Outcome Prediction in Infectious Disease

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ABSTRACT

Sepsis is a critical, life-threatening condition that demands precise prediction to mitigate adverse outcomes. The heterogeneity of sepsis leads to variable prognoses, making early and accurate identification increasingly difficult. Despite ongoing advancements, no single gold standard has emerged for sepsis prediction. Current research explores a range of prognostic tools, from traditional scoring systems and biomarkers to cutting-edge omics technologies and artificial intelligence. These tools can differ significantly across patient populations and clinical settings, such as the emergency department (ED) and intensive care unit (ICU). This review aims to critically evaluate the development and application of outcome prediction modalities in sepsis and other infectious diseases, highlighting the progress made and identifying areas for further research.

Keywords**:** *Outcome prediction, Infectious Disease, Sepsis*

INTRODUCTION

Sepsis is a life-threatening condition of organ dysfunction due to dysregulation of immune system response against infection.[1] This life-threatening condition needs to be predicted to prevent further deterioration. Delay in the recognition can lead to septic shock and eventually death. Furthermore, sepsis shows heterogeneous signs and symptoms which may lead to various outcomes, thus, identifying which patient with a high risk of poor progression is essential.[2] The recognition of poor outcomes leads to improvement in patient care, including fluid resuscitation, use of antibiotics, source control, and more aggressive treatment to increase patient outcomes.[3,4]

Numerous predictors have been debated for predicting the mortality of patients with infection. Some predictors solely rely on rapid bedside parameters, suitable for emergency department settings, while others involve more complex laboratory procedures. Some perform excellently in predicting short-term mortality, while others are best suited for long-term mortality. Thus, each predictor has its advantages and disadvantages based on its settings.[5,6] Other than timely identification, predictors also need to exhibit high accuracy, which is challenging given the heterogeneity of septic patients. The objective of this review is to discuss the development of different outcome prediction tools used in septic patients.

DEVELOPMENT OF SEPSIS DEFINITION

The definition of sepsis is critical for assessing the impact of infection on organ dysfunction and stratifying patients based on their risk of mortality. Furthermore, definition

is essential for advancing our understanding of sepsis pathogenesis, which contributes to the development of precision medicine and targeted therapies.

In the first consensus achieved in 1991, sepsis was defined as documented or suspected infection with Systemic Inflammatory Response Syndrome (SIRS) criteria. Severe sepsis was defined as sepsis accompanied by organ dysfunction, hypoperfusion, or hypotension, and septic shock was defined as sepsis with fluid/vasopressor-resistant hypotension and hypoperfusion.[7] These definitions were found to be unspecific and can also be observed in noninfectious conditions, such as burns, pancreatitis, and others, which led to the revision of sepsis definition in 2003.[8] In Sepsis-2, the definition of sepsis developed and included SIRS with addition of some variables that represent inflammatory, hemodynamic, and signs of organ dysfunction, while severe sepsis and septic shock definitions were unchanged. Organ dysfunction was evaluated using Marshal or Sequential Organ Failure Score (SOFA) score.[8]

Later in 2014, SIRS was found to be unspecific and unable to indicate dysregulated host response nor showed a life-threatening condition. Sepsis-3 defines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection, with a SOFA score of 2 or more indicating organ dysfunction. When sepsis progresses to septic shock, it is characterized by lactate levels exceeding 2 mmol/L and the need for vasopressors to maintain a mean arterial pressure above 65 mmHg, despite adequate fluid resuscitation.[1]

CONCEPT OUTCOME PREDICTION IN SEPSIS

Sepsis-3 mentioned the role of dysregulated immune system response in the pathogenesis of sepsis.[9] The infection will cause inflammation and further complicate immunological balance disruption of inflammations and anti-inflammation pathways, thus further dysregulating immune responses and eventually causing organ dysfunction (**Figure 2**).[10–12]

