmol/L; P < 0.001. AUC for proADM was 0.76 (95%CI: 0.71–0.81)-significantly higher than PCT, CRP, TLC	Pro ADM is a useful biomarker for risk stratification in patients with CAP
Charles *et al*[60], 2017	Prospective cohort	Adults	To assess the prognostic value of PCT, MR pro ADM, copeptin and CT proendothelin1 concentrations	173	Day 1 MR-ProADM levels significantly higher in non survivors [8.6 (5.9) *vs* 4.4 (3.9)] nmol/L; P < 0.0001	Day 1 MR-ProADM is a good predictor of short term clinical outcome as compared with others
Li *et al* [36], 2018	Meta-Analysis	Adults	To evaluate the ability of adrenomedullin and Pro Adm to predict mortality in septic patients	13 studies; 2556 patients	Increased AM or Pro ADM levels are associated with increased mortality (pooled RR = 3.31; 95%CI: 2.31-4.75); AUC 0.8 (95%CI: 0.77-0.84)	AM and Pro ADM may be used as prognostic markers in sepsis
Chen and Li [61], 2013	Observational	Adults	To evaluate the prognostic value of adrenomedullin in septic patients and compare it with PCT and MEDS	837	Mean levels (at admission of AM were 28.66 ± 6.05 ng/L in 100 healthy controls, 31.65 ± 6.47 ng/L in 153 systemic inflammatory response syndrome patients, 33.24 ± 8.59 ng/L in 376 sepsis patients, 34.81 ± 8.33 ng/L in 210 severe sepsis patients, and 45.15 ± 9.87 ng/L in 98 septic shock patients. The differences between the 2 groups were significant. ADM levels significantly higher in non survivors; AUC for in hospital mortality-AM-0.773; PCT-0.701; MEDS-0.721	Adrenomedullin is valuable prognostic biomarker for septic patients in ED
Caironi *et al*[62], 2017	Observational	Adults	To evaluate the role of Bio ADM	956	Plasma bio ADM (day 1) was higher in and associated with higher 90 d mortality, multi organ failures, extent of haemodynamic support and serum lactate time course over the 1st wk. Bio ADM trajectory during the 1st wk of treatment predicted 90 d mortality; Reduction to levels below 110 pg/ml at day 7 was associated with reduction in 90 d mortality	Bio ADM levels may help individualize haemodynamic support therapy in septic patients
Elke *et al* [63], 2018	Secondary analysis of RCT	Adults	To evaluate role of MR Pro Adm compared to conventional biomarkers (PCT, CRP, lactate) and clinical scores to identify disease severity in sepsis	1089	MR Pro Adm had strongest association with mortality and high disease severity; A decreasing concentration of PCT by ≥ 20 % from baseline to day 1 or ≥ 50 % from baseline to day 4 but a persisting high level of Pro Adm had significantly increased mortality risk [HR (95%CI)-19 (8-45.9) and 43.1 (10.1-184)]	MR Pro Adm assesses disease severity and treatment response more accurately than conventional biomarkers and scores

AM: Adrenomedullin; AUC: Area under the receiver operator characteristic curve; Bio ADM: Bio adrenomedullin; CAP: Community acquired pneumonia; CRP: C-reactive protein; MEDS: Mortality in Emergency Department Score; MR pro ADM: Mid Regional Pro adrenomedullin; PCT: Procalcitonin; Pro ADM: Pro adrenomedullin; PSI: Pneumonia severity Index; TLC: Total leukocyte count.

The PRORATA trial, which was a large trial conducted on 630 critically ill patients with a suspected bacterial infection in France aimed at studying the effectiveness of a procalcitonin-based algorithm to decrease antibiotic exposure. The algorithm included initiation of antibiotic if serum PCT was ≥ 0.5 ng/mL and continuation until the serial measurements showed levels less than 0.5 ng/mL or reduction by at least 80% of the baseline value. The trial results showed a statistically significant decrease in the duration of antibiotic treatment from 11.6 d in the PCT group to 14.3 d in the control arm (P < 0.0001). The rate of relapse and re-infection were comparable between the two arms but a trend towards higher mortality in the PCT group at 60 d[41]. On similar grounds, the SAPS trial was designed to study the discontinuation of antibiotic protocol based on serial PCT measurements. The results were similar to the PRORATA trial with a significant reduction in antibiotic exposure days in the PCT group [5 d *vs* 7 d in the SOC (P < 0.0001)]. However, in contrast to the PRORATA trial, the SAPS trial also found a reduction in 28-d (19.6% *vs* 25%, P = 0.0122) and 1-year mortality (34.8% *vs* 40.9%, P = 0.0158)[42].

CRP

A systematic review and meta-analysis published by Petel *et al*[43] evaluated the efficacy of CRP in septic patients. Based

Table 7 Soluble urokinase plasminogen activator receptor for prognosis of sepsis

Ref.	Type of study	Patient population	Aim	No. of patients	Results	Conclusion of study
Backes *et al*[64], 2012	Systematic review	Adults	To assess the usefulness of suPAR levels in critically ill patients with sepsis, SIRS, bacteraemia, focusing (diagnostic and prognostic value)	10 studies	Little diagnostic value in critically ill septic patients. Superior prognostic value in such patients as compared to other markers. Improved mortality prediction by combining suPAR with other markers or disease severity classifications. suPAR levels correlate positively with markers of organ dysfunction and severity of disease classification system scores	suPAR has a low diagnostic value for septic patients. It may add to prognostication with other markers and organ dysfunction scores
Huang *et al*[18], 2020	Systematic review	Adults	To evaluate the value of suPAR for diagnosis and prognosis of sepsis	30 studies, 6906 patients	Pooled sensitivity and specifity for predicting mortality-0.74 (95%CI: 0.67-0.8) and 0.7 (95%CI: 0.63-0.76) with AUC of 0.78 (95%CI: 0.74-0.82)	suPAR is a good maker for prognostication of sepsis
Pregernig *et al*[65], 2019	Meta-Analysis	Adults	To assess the prognostic value of suPAR and 6 other biomarkers in predicting mortality in adult septic patients	28 studies included	Pooled mean differences in marker concentrations (survivors-non survivors) at onset of sepsis for suPAR-5.2 ng/mL; 95%CI: 4.5-6; $P < 0.01$)	suPAR can provide prognostication information about mortality in adult septic patients
Ni *et al* [66], 2016	Meta-Analysis	Adults	To evaluate the usefulness of suPAR for diagnosis and prognosis of bacterial infections	17 studies included	High suPAR levels were related with a significantly increased risk of death with a pooled risk ratio of 3.37 (95%CI: 2.6-4.38). Pooled sensitivity and specificity for predicting mortality were 0.7 and 0.72 respectively, with AUC of 0.77	suPAR can be used for prognosis of bacterial infection

AUC: Area under the receiver operator characteristic curve; SIRS: Systemic inflammatory response syndrome; suPAR: Soluble urokinase plasminogen activator receptor.

Table 8 Soluble triggering receptor expressed on myeloid cells 1 for prognosis of sepsis

Ref.	Type of study	Patient population	Aim	No. of patients/studies	Results	Conclusion of study
Su *et al* [67], 2016	Systematic review	Adults	To determine prognostic value of sTREM1 in predicting mortality at the initial stage of infection	9 studies	High sTREM1 level was associated with higher risk of death in infection, with pooled RR 2.54 (95%CI: 0.61-0.86) using a random effects model; Pooled sensitivity and specificity of sTREM1 to predict mortality in infection were 0.75 (95%CI: 0.61-0.86) and 0.66 (95%CI: 0.54-0.75), respectively	Higher sTREM1 levels had a moderate prognostic significance in assessing the mortality of infection in adult patients; however sTREM1 alone is not sufficient to predict mortality as a marker
Su *et al* [68], 2012	Observational	Adults	To study the association of sepsis prognosis with dynamic changes in sTREM1 and its polymorphisms	160	sTREM1 levels were significantly raised in non survivors than in survivors ($P < 0.001$); Logistic regression showed that sTREM1, APACHE 2, and rs2234237 polymorphisms are risk factors for prognosis	Dynamic changes in sTREM1 and rs2234237 polymorphism could be used for prognostication in septic patients
Wang *et al* [69], 2011	Observational	Adults	To observe dynamic changes in plasma sTREM1 levels and to study its effect on predicting outcome of septic patients combined with SOFA score	57	Non survivors-sTREM1 levels were highest on Day 1 and a gradual elevation was seen over days 1, 3 and 7). Survivor-sTREM levels were highest on day 1 and then showed a gradual reduction over days 1, 3 and 7. sTREM levels were significantly higher in non survivors as compared to survivors ($P < 0.01$)	High plasma levels of sTREM1 are detected at initial stages in septic patients and sTREM1 level combined with SOFA score may be helpful in predicting outcomes in septic patients

RR: Risk ratio; sTREM1: Soluble triggering receptor expressed on myeloid cells 1.

on the results of this analysis, the CRP cut-off recommended for antibiotic discontinuation was < 10 mg/L for neonatal sepsis. The majority of the studies on adults included patients with respiratory tract infection and cut-offs used were similar, with most of them withholding antibiotics if CRP was < 20 mg/L and initiating or continuing the use of CRP was > 100 mg/L. The physician's discretion was followed for CRP values between 20 mg/L and 100 mg/L. The meta-analysis

concluded that CRP based algorithmic approach reduced the rate of antibiotic initiation with no significant differences in mortality, infection relapse and hospitalization rates[43].

A recent trial conducted in the critical care unit of a university hospital in Brazil by Borges *et al*[44] compared the days of antibiotic therapy between a CRP-guided protocol and an evidence-based judicious use strategy (not using the marker). The decision of antibiotic discontinuation in the intervention arm was based on serial CRP measurements (if CRP < 35 mg/dL or decrease to decrease ≥ 50%). The trial illustrated the efficacy of the CRP-based strategy in reducing the median duration of antibiotic use by 1 day for the index infection episode [6 (5-8) d in the CRP arm *vs* 7 (7-10) d in the control arm; $P = 0.011$]. However, despite such promising results, no significant differences were found in terms of antibiotic-free days and survival outcomes between the two arms[44].

Another multicenter RCT, including patients with Gram-negative bacteremia with randomization in a 1:1:1 ratio, compared an individualized CRP-guided antibiotic treatment (Duration based on the decrease in CRP levels ≥ 75% from its peak along with the absence of fever for 48 h) with a fixed 7-d and 14-d therapy. The primary outcomes of this trial in terms of incidence of clinical failure occurred in 2.4% of patients in the CRP arm, 6.6% in the 7-d arm, and 5.5% in the 14-d arm (difference in CRP *vs* 14-d arm was -3.1%; $P < 0.001$). The median duration of antibiotic therapy in the CRP-guided group was 7 d. The findings of this study hence concluded that antibiotic duration should not be predefined in the initial phase of illness and use of a biomarker-guided approach may prevent prolonged antibiotic exposure without increasing the failure rates[45].

Considering the results of these trials and meta-analysis, it may be inferred that CRP-guided protocolized therapy allows a lower antibiotic exposure and comparable rates of infection relapse and mortality with the control group.

NEWER BIOMARKERS WITH A ROLE IN ANTIBIOTIC STEWARDSHIP

Presepsin

Presepsin is a soluble form of CD14 that takes part in pathogen recognition by innate immunity. Masson *et al*[33] analyzed a subset of data from the ALBIOS trial and studied the relation between the circulating presepsin levels, the host response and mortality in patients with severe sepsis. The study concluded a direct correlation between a rise in presepsin concentration and a rise in SOFA score and the number of organ failures. Baseline levels of presepsin were found to be higher in patients who subsequently tested positive for bacterial infection (particularly with Gram-negative sepsis). The levels declined gradually in patients with negative cultures and appropriate antibiotic therapy[33]. Xiao *et al* [46], published a trial recently, comparing presepsin guidance to SOC in sepsis. In the intervention group, antibiotics were discontinued at serum presepsin concentration of < 350 pg/mL or a decline of more than 80% from baseline. Despite more antibiotic-free days in the presepsin group, there was no significant difference in mortality between the two arms [46]. These findings suggest a potential role of this biomarker in guiding antibiotic escalation and de-escalation strategies.

IL-1β and IL-18

The VAPrapid2 trial published in 2020 was the first trial to use biomarkers (IL-1β and IL-18 from the bronchoalveolar lavage fluid) to improve antibiotic stewardship by the early exclusion of infection in patients with suspected ventilator-associated pneumonia (VAP). Although the trial illustrated the efficacy of studied biomarkers (IL-1β and IL-18) in accurately excluding VAP, it could not achieve the endpoint of showing any statistically significant difference in the number of antibiotic-free days. Certain factors such as reluctance to BAL and non-adherence to the discontinuation protocol by treating clinicians could have contributed to the lack of difference in antibiotic duration between the intervention and control groups[47].

OMICS (GENOMICS, TRANSCRIPTOMICS, PROTEOMICS AND METABOLOMICS) IN SEPSIS

The host inflammatory response leads to the generation of by-products or metabolites and these have been used as the traditional biomarkers in sepsis. However, omics technology, including genomics, transcriptomics, proteomics and metabolomics are referred to as the systematic measurement at the level of DNA, RNA, protein and metabolite levels and the omics technology has resulted in the delineation of newer biomarkers in sepsis and sub-phenotyping in sepsis patients. We will explain omics in sepsis in a nutshell as a more comprehensive detail of omics in sepsis is beyond the scope of this review.

Genomics is the study of the genome to explain physiological or pathological processes. Variable response and susceptibility of individual patients to infection are different because of genetic factors. Genomics can be used to determine genetic polymorphisms and epigenetic markers that may be used as bioindicators in septic patients. Single Nucleotide Polymorphism (SNP) are a common type of genetic polymorphism and SNP genotyping of various genes may provide important information relevant to sepsis.

Tightly regulated gene expression leads to the regulation of pro and anti-inflammatory responses in septic patients and gene expression study forms the basis of transcriptomics. Micro RNAs (miRNAs) are short RNAs of 18 to 25 nucleotides that regulate gene expression in target mRNA. miRNA profiling of leukocytes and plasma in septic patients may be used to detect molecules that may be used as biomarkers. Similarly, long non-coding (involved in epigenetic control of gene expression) may be useful to detect diagnostic and therapeutic classes of biomarkers.

All sets of proteins expressed by an organism constitute a proteome and proteomics is the study of the expression, localization, function and interaction of the proteome. Proteomics may thus provide the basis for determining newer biomarkers in sepsis[48].

Metabolomics was defined way back in the 1990s and defines techniques aimed at measuring metabolites present within a cell, tissue or organism. The underlying principle in genetics describes the flow of information from DNA through mRNA transcripts and the subsequent translation of it into proteins. These proteins take part in tightly controlled metabolic pathways. Metabolome is the terminal downstream product of the genome and consists of all the low molecular weight molecules (metabolites) in a cell, tissue or organism required for growth, maintenance, or normal function in a specific physiological state. These metabolites generate the phenotype in an organism and these can be detected and measured to provide information about the particular process in question[49]. The pathophysiological pathways of sepsis may lead to inflammatory and anti-inflammatory metabolites being produced and identification of these metabolic products can help to detect sepsis early, and may also help to assess treatment response and estimate recovery[50].

