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MINIREVIEWS

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

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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.

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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

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