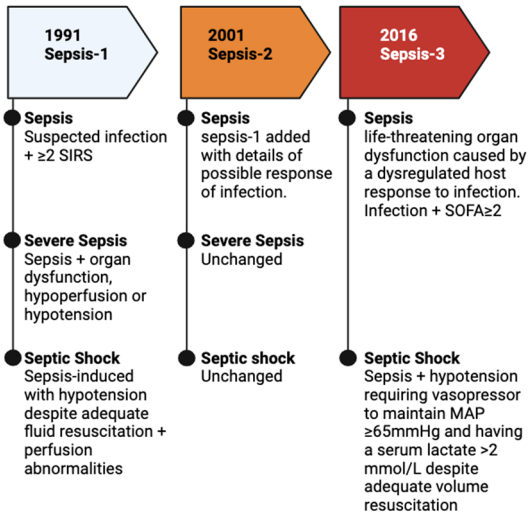

Figure 1. Development of sepsis definitions

Figure 2. Pathway of infection

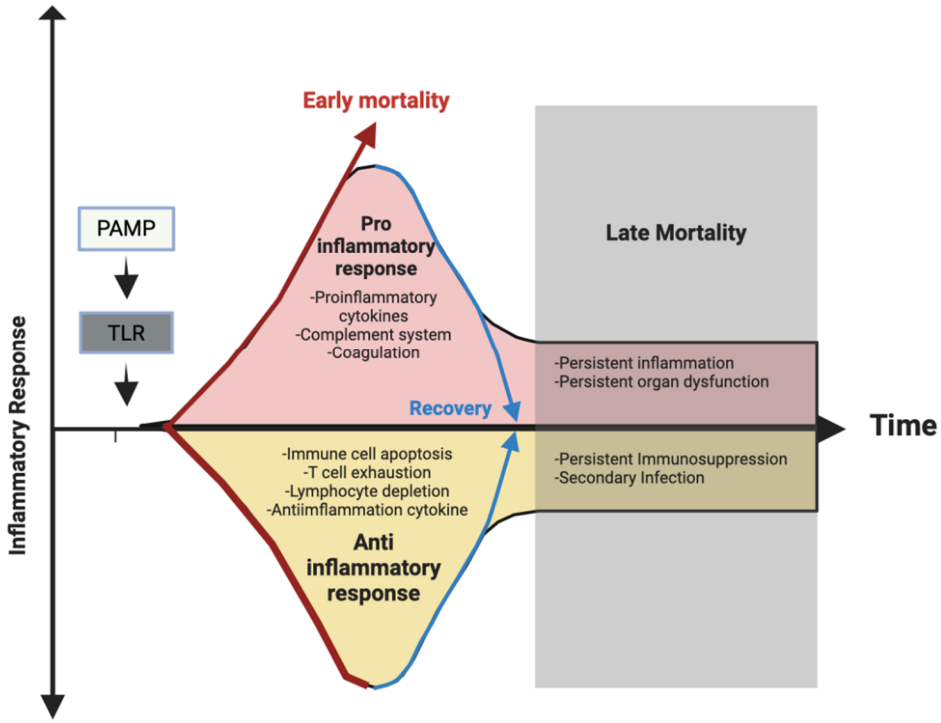

Figure 3. Concept of proinflammatory and anti-inflammatory response in sepsis

When an infection occurs, pathogen-associated molecular patterns (PAMPs) will be recognized by the specific receptors (e.g., Toll-Like Receptors). This will activate the transcription genes that have opposite activity. Both proinflammatory and anti-inflammatory mediators are upregulated, followed by inflammatory and immunosuppression processes which may happen concurrently.[13] Expression of early activation gene will increase proinflammatory cytokine, complement system, and coagulation factor. However, the dysregulated immune response causing excess immune system response also disrupts innate and adaptive immunity, hence, causing immunosuppression by extensive apoptosis of lymphocytes, decreased proinflammatory cytokines, reduced antigen-presenting capacity, decreased adhesion marker, enhanced proliferation of Treg and T cell anergy or exhaustion, and decreased antibody production. This subsequent condition is responsible for the protracted immunosuppression. The net of which hyperresponsiveness or hyporesponsiveness immunological phenotype state remains individualized.[12] Factors that determine the dysregulated immune condition include the endotype of patients, genetic predisposition of the host, phenotype, and clinical manifestation or response of the host during systemic inflammation.[12,14,15]

Hyperinflammation (cytokine storm) states usually result in acute organ failure and early mortality from sepsis. However, persistent immunosuppression generally causes secondary infection, inflammation, or organ dysfunction, resulting in late mortality (**Figure 2**).[14,16,17] These concepts influence sepsis research using patient-centered mortality rates. Most studies define short-term mortality rates as 14, 28, or 30 days and long-term mortality rates as 90 days, 6 months, 1 year, and 3 years.[18]

OUTCOME PREDICTION TOOLS

Numerous modalities have been used to predict mortality in sepsis, such as SIRS, quick Sequential Organ Failure Score (qSOFA) or SOFA, Early Warning Score (EWS), lactate, procalcitonin, and others (Supplementary **Table 1-3**). This article will discuss these modalities in predicting septic patient outcomes.