Su *et al*[51] identified metabolic biomarkers that can be useful to differentiate sepsis from SIRS. They assessed 65 patients (35 patients with sepsis, 15 patients with SIRS, and 15 normal individuals). They used liquid chromatography-mass spectrometry to analyze metabolites in serum samples. They reported significantly lower levels of lactitol dehydrate and S-phenyl-D cysteine and increased S-(3-methylbutanoyl)-dihydrolipamide-E and N-nonanoyl glycine in septic patients as compared to SIRS patients. Patients with severe sepsis and septic shock had low glyceryl-phosphoryl-ethanolamine, Ne, Ne dimethyllysine, phenylacetamide and D-cysteine ($P < 0.05$) in serum. S-(3-methylbutanoyl)-dihydrolipoamide-E, phosphatidylglycerol (22:2 (13Z,16Z)/0:0), glycerlophosphocholine and S-succinyl glutathione were significantly lower ($P < 0.05$) in serum (collected 48 h before death) of patients who died. These metabolites are reflective of the ongoing metabolome during sepsis and may be used to diagnose sepsis and estimate severity and mortality. However, larger studies are needed for validation.

CONCLUSION

Sepsis and septic shock are life-threatening conditions requiring prompt resuscitation and antibiotic administration. The sepsis biomarkers are still an area of active research with newer evidence adding to the knowledge base continuously. Sepsis is the result of a complex interplay of various pathways. A single biological marker may not be an answer for diagnosis, prognostication, follow up and guide to antibiotic escalation/de-escalation in sepsis. Regardless, understanding these sepsis biomarkers and their role in the sepsis pathway can help to further rationalize sepsis management alongside clinical judgement. Early targets for sepsis treatment would be to administer anti-microbials within 1 h of presentation and source control as early as possible. The 2021 surviving sepsis campaign guidelines suggest against using procalcitonin and clinical judgement to start initial antibiotic *vs* clinical judgement alone as waiting for procalcitonin may delay antibiotic administration. However, it is suggested to use procalcitonin in addition to clinical evaluation as compared to clinical evaluation alone to discontinue antimicrobials in patients with septic shock with adequate source control. The values of the biomarkers (like procalcitonin, Supar, nCD64, presepsin, *etc*.) may help guide the therapy by differentiating noninfective SIRS from infective SIRS. A combination of biomarkers has been found to increase their diagnostic accuracy.

The marker redefining our view on sepsis is yet a mirage that clinicians and researchers continue to chase. Many have become redundant and many more are still in the running to prove their worth. "Omics" (including genomics, transcriptomics, proteomics and metabolomics) will lead to the discovery of newer biomarkers and their applications in diagnosis, prognosis and therapeutic monitoring are going to increase.

FOOTNOTES

Author contributions: All the authors were equally involved in the designing, research methodology, data collection and writing of the manuscript.

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

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Corresponding Author's Membership in Professional Societies: Indian Society of Critical Care Medicine, No. 07-R/276.

S-Editor: Fan JR

L-Editor: Filipodia

P-Editor: Cai YX

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World Journal of Critical Care Medicine

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World J Crit Care Med 2023 September 9; 12(4): 204-216

DOI: 10.5492/wjccm.v12.i4.204

ISSN 2220-3141 (online)

MINIREVIEWS

Should we initiate vasopressors earlier in patients with septic shock: A mini systemic review

Hang-Xiang Zhou, Chun-Fu Yang, He-Yan Wang, Yin Teng, Hang-Yong He

Specialty type: Critical care medicine

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Bittner EA, United States; Karim HMR, India; Shelat VG, Singapore

Received: March 20, 2023
Peer-review started: March 20, 2023
First decision: June 14, 2023
Revised: June 28, 2023
Accepted: July 17, 2023
Article in press: July 17, 2023
Published online: September 9, 2023

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Abstract

Septic shock treatment remains a major challenge for intensive care units, despite the recent prominent advances in both management and outcomes. Vasopressors serve as a cornerstone of septic shock therapy, but there is still controversy over the timing of administration. Specifically, it remains unclear whether vasopressors should be used early in the course of treatment. Here, we provide a systematic review of the literature on the timing of vasopressor administration. Research was systematically identified through PubMed, Embase and Cochrane searching according to PRISMA guidelines. Fourteen studies met the eligibility criteria and were included in the review. The pathophysiological basis for early vasopressor use was classified, with the exploration on indications for the early administration of mono-vasopressors or their combination with vasopressin or angiotensinII. We

found that mortality was 28.1%-47.7% in the early vasopressors group, and 33.6%-54.5% in the control group. We also investigated the issue of vasopressor responsiveness. Furthermore, we acknowledged the subsequent challenge of administration of high-dose norepinephrine *via* peripheral veins with early vasopressor use. Based on the literature review, we propose a possible protocol for the early initiation of vasopressors in septic shock resuscitation.

Key Words: Septic shock; Resuscitation; Vasopressor; Norepinephrine; Vasopressin; Timing

Core tip: It remains unclear whether vasopressors should be used early in the course of treatment of septic shock. Here, we provide a systematic review of the literature on the timing of vasopressor administration. The pathophysiological basis for early vasopressors use was classified, with the exploration on indications for the early administration of mono-vasopressors or their combination with vasopressin or angiotensinII. We also investigated the issue of vasopressor responsiveness and the subsequent challenge of administrating high-dose norepinephrine *via* the peripheral vein with early vasopressor use. Based on the literature review, we propose a possible protocol for the early initiation of vasopressors in septic shock resuscitation.

Citation: Zhou HX, Yang CF, Wang HY, Teng Y, He HY. Should we initiate vasopressors earlier in patients with septic shock: A mini systemic review. *World J Crit Care Med* 2023; 12(4): 204-216
URL: https://www.wjgnet.com/2220-3141/full/v12/i4/204.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i4.204

INTRODUCTION

Sepsis and septic shock are still considered a major challenge in healthcare, associated with significant morbidity and mortality[1-3]. Septic shock is the most severe form, and considered one of the most prominent challenges in critical care medicine, characterized by persistent hypotension and the presence of tissue hypoperfusion, with a mortality of 28.6%[4-6].

The primary therapies to resuscitate septic shock are to hold the systemic blood pressure and promote the regional and microcirculatory perfusion. According to the Surviving Sepsis Campaign (SCC) guidelines, it is recommended to increase blood pressure with intravenous fluids and vasopressors, and fluid resuscitation without vasopressors is not recommended until a lack of hypotension correction is confirmed. However, recent studies have proposed that early initiation of vasopressors such as norepinephrine with fluid loading may allow for early resolve of hypotension by reaching the target arterial pressure[7]. Therefore, the timing of vasopressor therapy is speculated to be crucial to optimize the outcomes of septic shock patients[8]. Furthermore, adding other vasopressors such as vasopressin and angiotensinII to norepinephrine may decrease the norepinephrine dosage by raising arterial pressure[9-12]. Recent studies have also been focused on whether an early initiation of vasopressin or angiotensinII to norepinephrine as a combined therapy could lead to a better outcome in septic shock patients compared to norepinephrine monotherapy[13,14].

Here, we conducted a systematic review of the available evidence regarding the physiological and clinical effects of early initiation of single or combined vasopressors during septic shock treatment in adults, aiming to provide evidence on optimal timing and protocol for vasopressors administration during septic shock resuscitation.

RATIONALE FOR EARLY INITIATION OF VASOPRESSORS IN SEPTIC SHOCK

An early administration of vasopressors may exert several potential beneficial effects in septic shock. According to clinical and experimental studies, several possible mechanisms may support the idea to initiate vasopressors early in septic shock, mainly focused on perfusion improvement, blood flow increase and fluid overload prevention.

Early vasopressors can improve perfusion in septic shock

The early initiation of vasopressors could reduce the time of insufficient perfusion caused by hypotension. Previous studies have suggested a relation of risks for mortality and acute kidney injury with a long duration and a high severity of hypotension in septic patients[15-17]. As a result, the earlier administration of vasopressor, the quicker relief of the hypotension, and the shorter duration of organ hypoperfusion, thus achieving a better outcome[16].

Early initiation of vasopressor therapy raises the mean arterial pressure (MAP) to a contributing level to facilitate tissue perfusion and prevent the onset or progression of organ dysfunction[18]. It is widely recognized that organs require a critical MAP to allow an adequate perfusion. When the MAP is maintained below to organ's critical perfusion pressure, organ injury may occur[19].

Early initiation of vasopressors may promote the microcirculatory perfusion in septic shock[20-23]. Traditionally, the administration of vasopressors at the early phase of septic shock is concerned to potentially lead to the worsened microcirculation through excessive vasoconstriction of precapillary microvessels[24]. However, if the MAP is below the threshold of autoregulation of organ blood flow, severe hypotension can theoretically worsen organ hypoperfusion. When norepinephrine is added to fluid infusion on the basis of a low diastolic pressure, the increased MAP with norepinephrine significantly increases the tissue oxygen saturation (StO_2) recovery slope[22]. The StO_2 recovery slope reflects the capacity that microvessels are recruited in response to local hypoxia, as well as serving as a prognostic factor in septic shock patients. Furthermore, restoring arterial pressure with norepinephrine could significantly improve the microvascular reactivity during ischemia-reperfusion in severely hypotensive septic patients[22,25].

Early initiation of vasopressors modifies the coronary artery perfusion in septic patients by maintaining a proper diastolic arterial pressure[26]. Diastolic arterial pressure refers to the upstream pressure for the perfusion of the left ventricle. Indeed, the left ventricle is perfused only during the diastole, unlike the right ventricle during the whole cardiac cycle. Therefore, the low diastolic arterial pressure, as frequently the case in early septic shock due to arterial tone depression, induces an increased risk of myocardial ischemia[26]. Early regain of a target diastolic blood pressure could be recommended for patients with unstable coronary artery disease or chronic pulmonary hypertension at risk of low coronary perfusion pressure[27].

Early vasopressors can increase blood flow in septic shock

Vasopressors can allow a higher blood flow by enlarging the stroke volume and cardiac output in the early stage of septic shock[28]. In a study covering 105 patients with severely hypotensive septic shock, early administration of norepinephrine achieved an increase in stroke volume and cardiac output, which were revealed by an elevation of cardiac preload and systemic venous return in patients with preload responsiveness, through the α1-adrenergic-mediated effects of norepinephrine[23,29].

Early initiation of vasopressors increases organ blood flow and improves blood flow distribution. The improvement in MAP by norepinephrine was associated with maintenance of aortic and mesenteric blood flow, achieving a better tissue oxygenation compared with fluid alone[30]. Norepinephrine may optimize the distribution of blood flow to the mesenteric region with an earlier administration[31].

Early vasopressors can prevent fluid overload during resuscitation in septic shock

Early initiation of vasopressors was related to the decreased infused fluid volume. Two recent studies have demonstrated it in association with less fluid treatment volumes and the improved outcomes[32,33], and multiple studies have shown that large amounts of resuscitation fluids and positive cumulative fluid balance have correlation to the increased mortality in sepsis[32,34-38], and the increased incidence of pulmonary edema[39].

Early administration of vasopressors induces endogenous fluid recruitment by promoting venous return[40]. Vasodilation results in reduced mean systemic filling pressure, thus limiting venous return during septic shock. Vasopressors raise blood pressure through increased systemic vascular resistance. The venoconstrictive effect also contributes to increasing the venous return through mobilizing non-stress volume to stress volume[41,42]. Administration of vasopressors can therefore simulate a fluid bolus through endogenous fluid recruitment[29].

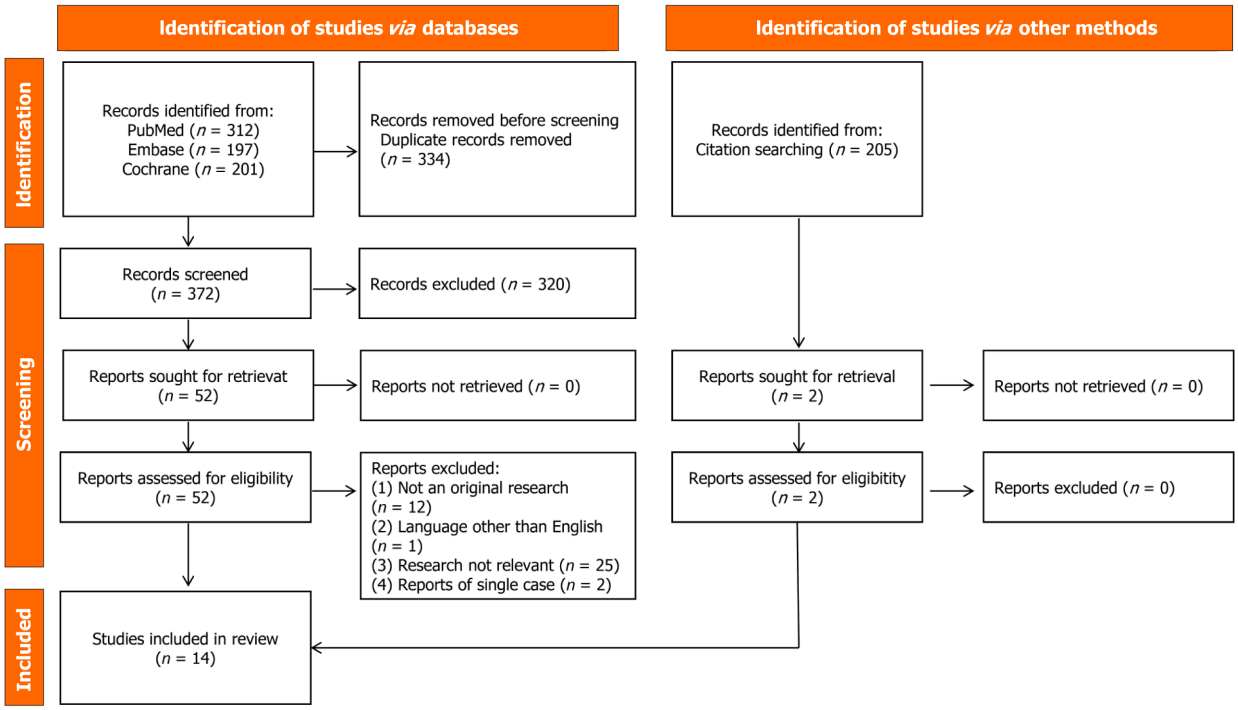
Early administration of vasopressors can diminish the capillary permeability by inhibiting inflammation. In one experiment, norepinephrine prominently reduced the endothelial permeability resulting from agonists of multiple Toll-like receptors *in vitro*, suggesting that both β1- and β2-adrenergic receptors mediate the stabilizing effects of norepinephrine on the endothelial barrier[43].

EVIDENCE THAT SUPPORTS EARLY INITIATION OF VASOPRESSORS: SYSTEMIC REVIEW OF CLINICAL STUDIES

Literature search

In accordance with the 2020 guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, www.prisma-statement.org/PRISMAStatement), a systematic review was conducted. Pubmed, Medline, Embase, and Cochrane database from 2012 to September 28, 2022 were searched using the following search terms: ("early"[All Fields] OR "Time Factors"[MeSH Terms] OR ("timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields]) OR "delay*"[All Fields]) AND ("vasopressor*"[All Fields] OR ("noradrenalines"[All Fields] OR "norepinephrin"[All Fields] OR "norepinephrine"[MeSH Terms] OR "norepinephrine"[All Fields] OR "noradrenalin"[All Fields] OR "noradrenaline"[All Fields] OR "norepinephrines"[All Fields]) OR "vasopressin*"[All Fields] OR "Vasoconstrictor Agents"[MeSH Terms]) AND "shock, septic"[MeSH Terms]).The search was slightly adjusted to different databases. We also reviewed the references listed in the identified articles, which were manually searched for the related articles to identify all relevant and eligible articles and to minimize publication bias.

Two researchers independently screened and evaluated the eligibility of all studies, and a third reviewer intervened if a disagreement emerged. Original research reports of septic shock patients, and studies in which patients were treated with vasopressors early were enrolled. The exclusion criteria were: (1) Languages other than English; (2) study protocols, review articles, abstracts, and editorials; (3) research on children or animals; and (4) case reports. The flow chart of the search strategies is depicted in Figure 1.



DOI: 10.5492/wjccm.v12.i4.204

Figure 1 The PRISMA flow diagram of literature search, screen, and selection criteria.

The primary outcome assessed was mortality, while the other endpoints included shock control rate, time to achieve target MAP, incidence of organ failure and lactate clearance rate.

Study characteristics

The characteristics of the included trials are summarized in Tables 1 and 2. A total of 14 studies were included in this systematic review, including three randomized controlled trials (RCTs) and 11 observational studies, covering 11327 patients. The 14 studies were conducted in the USA (*n* = 5), Canada (*n* = 1), China (*n* = 1), Thailand (*n* = 1), Egypt (*n* = 1), Colombia (*n* = 1), Korea (*n* = 1), France (*n* = 1), and two were international studies.

Definition of early initiation of vasopressors in septic shock: There were two definitions for early initiation of vasopressors in septic shock used in previous studies.

First, in most studies, early initiation was defined as the initiation of a vasopressor such as norepinephrine during the early stage of hypotension or shock onset as a mono-vasopressor therapy, and at the same time (< 1 h) or even before administration of loading fluid in three studies. Initiation of vasopressors after a short time (within 2, 3or 6 h) of hypotension or shock onset was used in other studies. Three studies defined the early start of vasopressors at an average of 30 or 90 min after emergency room arrival or even before hospital. The studies above were summarized in Table 1.

Second, in other recent studies, early initiation stood for early addition of a second vasopressor such as vasopressin or angiotensinII to the first-line norepinephrine as multi-vasopressor therapy in severe septic shock (Table 2).

Major outcomes and findings of studies for early administration of single vasopressors in septic shock: Mortality was 28.1%–47.7% in the early group and 33.6%–54.5% in the control group. In five studies, norepinephrine was used as a first-line vasopressor early in septic shock. The 28–30-day mortality and hospital survival were reported as the primary outcome in six and two studies, respectively. Lower mortality was reported in the early vasopressor group in seven studies. Other findings for early vasopressor initiation associated with lower occurrence of organ failure were reported in two studies; shorter time to MAP achievement in three studies; better lactate clearance in four studies; lower volume of fluid use in two studies; and less norepinephrine use (shorter duration or lower dose) in two studies (Table 1).

Major outcomes and findings of studies for early administration of a second vasopressor as a combination therapy in septic shock: A total of five studies involved vasopressin or angiotensinII as an early second vasopressor for catecholamine-resistant septic shock. In three studies, vasopressin was added at 4–6 h after addition of norepinephrine or one type of catecholamine. In two other studies, angiotensinII was added when the dose of norepinephrine reached >0.2 μg/kg/min. A lower mortality was reported in the angiotensinII group in one study. Three studies reported that early administration of the second vasopressor for septic shock contributed to achieving the target MAP (Table 2).

Table 1 Basic characteristics of studies on early initiation of vasopressors included in the systematic review

No.	Ref.	Study design and period	No.of patients/early/late group	Agents	Time 0	Definition for early initiation	Primary outcome reported	Primary outcome	Other points	Comments
1	Beck *et al* [31], 2014, Canada	Multicenter, retrospective cohort study 1996-2008	6514/-/-	NE, Dopamine, Phenyleph-rine, VP, Epinephrine			Survival to hospital discharge	A weak correlation between vasopressor delay and hospital mortality (adjusted OR 1.02/h, $P < 0.001$)	The significance was found between the delay to vasopressor initiation (> 14 h post hypotension) and the occurrence of organ failure	1 Markedly delayed initiation of vasopressor (> 14 h after hypotension) in septic shock patients is associated with a small increase in mortality risk. 2 Delays in vasopressor initiation is only weakly associated with mortality, while delays in antimicrobial is more higher
2	Bai *et al* [61], 2014, China	Two centers, retrospective cohort study, Jan. 2011-Dec. 2012	213/86/127	NE	Septic shock onset	NE administered within 2 h after onset of septic shock	28 d mortality	The early group was lower than the late group, 29.1% *vs* 43.3%, $P < 0.001$	1 Duration of NE was significantly shorter in the early-NE group (2.6 ± 0.6 d *vs* 2.9 ± 1.0 d, $P = 0.001$). 2 Serum lactate levels at 2, 4, 6 and 8 h after septic shock onset were significantly lower in the early-NE group ($P < 0.05$)	1 Early administration (within 2 h after the septic shock onset) of NE in septic shock patients is associated with an increased survival rate. 2 Early NE initiation can increase MAP, shorten the duration of hypotension and, improve vital organ perfusion and decrease serum lactate levels
3	Permpikul *et al*[39], 2019, Thailand	Single center, RCT, Oct. 2013-Mar. 2017	310/155/155	NE	ED arrival	Median time from emergency room arrival to NE administration was 93 min	Shock control rate	Early NE adminis-tration resulted in significant higher shock control rate than standard treatment, 76.1% *vs* 48.8%, $P < 0.001$	1 Achievement of target MAP (> 65 mmHg), urine output (> 0.5 mL/kg) and lactate clearance (> 10%) were all significantly higher in the early-NE group (all $P < 0.05$). 2 There was no difference between groups for the rates of mechanical ventilator support or RRT. 3 patients in the early-NE group had a lower rate of cardiogenic pulmonary edema (14.4% *vs* 27.7%, $P = 0.004$) and new-onset arrhythmia (11% *vs* 20%, $P = 0.03$)	This study confirms that the early use of NE, can enable septic shock patients to benefit in short-term endpoints, such as shock control rate, urine output and lactate clearance, represented both macro- and micro-circulation restoration
4	Colon *et al* [62], 2019, United States	Single center, retrospective cohort study Jan. 2017-Jul. 2017	119/76/43	Vasopress-ors	Initial hypotension	Received vasopressor within 6 h from initial hypotension	30 d mortality	Vasopressor initiation after 6 h from shock onset is associated with a significant increase in 30 d mortality, 25% *vs* 51.1%, $P < 0.01$	1 Logistic regression analysis: adminis-tration of vasopressors after 6 h from hypotension were independently associated with increased 30 d mortality. 2 The time to target MAP was shorter in the early vasopressor group (1.5 h *vs* 3 h, $P < 0.01$)	1 Demonstrates that there is a mortality benefit with early use of vasopressor. 2 Early adminis-tration of vasopressor in septic shock patients (< 6 h from initial hypotension) is associated with decreased mortality, that is likely secondary to faster achievement of MAP goals
5	Elbouhy *et*	Single center,	101/57/44	NE	ED admission	NE infusion started	In-hospital	Early NE in septic	1 MAP of 65 mmHg was achieved after 2 h	1 They found that early use of

	al[63], 2019, Egypt	RCT Jan. 2017-Dec. 2018				after 25 (20-30) min from ED admission, simultaneous administration of crystalloid fluids	survival	shock improved in-hospital survival, 71.9% *vs* 45.5%, P = 0.007	in the early group compared to 3 h in the late group (P = 0.003). 2 Post-resuscitation serum lactate level was 2 mmol/L in the early group and 2.9 mmol/L in the late group (P = 0.037). 3 Acute kidney injury developed in 24 of the early group (42%) compared to 23 of the late group (52%) (P = 0.3). 4 Patients in the early group were resuscitated by significantly lower volume of fluids, 25 mL/kg compared to 32.5 mL/kg in the late group (P = 0.000). 5 The in-hospital survival rate in the early group was 71.9% compared to 45.5% in the late group (P = 0.007)	NE initiated simultaneously with fluids was associated with earlier achievement of target MAP, earlier lactate clearance with earlier achievement of lactate < 2 mmoL/L and consequently higher in-hospital survival. 2 The significantly lower volume required for fluids resuscitationin the early-NE than in the late-NE group
6	Ospina-Tascón *et al* [64], 2020, Colombia	Single center, prospective cohort study, Jan.2015-Feb.2017	186/93/93	NE, VP	First resuscitative fluid load	Vasopressor support initiated within the next hour or even before the first fluid load with resuscitative intention (FRLoad)	Association between early vasopressor and 28 d mortality	Early vasopressor was associated with a significant reduction in the risk of death compared to delayed vasopressor (HR 0.31, 95%CI 0.17-0.57, P < 0.001) at day 28	1 Patients in the early vasopressor group received less resuscitation fluids in the first 8 h of resuscitation (P < 0.001). 2 There were no significant differences regarding the maximal dose of NE, steroids and VP use, or requirement of RRT. 3 No cases of severe digital or severe vasopressor-induced splanchnic ischemia were documented	1 Early vasopressor support is associated with less use of resuscitation fluids, less fluid accumulation, and shortening of hypotension time. 2 Early vasopressor was not associated with increased kidney injury or ischemia-related adverse effects, and it might decrease mortality in patients with septic shock
7	Yeo *et al* [65], 2021, Korean	Multicenter, prospective observational study Sep. 2019-Feb. 2020	298/149/149	NE, VP, epinephrine, dopamine	First resuscitative fluid load	Vasopressor was initiated within 1 h of the first resuscitative fluid load	28 d mortality	Vasopressor initiation within 1 h was associated with higher 28 d mortality, 47.7% *vs* 33.6%, P = 0.013	1 Volume of fluid given within the initial 6 h was significantly lower in the early group (P = 0.046). 2 The total SOFA score on day 3 in ICU was significantly lower in the late group than that in the early group (P = 0.045). Lactate levels were significantly lower on day 3 in the late group than that in the early group (P = 0.014)	1 Use of a vasopressor within 1 h of the first fluid loading was related to higher mortality in patients with septic shock. 2 Less fluid was administered to the early group, but inadequate fluid resuscitation exhibited worse organ function and lactate clearance 3 d after septic shock onset
8	Jouffroy *et al*[50], 2022, France	Multicenter, retrospective study, Apr. 2016-Dec. 2020	478/143/335	NE	Prehospital	Patients with prehospital NE administration (early NE)	30 d mortality	Prehospital NE infusion (early NE) is associated with a decrease in 30 d mortality	N/A	A strength of this study is that NE administration is started within 1 h after septic shock onset and before the completion of the fluid resuscitation
9	Xu *et al*[7], 2022, United States	Single center, retrospective observational cohort study 2008-2019	2862/1431/1431	NE	Septic shock onset	Receiving NE within the first 3 h	28 d mortality	Early group had lower 28 d mortality, 30.0% *vs* 37.8%, P < 0.001	Patients in the early-NE initiation group had a significantly shorter duration of ICU and hospital stay, shorter duration of supportive NE and invasive mechanical ventilation, lower incidence of acute kidney injury, and lower proportion of organ failure progression than patients in the delayed NE initiation group	NE initiation within the first 3 h, regardless of preload dependency, was associated with longer survival time and shorter duration of supportive NE and invasive mechanical ventilation and may delay or partially reverse rapid onset organ failure

Sum	USA 2, other countries 1	2 RCTs	11081/2190/2377	NE 5	Shock onset 3, ED arrival 2, First fluid 2, Prehospital 1	Within 2, 3 and 6 h after shock, Within 0, 0.5, 1 h of fluid start, Prehospital	28 d mortality 4 and 30 d mortality 2 hospital survival 2	Mortality was lower in early group in 7 studies; mortality in early group was 28.1%-47.7%, in control group was 33.6%-54.5%

ED: Emergency department; MAP: Mean arterial pressure; NE: Norepinephrine; RRT: Renal replacement therapy; SOFA: Sequential organ failure assessment; ICU:Intensive care unit; VP: Vasopressin; N/A: Not applicable.

MARKERS PREDICTING OR SUGGESTING VASOPRESSOR RESPONSIVENESS

A key point is which markers or indexes could provide a clue for selecting the most appropriate population from septic shock patients who could mostly benefit from an early initiation of vasopressors. Several potential markers predicting vasopressor requirements were proposed in previous studies, such as diastolic arterial blood pressure[26,44] and dynamic elastance to identify early initiation of norepinephrine in first-line mono-vasopressor therapy. The kinetics of norepinephrine dose increment, and serum lactate and rennin levels were used to identify the timing for early administration of vasopressin or angiotensinII based on a norepinephrine multi-vasopressor therapy.

Norepinephrine responsiveness predictors

Diastolic arterial pressure: Physiologically, a low diastolic arterial pressure can result from depression of arterial tone, bradycardia, or arterial stiffness. In case of tachycardia, diastolic arterial pressure < 40 mmHg strongly suggests a markedly depressed arterial tone and the requirement to prompt initiation of a vasopressor[24]. Therefore, a low diastolic arterial pressure could serve as a simple indicator to identify patients requiring norepinephrine urgently at the early stage of septic shock[26].

Dynamic arterial elastance: Dynamic arterial elastance (Ea_{dyn}) is defined as the pulse pressure variation/stroke volume variation ratio. Arterial pressure in a hypotensive patient is increased, if Ea_{dyn} is high and the cardiac output is increased. In contrast, low Ea_{dyn} does not elicit a proportionally increased arterial pressure despite the increased cardiac output in response to volume challenge. In such hypotensive cases, the addition of vasopressors should be considered to correct hypotension. Ea_{dyn} has been demonstrated to be superior to diastolic arterial pressure as a marker of early initiation of vasopressors in septic shock patients[45].

Vasopressin responsiveness predictors

Norepinephrine-equivalent dose: Norepinephrine-equivalent dose may serve as an easily accessible marker to utilize with a consideration of an early vasopressin initiation before doses higher than 10–15 μg/min (0.1–0.2 μg/kg/min in a patient weighing 80 kg)[14].

Norepinephrine dose escalating kinetics: Clinically, two dose-requirement profiles, refractory and controlled, can be observed at the patient's bedside. A refractory profile meets the requirements of exposure to an exponential increase in norepinephrine dose, and a controlled profile with a gradual increase in norepinephrine dose to a plateau does not reach toxic levels of norepinephrine. In the refractory profile, the earlier vasopressin is started, the greater the chance of avoiding norepinephrine surge and exposure to harmful norepinephrine doses. In the controlled profile, it may not be

Table 2 Basic characteristics of studies on early combination with another vasopressor included in the systematic review

No.	Ref.	Study design and period	No. of patients	Agents	Time 0	Definition for early combination	Primary outcome reported	Primary outcome	Other points	Comments
1	Reardon *et al* [56], 2014, United States	Single center, retrospective study Jan. 2010-Dec. 2011	71, 35 (early)/36 (late)	VP	Catecholamine initiation	VP was initiated within 6 h of catecholamine therapy	Impact of VP on catecholamine dose and duration	No difference in dose and duration of catecholamine or VP therapy between the 2 groups	1 There was a significant difference in incidence of new-onset arrhythmias between the early VP and late groups (P < 0.001). 2 There was a trend toward worsening troponin T and CK-MB in the late VP group	1 Early VP therapy was associated with no difference in total catecholamine requirements but decreased incidence of new-onset arrhythmias. 2 There was also a trend toward improvement in cardiac biomarkers in the early VP group
2	Hammond *et al*[11], 2018, United States	Single center, prospective trial Nov. 2015-Jun. 2016	82, 41 (VP)/41 (NE)	VP	NE initiation	VP was initiated within 4 h of NE	Time to target MAP	Early VP to NE achieved target MAP faster than those receiving initial NE alone (P = 0.058)	-	Early concomitant VP and NE achieved and maintained a target MAP faster than initial NE alone, particularly in those in whom absolute or relative VP deficiency is suspected or confirmed
3	Hammond *et al*[13], 2019, United States	Single center, retrospective cohort study, May 2014-Oct. 2015	93, 48 (VP)/48 (NE)	VP	NE initiation	VP was initiated within 4 h of NE	Time to target MAP	Early VP to NE achieved target MAP sooner than later or no initiation (P = 0.023)	1 Changes in SOFA at 76 h since septic shock onset, the early VP saw a significant decrease of 4 compared to a decrease of 1 for NE alone (P = 0.012). 2 Early VP were discharged from the hospital 10 d sooner than those in the NE alone (14.3 *vs* 25.2 d, P = 0.014). 3 Incidence and duration of RRT were comparable between groups (17% *vs* 25% and 6.7 *vs* 11.2 d, respectively)	Early VP in combination with NE achieved a target MAP faster than the NE alone and may be more likely to resolve organ dysfunction at 72 h, although the in-hospital and 28-d mortalities were similar between groups, patients who survived benefited from earlier achievement and maintenance of goal MAP
4	Khanna *et al* [66], 2017, International	Multicenter, RCT May. 2015-Jan 2017	321/163/158	ATII	NE initiation	> 0.2 μg/kg/min of NE	Response to MAP at 3 h	More patients in the ATII response to MAP at 3 h (69.9% *vs* 23.4%, P < 0.001)	1 At 48 h, mean doses of background vasopressors were consistently less in the AT II group. 2 At 48 h, the mean improvement in the cardiovascular SOFA score was greater in the ATII group (-1.75 *vs* -1.28, P = 0.01). 3 No difference between the two groups for serious adverse reactions. 4 No difference between the two groups for 28 d mortality	1 Demonstrates the safety and efficacy of widespread clinical use of ATII. 2 ATII reduces the need for catecholamines in patients with catecholamine-resistant vasodilatory shock (CRVS), while reducing the cardiovascular injury it causes
5	Bellomo *et al* [49], 2020, International	Multicenter, Retrospective study	255/127 (low)/119 (high)	ATII	NE initiation	> 0.2 μg/kg/min of NE	Renin kinetic changes and their prognostic value in CRVS	In patients with higher renin concentrations, ATII significantly reduced 28-d mortality compared with placebo (P = 0.012)	1 Baseline serum renin concentration was above the upper limits of normal in 194 of 255 (76%) patients with a median renin concentration of 172.7 pg/mL. 2 At 3 h after initiation of ATII therapy, there was a 54.3% reduction in renin compared with a 14.1% reduction with placebo (P < 0.0001)	Serum renin concentrations are significantly higher in CRVS and may identify patients in whom early combination with ATII has a beneficial effect on clinical outcome
Sum	United States 3, International 2	RCT 1, Retrospective study 3	822, 414/402	VP 3, ATII 2	Vasopressors initiation 5	Within 4, 6 h of catecholamine, > 0.2 μg/kg/min of NE	Time to target MAP 2	1 VP, Achieved target MAP faster 2, No difference 1. 2 ATII response to MAP 1		

	reduced mortality 1

ATII: Angiotensin-II; CRVS: Catecholamine-resistant vasodilatory shock; MAP: Mean arterial pressure; NE: Norepinephrine; RRT: Renal replacement therapy; SOFA: Sequential organ failure assessment; VP: Vasopressin.

necessary to add vasopressin at the norepinephrine threshold of 0.5 μg/kg/min[46].

Angiotesin-II responsiveness predictors

It appears that a subgroup of patients with an impaired endogenous renin-angiotensin system[47] exhibit a pronounced response to angiotensinII and may derive benefits from earlier administration. Therefore, due to the robust relationship between hyper-reninemia and favorable angiotensinII response, renin is rapidly emerging as a promising prognosticator for the early initiation of angiotensinII in septic shock[14,48]. Bellomo *et al*[49] investigated the role of angiotensinII in patients with catecholamine-resistant vasodilatory shock and revealed the high renin levels in most of these patients (76%). Using a cutoff of 173 pg/mL, angiotensinII administration improved mortality in the subset of patients with high renin levels, suggesting that measurement of renin levels may contribute to identifying patients who might benefit from angiotensinII therapy. Median renin level of 173 pg/mL in the study cannot be directly applied in clinical practice; therefore, further prospective trials are required to confirm these findings.

POSSIBLE ADVERSE EFFECTS OF EARLY INITIATION OF VASOPRESSORS

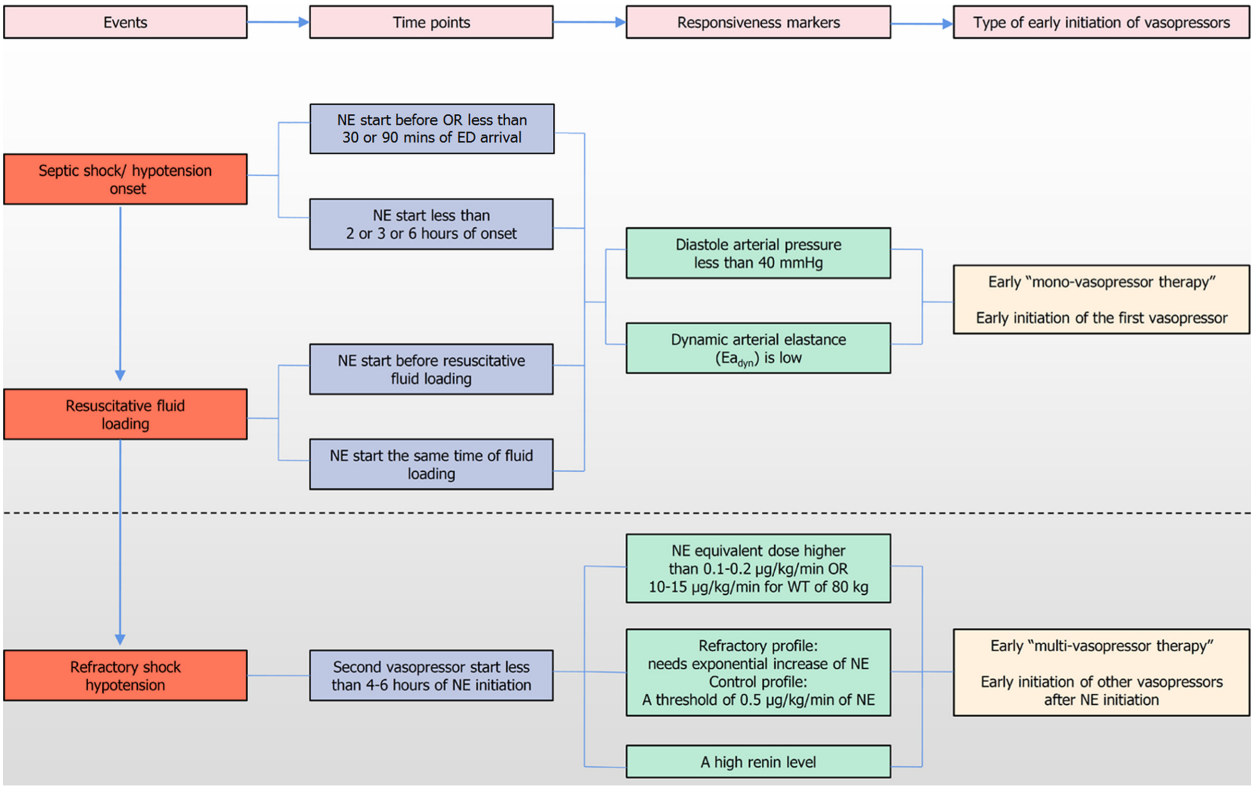
Feasibility and safety of peripheral infusion of high concentration of norepinephrine

The application of high concentrations of norepinephrine *via* the peripheral vein is considered an option for the early administration of vasopressors in patients with septic shock who meet the indications. Considering the strong vasoconstriction due to norepinephrine, the most appropriate approach is to administer the drug in intensive care units (ICUs) after placing a central venous catheter. However, if the timing of norepinephrine administration is advanced to admission to ICUs, emergency departments, or even prehospital[50], central venous catheter placement may not be generally feasible.

A previous study[51] has systematically reviewed the literature on the peripheral infusion of norepinephrine and noted that the available data failed to reveal a correlation between the occurrence of adverse events and the application of peripheral vein access. The administration of norepinephrine through the peripheral vein requires knowledge of concentration, dose, duration, and infusion site. In a study by Nguyen *et al*[52], the concentration of norepinephrine administered *via* the peripheral vein was 64 μg/mL, and the median dose as 10 μg/min, which was considered to be a high dose; the anterior elbow/external jugular vein was considered the site of infusion, with a median duration of infusion of 62 min; and the incidence of adverse events was 4.5%.

Myocardial ischemia in septic shock with early initiation of vasopressors

Septic shock is complicated by myocardial ischemia, which exacerbates diastolic shock symptoms such as tachycardia and hypotension. Norepinephrine can be administered after adequate fluid resuscitation. An RCT[53] comparing the efficacy of norepinephrine and epinephrine in patients with diastolic shock complicated by acute myocardial infarction revealed no significant difference in cardiac index. It does, however, show a notable disparity in heart rate; epinephrine



DOI: 10.5492/wjccm.v12.i4.204

Figure 2 A possible protocol for early administration of vasopressors in septic shock patients. During septic shock resuscitation, although not mentioned in the protocol, volume status and responsiveness should be assessed repeatedly and titrated crystalloids. NE: Norepinephrine.

results in a faster heart rate, which is particularly unfavorable for patients with myocardial ischemia. Additionally, dobutamine also elevates heart rate and directly contributes to increased morbidity and mortality[54], and should be avoided in these patients. An RCT[55] also compared early use of vasopressin *versus* norepinephrine, revealing a higher incidence of life-threatening arrhythmia in the norepinephrine group (0.98% *vs* 2.5%), and a higher incidence of acute coronary syndrome in the vasopressin group (3.4% *vs* 1.0%). These findings suggest that patients with coronary artery disease may benefit from avoiding vasopressin, while those with tachyarrhythmia may consider early co-administration of this drug. In contrast, Reardon *et al*[56] found a trend toward improvement in cardiac biomarkers in the early vasopressin group; however, no specific etiology was identified and the research was limited to a single-center retrospective analysis.

POSSIBLE PROTOCOL FOR CONSIDERING EARLY INITIATION OF VASOPRESSORS IN SEPTIC SHOCK

A possible protocol for early administration of vasopressors in septic shock patients is depicted in Figure 2, based on the literature reviewed above.

The timing of vasopressor initiation was the primary focus of our protocol, control of the source of infection in sepsis, use of albumin, and early steroid use are not included in the figure. However, four prominent RCTs investigated the administration of corticosteroids in patients with septic shock, but they yielded contradictory results. The enrollment time across the four studies was from 8 h[57] to 24 h[58,59] and 72 h[60]. Two trials demonstrated that early addition of corticosteroids to vasopressors significantly reduced all-cause mortality among patients with septic shock. Additionally, it is noteworthy that the majority of these trials initiated hydrocortisone administration concurrently with norepinephrine at a dose range of 0.5-1 μg/kg/min. The Surviving Sepsis Campaign guidelines recommend administering intravenous corticosteroids to septic shock patients who require ongoing vasopressor therapy, commencing as early as 4 h after the initiation of vasopressors and at a minimum norepinephrine dose of 0.25 μg/kg/min.

Control of the source of infection should be required as an emergency intervention as soon as a specific anatomical diagnosis of infection is identified. Early albumin infusion also should be considered when patients receive large volumes of crystalloids.

CONCLUSION

In septic shock, early initiation of vasopressors may exert several potential beneficial effects. Several mechanisms support

initiation of vasopressors early in septic shock, mainly focused on perfusion improvement, blood flow enlargement and fluid overload prevention. Clinical evidence has suggested possible benefits of early initiation of single or combined vasopressors in the resuscitation of septic shock. Several potential markers predicting vasopressor requirements were mentioned. Diastolic arterial blood pressure and dynamic elastance indicated early initiation of norepinephrine in first-line mono-vasopressor therapy. Kinetics of norepinephrine dose increment, serum lactate and rennin levels were applied to identify the timing of early initiation of vasopressin or angiotensin II based on norepinephrine multi-vasopressor therapy. Administration of high concentrations of norepinephrine *via* the peripheral vein is considered an option for the early administration of vasopressors in patients with septic shock.

FOOTNOTES

Author contributions: Zhou HX, Yang CF, and Wang HY drafted the manuscript; Teng Y and He HY designed and reviewed the manuscript, and revised it for critical intellectual content; all authors have read and approved the final version.

Conflict-of-interest statement: All authors declare that they have no competing interests.

Country/Territory of origin: China

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S-Editor: Liu JH
L-Editor: Kerr C
P-Editor: Zhang YL

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World J Crit Care Med 2023 September 9; 12(4): 217-225

DOI: 10.5492/wjccm.v12.i4.217

ISSN 2220-3141 (online)

MINIREVIEWS

Improving environmental sustainability of intensive care units: A mini-review

Kay Choong See

Specialty type: Critical care medicine

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Juneja D, India; Kvolik S, Croatia

Received: April 24, 2023
Peer-review started: April 24, 2023
First decision: July 4, 2023
Revised: July 8, 2023
Accepted: July 17, 2023
Article in press: July 17, 2023
Published online: September 9, 2023

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Abstract

The carbon footprint of healthcare is significantly impacted by intensive care units, which has implications for climate change and planetary health. Considering this, it is crucial to implement widespread efforts to promote environmental sustainability in these units. A literature search for publications relevant to environmental sustainability of intensive care units was done using PubMed. This mini-review seeks to equip intensive care unit practitioners and managers with the knowledge necessary to measure and mitigate the carbon cost of healthcare for critically ill patients. It will also provide an overview of the current progress in this field and its future direction.

Key Words: Carbon footprint; Critical care; Global warming; Greenhouse effect; Greenhouse gases; Plastics

Core Tip: To achieve environmental sustainability in the intensive care unit (ICU), healthcare professionals must have the knowledge and tools to measure and mitigate the carbon cost of healthcare for critically ill patients. Two complementary methods have been used in the ICU to measure the environmental cost of critical care: Life cycle assessment and material flow analysis. Various methods can decrease waste generation in the healthcare industry, such as preventing the progression of illnesses and inpatient admissions, avoiding unnecessary ICU admissions, minimizing overdiagnosis and over-investigation, and curtailing overtreatment. Interventions can also focus on reducing energy consumption and reusing/recycling products.

Citation: See KC. Improving environmental sustainability of intensive care units: A mini-review. *World J Crit Care Med* 2023; 12(4): 217-225
URL: https://www.wjgnet.com/2220-3141/full/v12/i4/217.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i4.217

INTRODUCTION

Slowing down the harmful effects of climate change and improving planetary health are crucial for humankind[1]. Sustainability involves protecting ecosystems and staying within planetary boundaries[2], which are limits that, if exceeded, could lead to catastrophic environmental changes. One of these boundaries relates to climate change and is measured by atmospheric carbon dioxide concentration, with a threshold of 350 ppm proposed, which has already been exceeded[2]. This highlights an urgent need to reduce greenhouse gas emissions.

It is important for healthcare professionals to promote environmental sustainability, with intensive care units (ICUs) being in a unique position to implement solutions due to their intersection with healthcare and high resource use for critically ill patients. For instance, a life cycle assessment conducted in a United States hospital showed that compared to acute care units, an ICU generates 1.3 times more solid waste (7.1 kg *vs* 5.5 kg) and 3.1 times more greenhouse gases [138 kg *vs* 45 kg CO2-equivalents (CO2e)] per bed day[3]. The major contributors to emissions were consumable goods, building energy consumption, capital equipment purchases, food services, and staff travel.

While ICU staff may be familiar with the need for environmental sustainability, the ability to implement improvements requires knowledge regarding measuring and mitigating the carbon cost of healthcare for critically ill patients. To equip ICU practitioners and managers with such knowledge, this mini-review was therefore done to provide an overview of the current progress in this field and its future direction.

METHODS

An updated search on 8 July 2023 of PubMed® (pubmed.ncbi.nlm.nih.gov) using the search term ("environmental sustainability" OR "ecological sustainability" OR "planetary health" OR "waste recycling" OR "recyclable waste" OR "climate change" OR "climate action" OR "carbon footprint" OR "carbon cost" OR "environmental footprint" OR "life cycle assessment" OR "life cycle analysis" OR “plastic waste”) AND ("ICU" OR "intensive care" OR "critical care") yielded 269 publications. This search was done to update the author's personal library of articles. When they were relevant to environmental sustainability of ICUs, articles were included in this narrative review.

IMPACT OF THE ENVIRONMENT ON HEALTH

The burning of fossil fuels results in the release of greenhouse gases, which include carbon dioxide, methane, and nitrous oxides, as well as particulate matter and sulphur dioxides. The accumulation of these gases in the atmosphere contributes to global warming, which is estimated to cause a rise in temperature of 1 degree Celsius per decade. This increase in temperature can lead to heat-related injuries, dehydration, renal dysfunction, skin cancer, mental health issues, pregnancy complications, allergies, cardiorespiratory illnesses, and an elevated risk of death from cardiovascular causes such as ischemic heart disease, stroke, and heart failure[4]. Additionally, there may be changes in vector-related diseases, rising sea levels, and an increase in wildfires[5,6]. Regions that experience warmer climates such as central and south America, central and south Europe, and southeast Asia may experience an increase in mortality[7]. Burning fossil fuels also generate particulate matter, which further damage the respiratory system, worsen respiratory and cardiovascular diseases, have various non-cardiorespiratory health effects, and increase the number of excess deaths[8].

Plastics, which are widely used in healthcare, are derived from fossil fuels and their extraction, refining, and manufacturing processes contribute to greenhouse gas emissions and global warming. In addition to their impact on global warming, plastics can also harm human health through the presence of microplastics. These are tiny plastic particles with a diameter of less than 5 mm, which can be synthetic or formed from the natural breakdown of larger plastic pieces. Microplastics can be found in air, water, and soil, and can enter plants and animals, including humans, where they have been found in the lungs, blood, stool, and placenta[9]. Per- and polyfluoroalkyl substances (PFAS) are a type of plastic material that is resistant to water, oil, and fire and are commonly used in a wide range of products, including containers, wrapping, and personal protective equipment. However, these chemicals are long-lasting and can accumulate in the blood, brain, liver, and kidneys, leading to adverse health effects. PFAS exposure has been linked to decreased antibody response, dyslipidaemia, decreased growth in infants and foetuses, neurotoxicity in developing brains, and an increased risk of kidney and breast cancer[10,11]. These chemicals are poorly excreted from the body and can persist for years or decades.

IMPACT OF HEALTHCARE ON PLANETARY HEALTH

Health systems are responsible for 1%-5% of the world's carbon footprint[12]. Within health systems, there are several sources of carbon emissions within the ICU. For instance, in patients receiving treatment for septic shock, a carbon footprint evaluation conducted in two ICUs located in Australia and the United States found that energy consumption related to heating, ventilation, and air conditioning accounted for 76%-87% of the carbon footprint, while the use of single-use materials and other consumables were less significant contributors[13].

On a related note, the use of plastics in healthcare has a significant negative impact on the environment, as it contributes to various harmful effects at different stages of the plastic life cycle[11]. These include the extraction of coal, oil, and gas, which are the primary raw materials for plastic production, the energy-intensive manufacturing process, and the inefficient disposal methods, which involve landfilling, controlled burning, and uncontrolled incineration. The use of single-use plastic products, which now make up 35%-40% of plastic production, has contributed to the growing plastic use trend. However, the global recovery and recycling rates for plastics are below 10%, which exacerbates the harmful effects of plastic waste. Plastic production is estimated to be responsible for 3.7% of global greenhouse gas emissions, and this figure is projected to increase to 4.5% by 2060 if no action is taken to curb plastic use.

MEASURING THE ENVIRONMENTAL COST OF HEALTHCARE

Two complementary methods have been used in the ICU to measure the environmental cost of critical care: life cycle assessment (LCA)[13] and more recently, material flow analysis (MFA)[14]. An LCA involves analysing the environmental impact of products or processes, at every stage of a product or process life cycle[13]. This life cycle includes natural resource extraction, manufacturing, packaging, transport, use/reuse, and recycling/waste disposal. In other words, an LCA is a scientific approach that evaluates the environmental impact of a product or process from the beginning of its life cycle to its disposal.

Two main types of LCAs are relevant to healthcare, namely process-based LCAs and Environmentally Extended Economic Input Output (EEIO) LCAs. Process-based LCAs directly measure the environmental impact of a product or activity by assessing material inputs and emissions. These LCAs are useful for comparing related products or processes, such as reusable *vs* disposable equipment. On the other hand, EEIO LCAs are suitable for analysing large data sets where process-based LCA is not feasible. These LCAs rely on nationally reported economic input output tables and pollution emissions tables to estimate the environmental impact of a system. By assigning an environmental footprint to monetary value spent, approximations of entire healthcare systems' CO2e emissions are possible. For example, the UK-MRIO (multi-region input-output) model of Greenhouse Gas emissions[15] and the Eora multiregional input-output database [12] are commonly used in multiregional input-output analysis. This approach covers the entire supply-chain network underpinning the operation of healthcare services and yields comprehensive estimates for environmental footprints. The use of international input-output tables (MRIO in terms of nations/countries as regional units) in EEIO LCA allows for the expansion of the system boundaries from a single country to surrounding regions.

While LCAs focus on a particular product or patient pathway, MFAs provide a broader perspective on all materials entering and leaving the ICU. MFAs quantify all goods and waste flows, making them useful for waste management and raising awareness among ICU staff. They also identify environmental hotspots, which are areas that cause significant environmental impacts and require urgent attention. These hotspots often include products with the highest mass and environmental footprint assessment. By highlighting these hotspots, ICU personnel can then target areas for improvement. In a 2019 case study of a Dutch ICU, 2839 patients were admitted, with an average stay of 4.6 d and a material mass inflow of 247000 kg. Of this, 50000 kg were incinerated as hazardous hospital waste. MFA analysis showed that each patient had an environmental impact of 17 kg of mass, 12 kg CO2e, 300 L of water usage, and 4 m^2 of agricultural land occupation per day. The five identified hotspots were non-sterile gloves, isolation gowns, bed liners, surgical masks, and syringes (including packaging)[14].

PRACTICAL SOLUTIONS FOR IMPROVING ENVIRONMENTAL SUSTAINABILITY IN ICU

Reduce

Categories of interventions include reduce, reuse, and recycle[16]. The category that has the most significant impact is reduction of waste generation since it prevents the creation of environmental pollution from the outset. A review of 54 studies revealed that there is substantial waste in the US healthcare system, with a cost ranging from USD 760-935 billion, representing 25% of all spending[17]. Among this waste, USD 75.7-101.2 billion is attributed to overtreatment or low-value care. Efforts to reduce overtreatment or low-value care could save USD 12.8-28.6 billion.

There are various methods to decrease waste generation in the healthcare industry, such as preventing the progression of illnesses and inpatient admissions, avoiding unnecessary ICU admissions through accurate triage and avoiding futile care, reducing overdiagnosis by not detecting harmless conditions that could be safely left undiagnosed and untreated [18], minimizing over-investigation by avoiding routine blood tests[19], changing central venous catheter infusion sets not earlier than 7 d[20], and curtailing overtreatment such as routine use of proton pump inhibitors for low-risk patients or continued thromboprophylaxis in ambulatory patients. Other solutions for reducing healthcare resources include managing the supply chain prudently to reduce unused medical waste, replacing intravenous drug use with oral altern-

atives, avoiding unnecessary vehicular transport by utilizing telepresence enabled by medical robots[21], reducing facility energy consumption for HVAC (heating, ventilation, and air conditioning) by setting a moderate room temperature[13], improving first-pass success of procedures through better training, decarbonizing energy sources by using natural rather than artificial lighting, reducing paper printouts and forms, minimizing plastic use, and reducing healthcare-associated infections and iatrogenic complications.

Another example of reducing waste generation in healthcare involves avoiding the routine use of supplemental oxygen, which can prevent harmful gas emissions during the production of medical oxygen and disposable plastic masks and tubing[22]. Although avoiding unnecessary computed tomography (CT) or magnetic resonance imaging (MRI) is ideal[23], when necessary, chest X-ray (CXR) or point-of-care ultrasound could also help reduce the carbon footprint. A study showed that the mean CO2e emissions were much higher for MRI and CT scans compared to CXR and ultrasound (17.5 kg/scan for MRI and 9.2 kg/scan for CT, compared to 0.8 kg/scan for CXR and 0.5 kg/scan for ultrasound[24]). In some paediatric ICUs, isolation rooms contribute to over 75% of unused medical waste, which includes endotracheal tubes, diapers, disposable under pads, and flexible suction catheters[25]. Interventions for reducing this waste include stocking fewer items inside patient rooms and keeping them in supply carts outside patient rooms, protecting bedside resuscitator bags, positive end-expiratory pressure valves, and oropharyngeal airways in plastic bags for re-use. Another interesting intervention is to reduce the use of super-pollutants such as inhalational anaesthetics[26,27] (*e.g.*, replace with total IV anaesthesia) and hydrofluorocarbon-containing MDI[28] (*e.g.*, replace with mesh nebulizer), which have high global warming potential.

Reuse

If direct reduction of waste generation is not possible, then indirect methods of reusing and recycling are important. Choosing reusable equipment over single-use disposable ones is one such method[29]. Examples of reusable equipment include stethoscopes, procedural kits, laryngoscope blades, bronchoscopes, laryngeal mask airways, and metal scissors [30]. In one hospital, reusable flexible bronchoscopes were preferred over single-use devices due to their lower environmental impact, lower cost, and technical reliability for tracheal intubation. Another approach to reducing waste is single-use device reprocessing, where used single-use devices are sent to a third-party facility for cleaning, sterilization, and sale back to hospitals. Investing in durable equipment with modular components that are repairable and upgradable can also reduce waste. When making procurement decisions, factors such as energy efficiency and equipment quality must be considered. Extending product lifespans through repairing and upgrading equipment as much as possible can also be effective.

Recycle

The final approach to reducing waste is recycling used fluid bags and non-sharps, with appropriate segregation of registered medical waste (*i.e.*, biohazard waste, which is expensive to process) and non-medical waste. However, recycling has the lowest impact because most life cycle emissions occur during the upstream manufacturing and distribution of products, and recycling requires additional energy and materials, which can create emissions. While there are many practical solutions for reducing, reusing, and recycling (Table 1), few have been validated and peer-reviewed (Table 2).

IMPLEMENTATION OF ENVIRONMENTAL SUSTAINABILITY IN ICU

The COM-B model of behaviour change identifies three essential conditions: capability, opportunity, and motivation[31]. Education can improve motivation among staff, but simply having willpower is not sufficient. Health systems must also provide the opportunity (space), logistics (stuff), and capability (system) for sustainability interventions. Batcup and colleagues conducted a recent systematic review of behavioural change interventions designed to encourage clinicians to reduce carbon emissions in clinical activity. They analysed six full-text studies and 14 conference abstracts and found that the most common behaviour change techniques used were social support, highlighting the consequences, restructuring the physical environment, using prompts and cues, providing feedback on behaviour outcomes, and sharing information about environmental consequences[32].

Education has played a significant role in decreasing the usage of inhalational anaesthetics with high global warming potential (GWP). According to the GWP100 (100 year time horizon GWP), which is used as the standard comparison of long-lived effects, carbon dioxide has a GWP of 1, while desflurane has a GWP100 of 2540, sevoflurane 130, isoflurane 510, and nitrous oxide approximately 265 (nitrous oxide also having ozone-depleting potential)[33]. In one example, staff education on desflurane-sparing practices and distribution of posters has allowed for a gradual removal of desflurane from operating theatres, resulting in a 95.63% reduction in desflurane bottles purchased (from 800 bottles in January 2016 to 35 bottles in December 2021). In contrast, the number of sevoflurane bottles purchased (which has a low global warming potential) increased by 6.13% from 1191 bottles to 1264 bottles, leading to an overall 87.9% decrease in carbon emissions[34].

Improving environmental sustainability in critical care involves the concepts of "greening" and environmental stewardship. "Green" teams, made up of critical care leaders and frontline staff, can be formed to undertake these measures[16,25]. Change management is important, which involves convincing others, obtaining leadership support, and acquiring necessary resources, time, and staffing. Audit, feedback, and continuous improvement cycles are also crucial. Multidisciplinary team members can help reduce waste, such as pharmacists who can review drug charts to identify unnecessary medications and implement antimicrobial stewardship. Ultimately, reducing waste in healthcare is crucial

Table 1 Clinical practices which may aid in reducing the environmental impact of intensive care unit

Category	Clinical practices
Reduce	Avoid unnecessary ICU admissions through accurate triage
	Avoid futile care
	Avoid overdiagnosis
	Avoid over-investigation and routine testing
	Avoid overtreatment
	Avoid overuse of supplemental oxygen
	Avoid routine prophylaxis (*e.g.*, proton pump inhibitors, thromboprophylaxis) for low-risk patients
	Change central venous catheter infusion sets not earlier than 7 d
	Manage supply chain to reduce unused medical waste
	Replace intravenous drug use with oral alternatives
	Avoid unnecessary vehicular transport by utilizing telepresence
	Reduce facility energy consumption for heating, ventilation, and air conditioning, by setting a moderate room temperature
	Improve first-pass success of procedures through better training
	Decarbonize energy sources by using natural rather than artificial lighting
	Reduce paper printouts and forms
	Minimize plastic use
	Reduce healthcare-associated infections and iatrogenic complications
	Stock fewer items inside patient rooms and keep them in supply carts outside patient rooms
	Replace inhalational anaesthetics with total intravenous anaesthesia
	Replace hydrofluorocarbon-containing metered dose inhaler with mesh nebulizer
Reuse	Choose reusable equipment over single-use disposal ones
	Consider single-use device reprocessing
	Extend product lifespans through repairing and upgrading equipment as much as possible
Recycle	Recycle used fluid bags and non-sharps

ICU: Intensive care unit.

for better patient care, improved efficiency, and a healthier planet.

FUTURE DIRECTION

Improving environmental sustainability in healthcare is not only good for the planet but may also reduce healthcare costs. However, it is important to validate interventions to ensure their effectiveness and avoid unintended consequences, such as limiting patients' access to necessary products[35,36]. Education on planetary health and sustainability should be included in medical education[37] and training for all stakeholders[38,39]. Education platforms include virtual learning spaces like the Virtual Health Academy, which provides lectures and workshops on transformative planetary health education in Germany[40]. Education for sustainable healthcare should also be included in faculty development to improve knowledge and teach community-building and leadership skills[41].

Collaboration between humans and artificial intelligence (AI)[42] can contribute to environmental sustainability. Clinicians can input clinical data into electronic health records, while AI can use big data to accurately triage patients for ICU admission[43], potentially reducing unnecessary ICU utilization and healthcare waste. Additionally, ICU staff members can use Radio Frequency Identification systems or AI-driven contactless visual systems[44] to provide real-time data on consumable and equipment usage. Predictive AI models can then assist with forecasting resource utilization[45] and optimizing inventory management, reducing losses from expired consumables and equipment. In other words, AI-enabled effective supply chain management and stocking systems may help minimize overstocking and waste of expired equipment.

Table 2 Published environmental sustainability efforts done in intensive care unit

Category	Method	Outcome	Ref.
Reduce	Redesign pharmaceutical doses and packaging; install waste containers for non-recyclables and chemical wastes; educate staff	Decreased solid waste generation by 39% (13.7 to 8.4 kg/patient/d)	Furukawa *et al* [47], 2016
Reduce	Four-step action plan: (1) Audit local practice; (2) develop clinical guideline for rational ordering; (3) educate stakeholders; and (4) measure impact through re-audit	Comparing July-December 2017 *vs* July-December 2018 in a 58-bed ICU, number of ABG tests decreased by 31.3%, saving A$770000, 100 L of blood, and reducing emissions of 1038 kg CO2e (akin to driving 6782 km in an average Australian car). Inappropriate ABG testing decreased by 47.3%, and the number of inappropriate tests per bed-day decreased by 71%, without worsening patient mortality	Walsh *et al* [48], 2020
Reduce	Relocating in-room disposable equipment to supply carts situated outside the patient rooms, while using small baskets for basic admissions with expected short lengths of stay. Additionally, instead of refilling all items to quota, daily room restocking was customized based on nursing requirements	A Canadian ICU with 16 beds implemented a strategy to reduce the amount of unused equipment waste, resulting in a large 80% decrease. This reduction translated to an approximate annual saving of Can$110000	Yu *et al*[49], 2021
Recycle	Recycling program in ICU	An Australian ICU produced 540 kg total waste/week in 2008, which reduced to 505 kg after introducing a recycling program in 2013, with 14% of the total waste being recycled	McGain *et al* [50], 2009; Kubicki *et al* [51], 2015

ABG: Arterial blood gas; ICU: Intensive care unit.

Promoting environmental sustainability requires the active participation of stakeholders beyond the ICU, *e.g.*, manufacturers and healthcare regulators. On the one hand, manufacturers should strive to prioritize sustainability in their product designs and production processes, aiming for environmentally friendly alternatives whenever feasible. For non-recyclable products, these should offer substantial advancements in device performance compared to their recyclable counterparts, to justify their purchase. On the other hand, healthcare regulators should preferentially approve products that can be reusable or recycled, lessening waste accumulation and environmental degradation. For instance, the World Health Organization has recommended that when purchasing equipment and supplies, environmentally friendly products should be prioritized, such as those with minimal packaging, reusable and recyclable parts, and minimal hazardous chemicals and non-degradable plastics[46].

CONCLUSION

Promoting environmental sustainability in healthcare, specifically in the ICU, is essential for mitigating the environmental impact of critical care and improving planetary health. Sustainability involves staying within planetary boundaries, which if exceeded, could lead to catastrophic environmental changes. One of these boundaries relates to climate change, and the atmospheric carbon dioxide concentration has already exceeded the proposed threshold of 350 ppm. Therefore, reducing greenhouse gas emissions is urgent.

To achieve environmental sustainability in the ICU, healthcare professionals must have the knowledge and tools to measure and mitigate the carbon cost of healthcare for critically ill patients. Two complementary methods have been used in the ICU to measure the environmental cost of critical care: LCA and MFA. Various methods can decrease waste generation in the healthcare industry, such as preventing the progression of illnesses and inpatient admissions, avoiding unnecessary ICU admissions, minimizing overdiagnosis and over-investigation, and curtailing overtreatment. Interventions can also focus on reducing energy consumption and reusing/recycling products.

ICU staff should take a lead role in implementing solutions due to their intersection with healthcare and high resource use for critically ill patients. However, reducing the environmental footprint of critical care requires a collective effort from healthcare providers, patients, policymakers, and other stakeholders. Collaborative efforts, including those with artificial intelligence, can result in more sustainable healthcare systems and better health outcomes for individuals and the planet.

FOOTNOTES

Author contributions: See KC collected the data, wrote the paper, read and approved the final manuscript.

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

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

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World Journal of Critical Care Medicine

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World J Crit Care Med 2023 September 9; 12(4): 226-235

DOI: 10.5492/wjccm.v12.i4.226

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Retrospective Study

Delayed inflammatory pulmonary syndrome: A distinct clinical entity in the spectrum of inflammatory syndromes in COVID-19 infection?

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Specialty type: Critical care medicine

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Gupta MK, Germany; Luo W, China

Received: May 11, 2023
Peer-review started: May 11, 2023
First decision: June 15, 2023
Revised: June 24, 2023
Accepted: July 6, 2023
Article in press: July 6, 2023
Published online: September 9, 2023

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Abstract

BACKGROUND

During the second wave of the coronavirus disease 2019 (COVID-19) pandemic, a subset of critically ill patients developed delayed respiratory deterioration in the absence of new infection, fluid overload or extra-pulmonary organ dysfunction.

AIM

To describe the clinical and laboratory characteristics, outcomes, and management of these patients, and to contrast this entity with other post COVID-19 immune dysregulation related inflammatory disorders.

METHODS

This was a retrospective observational study of adult patients admitted to the medical intensive care unit of a 2200-bed university affiliated teaching hospital, between May and August 2021, who fulfilled clearly defined inclusion and exclusion criteria. Outcome was assessed by a change in PaO_2/FiO_2 ratio and levels of inflammatory markers before and after immunomodulation, duration of mechanical ventilation after starting treatment, and survival to discharge.

RESULTS
Five patients developed delayed respiratory deterioration in the absence of new infection, fluid overload or extrapulmonary organ dysfunction at a median interquartile range (IQR) duration of 32 (23-35) d after the onset of symptoms. These patients had elevated inflammatory markers, required mechanical ventilation for 13 (IQR 10-23) d, and responded to glucocorticoids and/or intravenous immunoglobulin. One patient died (20%).

CONCLUSION
This delayed respiratory worsening with elevated inflammatory markers and clinical response to immunomodulation appears to contrast the well described Multisystem Inflammatory Syndrome – Adults by the paucity of extrapulmonary organ involvement. The diagnosis can be considered in patients presenting with delayed respiratory worsening, that is not attributable to cardiac dysfunction, fluid overload or ongoing infections, and associated with an increase in systemic inflammatory markers like C-reactive protein, inteleukin-6 and ferritin. A good response to immunomodulation can be expected. This delayed inflammatory pulmonary syndrome may represent a distinct clinical entity in the spectrum of inflammatory syndromes in COVID-19 infection.

Key Words: COVID-19; ARDS; Multisystem Inflammatory Syndrome in Adults; Long COVID; Organizing pneumonia

Core Tip: Delayed respiratory deterioration in critically ill coronavirus disease 2019 (COVID-19) in the absence of new infection, fluid overload, pneumothorax, or lung collapse is seen in a subset of patients admitted to the intensive care unit. This presentation does not fit in to the definition of Multisystem Inflammatory Syndrome Adults, owing to the predominance of pulmonary symptoms and the notable absence of cardiac, gastrointestinal, and mucocutaneous manifestations. In the current study, five patients developed worsening respiratory function requiring escalation of ventilatory support after the third week of COVID-19 illness. This was accompanied by elevated inflammatory markers. All five patients showed clinical response to immunomodulation. This delayed inflammatory pulmonary syndrome contrasts Multisystem Inflammatory Syndrome Adults where extrapulmonary organ involvement predominates.

Citation: Bose P, Chacko B, Arul AO, Robinson Vimala L, Thangakunam B, Varghese GM, Jambugulam M, Lenin A, Peter JV. Delayed inflammatory pulmonary syndrome: A distinct clinical entity in the spectrum of inflammatory syndromes in COVID-19 infection? *World J Crit Care Med* 2023; 12(4): 226-235
URL: https://www.wjgnet.com/2220-3141/full/v12/i4/226.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i4.226

INTRODUCTION

While much has been written about coronavirus disease 2019 (COVID-19) Associated Acute Respiratory Distress Syndrome (CARDS)[1], less is known about the clinical presentations that evolve after the acute infection has subsided. The Centre for Disease Control (CDC) has grouped a cluster of organ failure syndromes under the umbrella of multisystem inflammatory syndrome (MIS). This entity is characterised by dysregulated host immune response causing widespread organ dysfunction and usually follows the period of viremia[2]. MIS was first described in COVID-19 in the paediatric population and was termed MIS-C (Children)[2]. Although a similar phenomenon was subsequently reported in adults (MIS-A) in 2021[3], the MIS-A criteria, in contrast to the MIS-C, is strikingly bereft of respiratory involvement. It has encompassed primarily an extrapulmonary syndrome with cardiac, neurologic, and gastrointestinal manifestations [3].

While managing COVID-19 patients in the intensive care unit (ICU), we observed that a small subset of patients with CARDS developed worsening respiratory function after an initial period of improvement that could not be attributed to the usual causes such as superadded infection, lung collapse, pleural effusion, pulmonary embolism, or fluid overload. Unlike CARDS or the fibrotic phase of ARDS which are a continuum of the initial insult, this phenomenon was observed in patients with increasing ventilatory requirements between the third and fourth weeks after the diagnosis of COVID-19. Respiratory deterioration was associated with an increase in inflammatory markers with minimal or no extrapulmonary organ involvement. This clinical picture suggested an entity not fitting into the classical MIS-A definition but nevertheless befitting a distinct position in the spectrum of inflammatory syndromes in COVID-19.

The study was thus aimed to describe the clinical and laboratory characteristics of this delayed inflammatory pulmonary syndrome (DIPS) through a retrospective review of cases admitted in the ICU during the second wave of the pandemic, along with clinical outcomes and caveats in management.

MATERIALS AND METHODS

Study setting and design

This was a retrospective observational study of adult patients admitted to the medical ICU of a 2200-bed university affiliated teaching hospital, between May and August 2021.

Study approval

The study was approved by the Institutional Review Board of the institution. In view of the retrospective nature of the study and the large number of COVID-19 patients admitted in the ICU, informed consent waiver was obtained from the institutional review board.

Data harvesting

Computerised records of patients admitted in the medical ICU during the period of study was accessed and those fulfilling the following diagnostic criteria for delayed inflammatory pulmonary syndrome were included in the analysis.

Criteria for the diagnosis of delayed inflammatory pulmonary syndrome (modified from CDC criteria for MIS-A)

Patients were considered to have DIPS if they fulfilled ALL the following clinical and laboratory criteria.

Clinical criteria: Documented fever (≥ 38.0°C) along with evidence of respiratory involvement in the form of:

(a) Development of respiratory failure or worsening respiratory failure following a period of initial improvement, occurring after the third week of COVID illness and requiring either non-invasive or invasive mechanical ventilation, with documented acute drop in PaO_2/FiO_2 (PF) ratio, resulting in a change in the respiratory Sequential Organ Failure Assessment (SOFA) score by at least one point over 24 h.

(b) New or worsening bilateral diffuse infiltrates on chest radiograph or computed tomography (CT) scan, not due to pleural effusion, lobal collapse, pulmonary nodules, or pulmonary embolism.

(c) Respiratory failure not explained by left atrial hypertension or cardiac failure or fluid overload.

(d) Exclusion of infection as the cause of worsening lung function.

Laboratory evidence: The presence of laboratory evidence of inflammation AND SARS-CoV-2 infection.

(a) Elevated levels (exceeding the upper limit of normal specific to age and gender) of at least TWO of the following: C-reactive protein (CRP), ferritin, interleukin-6 (IL-6), or erythrocyte sedimentation rate.

(b) A positive SARS-CoV-2 test by reverse transcriptase polymerase chain reaction (RT-PCR), serology, or antigen detection in the current admission or in the previous 12 wk[3].

(c) Negative blood culture and endotracheal aspirate cultures collected at the time of worsening of lung function and not fulfilling the CDC definition of ventilator associated pneumonia (VAP)[4].

Management protocol

Adult patients aged ≥ 18 years fulfilling criteria for CARDS received as part of the protocol, dexamethasone 6 mg once daily for 10 d and therapeutic anticoagulation if D-Dimer was more than 1000 ng/mL. Following the diagnosis of DIPS, patients were treated with intravenous immunoglobulins (IVIG) at a dose of 2 g/kg over three to five days, or with steroids (6 mg dexamethasone once or twice daily or hydrocortisone 50 mg every six hours, as per the treating clinician's assessment and discretion). The decision on the use of IVIG was left to the treating physician and also guided by financial feasibility. Daily clinical monitoring and blood gas analysis was done to track improvement in respiratory function.

Statistical analysis

The data was tabulated and analysed using Microsoft Excel version Office 365. Continuous variables were presented as mean, standard deviation (SD) for normally distributed data and as median, interquartile range, (IQR) for skewed data. Categorical data were reported as proportions. Paired-t test was done to analyse the change in PF ratio before and after the onset of DIPS.

Main outcomes and measures

The outcome measures that were assessed were survival to discharge, change in the PF from the onset of DIPS to after immunomodulation, change in inflammatory markers before and after DIPS and duration of mechanical ventilation after the onset of DIPS.

RESULTS

Five patients, with mean (SD) age of 48.2 (14.2) years and median (IQR) Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score of 19 (IQR 10-21), fulfilled the case definition of DIPS. One patient who was included had a positive endotracheal aspirate culture (patient 4) but did not fulfil the CDC criteria for VAP[4]. All five patients underwent point of care echocardiography for assessment of left ventricular function. There was no evidence of left ventricular dysfunction; in addition, 3 of the 5 patients in whom an NT pro-BNP was done had values of 449, 132 and 146 pg/mL (reference range: Up to 125 pg/mL). There was a male preponderance (80%); the lag time from symptom onset to

deterioration was a median 32 d (IQR 23-35 days). One patient (patient 2) had received 2 doses of vaccination with the Oxford-AstraZeneca ChAdOx1 nCoV-19 recombinant vector Corona Virus Vaccine (Brand: Covishield™, manufactured by the Serum Institute, India) prior to admission. Two patients (patients 3 and 5) were not vaccinated. The vaccination history of the remaining two patients (patient 1 and 4) could not be ascertained as contact could not be established through telephone.

Clinical and laboratory characteristics at baseline and at the time of respiratory deterioration are summarised in Table 1. Figure 1 illustrates that respiratory SOFA scores contributed predominantly to the total SOFA score in all subjects on the day of deterioration. Representative chest radiographs and high-resolution CT scan images taken before the onset of symptoms, at the nadir of PF ratio and during recovery show the evolution of diffuse infiltrates and resolution following treatment (Figure 2).

There was a significant drop in the PF ratio from a peak of 323 ± 96.2 (mean ± SD) prior to DIPS to 169.8 ± 33.7 (mean ± SD) after the onset of DIPS (P = 0.043). There was an increase in the levels of inflammatory markers (CRP, Ferritin) at the onset of DIPS when compared with baseline (Table 1); IL-6 levels were also elevated (Table 1). The median duration of mechanical ventilation prior to the onset of DIPS was 9 (2-16) d.

At the time of deterioration of respiratory function, of the 5 patients, two patients (patients 2 and 4) deteriorated while on a spontaneous mode of invasive ventilation to require high ventilatory support. Both these patients were subsequently weaned off the ventilator following immunomodulation and extubated; at the time of discharge, they were on room air. Two other patients (patients 1 and 3) were on intermittent non-invasive ventilation (NIV) at the time of deterioration, worsening to require continuous NIV with increased oxygen support and higher positive end-expiratory pressure. Following immunomodulation, patient 3 improved and was discharged stable while patient 1 developed a tension pneumothorax, and subsequently a nosocomial infection and succumbed. Patient 5 who was initially admitted for moderate COVID-19 infection and discharged home re-presented on day 36 with worsening respiratory failure needing intubation and mechanical ventilation. She improved with immunomodulation and was discharged stable.

All 5 patients were on anticoagulation at the time of respiratory deterioration. Of these, 2 were on therapeutic anticoagulation with low molecular weight heparin (enoxaparin) at a dose of 1 mg/kg every 12 h (monitoring of anti- factor Xa levels was done on one patient) while the other 3 patients were on unfractionated heparin with monitoring of activated partial thromboplastin time.

Following the diagnosis of DIPS, two patients received IVIG at 2 g/kg over 5 days, while one received dexamethasone at 6 mg twice daily for 5 d followed by once daily for 5 d, one received dexamethasone 6 mg once daily for 10 d, and the fifth received hydrocortisone 50 mg every six hours for 5 d. Following immunomodulation there was a significant improvement in the PF ratio from 169.8 ± 33.7 at the onset of DIPS to 349.2 ± 57.6 (P = 0.001) over time. The trends of PF ratios over time for the 5 individual patients is shown in Figure 3. Mechanical ventilation was required for a median duration of 13 (10-23) d after the onset of DIPS. Four out of the five patients (80%) survived to hospital discharge.

DISCUSSION

This series describes five critically ill patients with CARDS who developed unexplained worsening respiratory function after a median interval of 32 d (IQR 23-35 d) from the onset of symptoms of COVID-19. These patients had increased inflammatory markers and responded to immunomodulation. This syndrome of worsening gas exchange appears to be part of a dysregulated host immune response; however, the clinical characteristics of our subset of patients did not fit in to criteria described for the diagnosis of MIS-A.

Lung hyperinflammation is an established phenomenon in the context of CARDS and occurs as part of the initial presentation of COVID-19 infection, generally in the second week following onset of symptoms[5]. Our novel observation of ventilated CARDS patients developing delayed pulmonary hyperinflammation three to four weeks after of the onset of initial symptoms, which improved with immunomodulation, has hitherto not been reported.

In a large cohort of MIS-A, patients developed MIS-A at a median time of 28 d from the onset of COVID-19–like illness [6]. The time of presentation in our cohort was similar (median 32 d). However, the paucity of extrapulmonary organ dysfunction and the predominance of lung involvement sets it apart from MIS-A cohorts[6]. It is unclear if DIPS represents a distinct clinical entity or is part of the spectrum of MIS-A. The differences between DIPS, CARDS and MIS-A are summarised in Table 2[2,6-12].

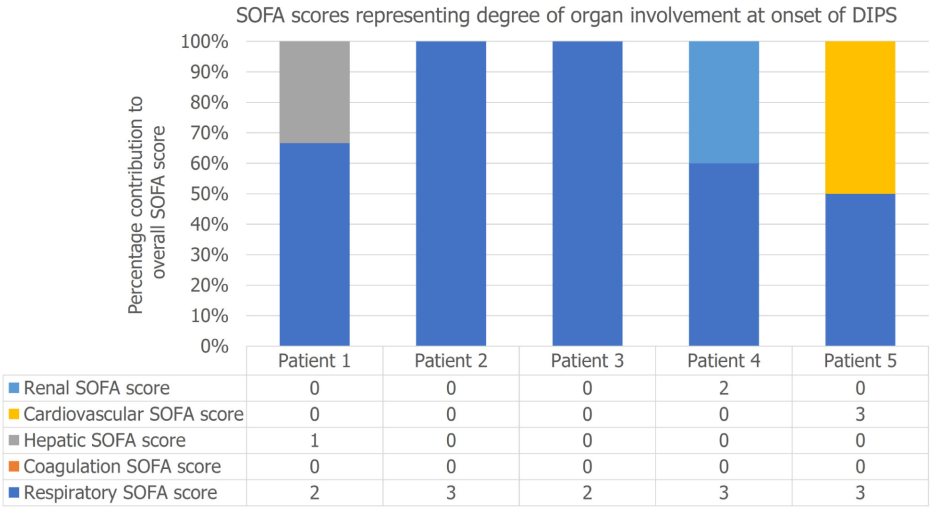
Deteriorating lung function occurring beyond 4 wk after COVID-19 illness, in the absence extra-pulmonary organ involvement has also been previously reported from a few centres either as persistent post COVID-19 interstitial lung disease (ILD), organising pneumonia, secondary organising pneumonia[7-9] or pulmonary fibrosis[13]. Although the time of onset of symptoms may imply a similar pathology in our cohort, there are several differences that merit consideration. All the 35 patients described in the ILD case series[9] were reviewed 4-weeks after discharge following a telephone interview, in the outpatient clinic, for persistence of respiratory symptoms. In another report[7], two patients presented two months after discharge: one with new onset breathlessness for 3 d and the other with a 1-week history of worsening cough and right sided pleuritic chest pain. The case report of a 36-year-old male with diffuse large B-cell lymphoma[8] was an acute presentation with high fever and fatigue, 40 d after a COVID infection. All the patients described in these publications were discharged from hospital after the initial illness and on review reported persistence of respiratory symptoms[7,9] or presented with new symptoms after recovery[8] that were not severe enough to warrant ventilatory support. In contrast, all the patients in our cohort barring one, developed worsening symptoms while in hospital, occurring as a continuum after the initial improvement following treatment for CARDS, were much sicker, and required ventilatory support. The radiological features in the reports[7-9] ranged from focal consolidation, ground-glass

Table 1 Patient characteristics

Baseline characteristics of the study cohort (*n* = 5)	
Age (mean ± SD) yr	48.2 (14.2)
Male: Female ratio	4: 1
APACHE-II score at admission (median, IQR)	19 (10-21)
Day of worsening from date of onset of symptoms (Median, IQR)	32 (23-35)
Oxygenation parameters (median, IQR) PF ratio	
Peak PF ratio prior to onset of DIPS	326 (243-329)
PF ratio at onset of DIPS	182 (156-190)
Peak PF ratio after immunomodulation	353 (327-353)
Ventilation data (median, IQR) d	
Duration of mechanical ventilation[a] prior to the onset of DIPS	9 (2-16)
Duration of mechanical ventilation after the onset of DIPS	13 (10-23)
Inflammatory markers (median, IQR)	
CRP (mg/L) at baseline	142 (113-182)
CRP (mg/L) at onset of DIPS	165.5 (157-212)
Ferritin (ng/mL) at baseline	270.2 (191-349)
Ferritin (ng/mL) at onset of DIPS	677.5 (382-1893)
IL-6 (pg/mL) at onset of DIPS (median, IQR)	207.4 (163-311)

[a]Mechanical ventilation includes both invasive and non-invasive ventilation.

SD: Standard deviation; APACHE: Acute Physiology and Chronic Health Evaluation; PF: (PaO_2/FIO_2); IQR: Interquartile range; DIPS: Delayed inflammatory pulmonary syndrome; CRP: C reactive protein (reference range: < 6 mg/L). Ferritin reference range (male: 22-322 ng/mL; female: 10-291 ng/mL); IL: Interleukin (reference range: < 7 pg/mL);



DOI: 10.5492/wjccm.v12.i4.226

Figure 1 Sequential Organ Failure Assessment score representing degree of organ involvement in Delayed Inflammatory Pulmonary Syndrome. The contribution of respiratory Sequential Organ Failure Assessment (SOFA) to the overall SOFA score is depicted for all the five patients. It is evident that in all patients, respiratory SOFA contributed to > 50% of the total SOFA score. In two patients, there was no extrapulmonary organ dysfunction, while in the remaining three patients, there was some hepatic, renal and cardiovascular dysfunction. DIPS: Delayed Inflammatory Pulmonary Syndrome; SOFA: Sequential Organ Failure Assessment.

attenuation, and linear opacities[7] to extensive pulmonary infiltrates[8] and peri-bronchial and peri-lobar dense consolidation with traction bronchiectasis in the ILD series[9]. In the ILD series, 21 patients with pure ground glass opacities involving < 15% of the lung and 3 patients with fixed minor ground glass opacities were excluded and offered follow-up

Table 2 Comparison of characteristics of coronavirus disease 2019 (COVID-19) associated acute respiratory distress syndrome, multisystem inflammatory syndrome Adults, multisystem inflammatory syndrome Children, post COVID-19 secondary organising pneumonia, post COVID-19 interstitial lung disease and Delayed Inflammatory Pulmonary Syndrome

Syndrome	Time of onset (Median, IQR) d	Primary organ affected	Other organs affected	Inflammatory markers	Treatment	Intensive care required (%)	Mortality, %
CARDS[11,12]	8 (5-13) d from onset of infection	Lungs	Gastro-intestinal	Elevated IL-2, IL7, TNF-α	Corticosteroids, Baricitinib (JAK-2 inhibitor) and Tocilizumab (IL-6 inhibitor) in severe hypoxia and evidence of hyperinflammation	Yes (17)	39
MIS-A[6]	28 (20-36) d after SARS-CoV-2 infection	Cardio-vascular	Gastro-intestinal, muco-cutaneous, haematological	Fibrinogen, D-dimer, CRP, ferritin, IL-6 elevated in > 90%	IVIG (55%), corticosteroids (74%), IL-6 inhibitors (21%)	Yes (57)	7
MIS-C[2]	Within 4 wk of SARS-CoV-2 infection (13)	Gastro-intestinal tract	Muco-cutaneous	CRP, ferritin, procalcitonin, IL-6 elevated	IVIG (76.4%) and corticosteroids (52.3%), IL-1ra inhibitor (8.5%) and IL-6 inhibitors (6%)	Yes (73.8)	1.9
Secondary OP[7,8]	Beyond 4 wk of SARS-CoV-2 infection	Lungs	Nil	CRP (mild elevation: 3.45 to 11.7 mg/dL)	Corticosteroids	No	Nil
Secondary ILD[9]	6 wk after discharge from hospital	Lungs	Uncommon	CRP and ferritin significantly elevated	Corticosteroids	No	Nil
DIPS (Current study)	32 (23-35) d after symptom onset	Lungs	Uncommon	Elevated CRP, ferritin, and IL-6	Good response to IVIG/steroids	Yes (100)	20

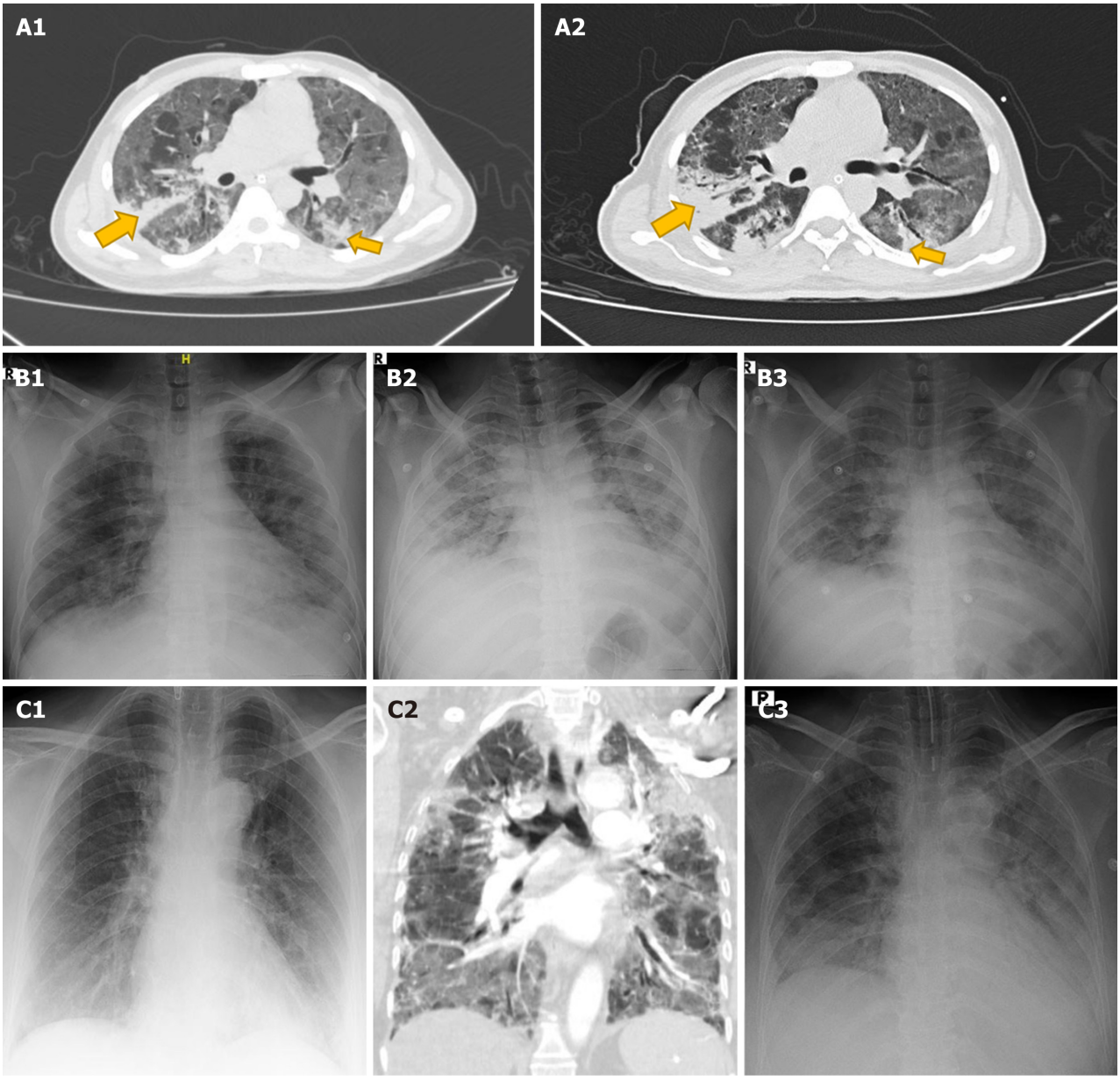
CARDS: COVID-19 associated acute respiratory distress syndrome; MIS-A: Multisystem inflammatory syndrome Adults; MIS-C: Multisystem inflammatory syndrome Children; OP: Organising pneumonia; ILD: Interstitial lung disease; DIPS: Delayed inflammatory pulmonary syndrome; IQR: Interquartile range; equivalent of dexamethasone 6 mg once daily recommended in hypoxic patients; IVIG: Intravenous immunoglobulin; CRP: C-reactive protein.

[9]. The patients in our cohort had radiological features of focal or diffuse ground glass opacities in addition to pulmonary infiltrates and tractional bronchiectasis. The radiological features in our series may thus reflect mixed pathology or evolution from one pathological phase of the illness to another, as occurs in ARDS and may not be pathognomonic of a specific diagnosis. Although histopathology would have helped characterise the syndrome further, this was not done in our series due to concerns of performing lung biopsy in patients on high ventilatory support. In the other case reports, the histological features were consistent with organising pneumonia[7,8]; biopsy was not done in the ILD series[9].

Pulmonary fibrosis as a cause for clinical deterioration is unlikely in our patients for the following reasons. The rapid deterioration of symptoms correlated with an increase in serum inflammatory markers and imaging (ground glass opacification) that was consistent with an inflammatory process. This clinical picture contrasts the more subacute presentation and imaging characteristics of pulmonary fibrosis of architectural distortion in the form of irregular reticulation, traction bronchiectasis and honeycombing[14]. The rapid resolution of symptoms and radiological opacities with immunomodulation also makes pulmonary fibrosis less likely.

Other causes for worsening lung function need to be considered. It is possible that prior vaccination could have contributed to ARDS[15]. Vaccination history could not be obtained for all patients and hence association or lack of it could not be ascertained. There is also evidence that microvascular thrombosis contributes to the pathophysiology of COVID-19 infection[16,17]. Although it is possible that micro-thrombosis may have contributed to the manifestations, worsening of respiratory function cannot be explained only by ongoing thrombosis given that all patients received anticoagulation, and the observation that patients responded rapidly to immunomodulation. However, the debate on the appropriate level of anticoagulation for COVID-19 patients remains unresolved.

The number of patients described in this cohort as well as on persistent post-COVID-19 ILD[9] or post COVID organising pneumonia[8] is small in relation to the proportion of COVID-19 infected patients; however, subsets with varying clinical presentation and course of illness is not unique to COVID-19 and needs to be documented and reported for better understanding of any disease. The response to immunomodulation in our patients highlights the importance of considering this syndrome among the differential diagnosis for delayed respiratory deterioration. Various biomarkers that have been postulated to correlate with increased incidence of the post-acute sequelae of SARS-CoV-2 infection are TNF-α, IP-10 (Interferon-inducible protein-10) and IL-6, also need to be explored further[18]. Although larger studies are required to provide additional insights on these preliminary observations, awareness of this clinical entity will help in



DOI: 10.5492/wjccm.v12.i4.226

Figure 2 Representative Cross sectional computed tomography and plain radiograph images of patients with Delayed Inflammatory Pulmonary Syndrome. A: High resolution transverse computed tomography (CT) sections of patient 4, showing the evolution of infiltrates from day -2 of Delayed Inflammatory Pulmonary Syndrome (DIPS) (A1) till day +15 (A2). The diffuse ground glass opacities seen in A1 have reduced, while the areas of consolidation (marked with yellow arrows) have increased slightly, along with features of tractional bronchiectasis, suggestive of coronavirus disease (COVID) sequelae. The overall improvement in clinical status from A1 to A2 could suggest that the ground glass opacities were part of the inflammatory changes in the lungs and responded to immunomodulation; B: Representative plain radiographs (portable) of patient 1 showing the evolution of infiltrates from day -7 of DIPS (B1) till day 0 (B2), followed by improvement on day +1 (B3), after the initiation of glucocorticoids; C: Representative chest radiograph and coronal high resolution CT sections on day -26 (C1, taken in the index admission for mild COVID on day 10 of symptom onset) before the onset of DIPS, significant increase in diffuse ground glass opacities on day 0 of DIPS (C2), followed by improvement on day +1 of DIPS (C3).

timely diagnosis and treatment of a potentially lethal cause of respiratory failure in the ICU.

CONCLUSION

Delayed inflammatory pulmonary syndrome is a serious and life-threatening complication of long COVID, occurring commonly in the fourth week of illness and characterised by a predominance of pulmonary hyperinflammation in the absence of secondary infections or fluid overload or extrapulmonary organ system involvement. This entity can be considered in the differential diagnoses in a patient with delayed deterioration in pulmonary function, after a period of initial improvement. The diagnosis is supported by raised inflammatory markers. Treatment with immunomodulation (systemic glucocorticoids or intravenous immunoglobulin) can be considered and a good response expected.

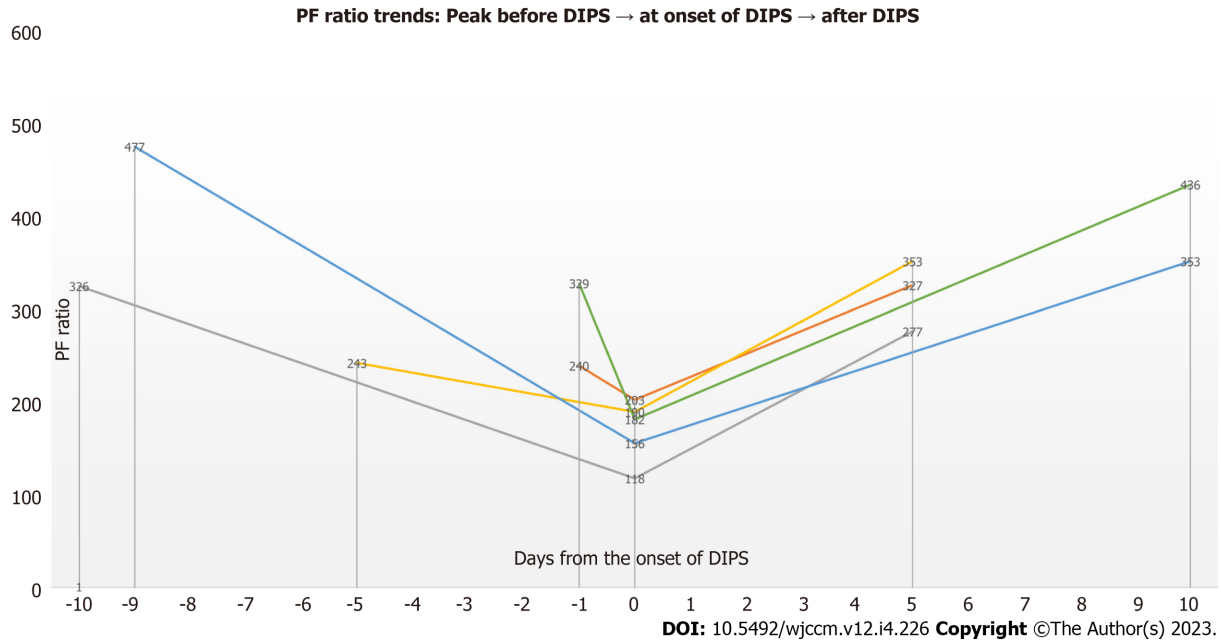


Figure 3 PaO_2/FiO_2 ratio trends of patients prior to, during and post Delayed Inflammatory Pulmonary Syndrome. The PaO2/FiO2 (PF) ratio of the individual patients is shown in the y-axis. The x-axis depicts day 0 as the day of onset of Delayed Inflammatory Pulmonary Syndrome (DIPS). The highest PF ratio of each patient in the period prior to DIPS and following recovery from DIPS is plotted. The figure shows that the respiratory deterioration occurred gradually over several days in 3 patients and acutely over a day in 2 patients. Recovery was gradual over 5 to 10 d. DIPS: Delayed Inflammatory Pulmonary Syndrome; SOFA: Sequential Organ Failure Assessment.

ARTICLE HIGHLIGHTS

Research background

Delayed deterioration in pulmonary function, following initial improvement, was seen in a subset of patients admitted to the intensive care unit (ICU) during the coronavirus disease 2019 (COVID-19) pandemic. These patients had no evidence of ongoing infection, fluid overload or cardiac dysfunction, but had elevated systemic inflammatory markers. They did not satisfy the diagnostic criteria for Multisystem Inflammatory Syndrome- Adults (MIS-A) due to the paucity of extra-pulmonary organ manifestations (mainly cardiac, gastrointestinal and mucocutaneous), but responded well to immunmodulation.

Research motivation

Delayed worsening of respiratory function in the ICU is generally attributable to infection, cardiac dysfunction, or fluid overload. But non-infectious inflammatory complications of post COVID-19 immune dysregulation is a distinct clinical entity that may play a role in worsening organ dysfunction in patients who have no evidence of the above.

Research objectives

The objectives of the current study were to describe the clinical and laboratory characteristics of post COVID-19 delayed inflammatory pulmonary syndrome (DIPS), the outcomes and management caveats encountered in the management of these patients, and to contrast DIPS with other post COVID-19 immune dysregulation related inflammatory disorders.

Research methods

This was a retrospective observational study of adult patients admitted to the medical ICU of a 2200-bed university affiliated teaching hospital, between May and August 2021, who fulfilled clearly defined inclusion and exclusion criteria. Outcome was assessed by a change in PaO_2/FiO_2 ratio and levels of inflammatory markers before and after immunomodulation, duration of mechanical ventilation after starting treatment, and survival to discharge.

Research results

Five patients developed delayed respiratory deterioration in the absence of new infection, fluid overload or extra-pulmonary organ dysfunction at a median interquartile range (IQR) duration of 32 (23-35) d after the onset of symptoms. These patients had elevated inflammatory markers, required mechanical ventilation for 13 (IQR 10-23) d, and responded to glucocorticoids and/or intravenous immunoglobulin. One patient died (20%).

Research conclusions

This delayed respiratory worsening with elevated inflammatory markers and clinical response to immunomodulation

appears to contrast the well described MIS-A by the paucity of extrapulmonary organ involvement. The diagnosis can be considered in patients presenting with delayed respiratory worsening, that is not attributable to cardiac dysfunction, fluid overload or ongoing infections, and associated with an increase in systemic inflammatory markers like C-reactive protein, inteleukin-6 and ferritin. A good response to immunomodulation can be expected. This delayed inflammatory pulmonary syndrome may represent a distinct clinical entity in the spectrum of inflammatory syndromes in COVID-19 infection.

Research perspectives

Larger prospective studies are required to validate these preliminary observations and formulate treatment guidelines for this inherently reversible entity.

ACKNOWLEDGEMENTS

The authors acknowledge the contributions of the healthcare team in the management of patients during the COVID-19 pandemic.

FOOTNOTES

Author contributions: Bose P, Chacko B, Oliver A, and Peter JV designed and performed the research and wrote the paper, performed literature search, reviewed the final manuscript, and approved for publication; Leena RV, Balamugesh T, George MV, Mohan J, and Audrin L provided clinical advice, literature review, reviewed the final manuscript and approved the manuscript for publication; Peter JV designed the research and supervised the report.

Institutional review board statement: The study was approved by the Institutional Review Board of the institution, (CDSCO- Ethics Committee Registration number: ECR/326/INST/TN/2013/RR-2019; DHR provisional registration number: EC/NEW/INST//2020/818; IRB Min No. 14513, approval date 23.02.2021, study title: "Pulmonary hyperinflammation syndrome in survivors of critically ill COVID-19 Long stayers in ICU – a case series").

Informed consent statement: In view of the retrospective nature of the study, the large number of COVID-19 patients admitted in the ICU, and deidentification of clinical data, informed consent waiver was obtained from the institutional review board.

Conflict-of-interest statement: There was no conflict of interest or any financial disclosure for all the authors listed in the manuscript.

Data sharing statement: No additional data are available.

Country/Territory of origin: India

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

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