SIRS

SIRS is a term introduced by the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) in 1991 to define a systemic inflammatory response associated with patients' clinical conditions. In Sepsis-1 and Sepsis-2, SIRS combined with infectious processes define sepsis.[7] The sensitivity and specificity of SIRS in predicting mortality are 0.82 (95% CI:0.78-0.85) and 0.24 (95% CI:0.19-0.29), respectively.[19] Although it is sensitive, SIRS is unspecific, which leads to patient overdiagnosis. SIRS discrimination of hospital mortality in septic patients was significantly lower than SOFA.[1] In addition, research found that proportions of patients with sepsis who did not have two or more SIRS criteria, and the SIRS criterion is not equivalent to the risk of organ dysfunction.[20] Moreover, SIRS is observed in non-infectious conditions, such as burns, pancreatitis, etc.

SOFA

The European Society of Intensive Care Medicine (ESICM) and the SCCM replaced SIRS with SOFA scores for prognostication of mortality in 2016. This happened because a study found that SOFA's predictive validity was superior to that of SIRS.[10] It was initially named as the sequential organ failure assessment score for ICU patients but then renamed as sepsis-related organ failure assessment due to its ability to predict mortality in septic patients. The SOFA parameter accounts for systems with organ dysfunction.

The initial SOFA score on admission is an excellent prognostic tool. In addition, serial daily SOFA score evaluation correlates with patient mortality, as shown by both the serial mean score and the highest SOFA score.[21,22] The predictive validity (AUROC) of SOFA in predicting in-hospital mortality in patients with sepsis was 0.74-0.78.[1] Large cohorts of ICU and non-ICU settings for diagnosis of sepsis have validated SOFA scores and showed great performance ability in the ICU population.[1,23]

One issue is the unequal weighting of its components, meaning that each organ dysfunction does not contribute equally to the overall score. Research has shown the occurrence of organ dysfunction varies in association with mortality, suggesting some organ failures may have a stronger impact on predicting outcomes than the others.[24–26] This disparity can affect the accuracy of the SOFA score in assessing sepsis severity and predicting patient prognosis. Due to its several biomarker requirements, the SOFA score is not accessible in peripheral clinics or hospitals. A modified SOFA score (mSOFA) provides a feasible alternative for general practical settings as a triage.[27] The other shortcoming of the SOFA score is that it cannot differentiate between presenting organ failure due to sepsis or underlying disease, e.g., high creatinine level in underlying chronic kidney disease or high bilirubin in obstructive icteric patients.

qSOFA

The SCCM (2016) mentioned qSOFA for the quick and rapid stratification of patients with suspected sepsis, as a more accessible tool compared to SOFA. This tool comprises three components, i.e., blood pressure for detecting hemodynamic organ failure, respiratory rate for detecting host response as in SIRS, and Glasgow Coma Scale (GCS) under 15 for detecting organ failure.

One study reported that qSOFA has the specificity and sensitivity of 0.82 (95% CI: 0.76-0.86) and 0.46 (95% CI:0.39-0.53) in predicting mortality of suspected septic patients, respectively.[19] The study showed that qSOFA is more specific but less sensitive than SIRS for early identification of organ dysfunction; hence, it cannot screen septic patients in prehospital or emergency settings.[28–33] This limits the ability of qSOFA as a single screening tool for the timely identification of high-risk patients with infection. A meta-analysis comparing the qSOFA, SIRS, and NEWS also showed that none of the scoring systems has equal high sensitivity and specificity.[19] The SCC 2021 guideline was against the use of qSOFA as a single predictor of sepsis outcome.[3]

Early Warning Score

EWS is a simple aggregate scoring system that contains physiological measurements consisting of rapid quantitative measurements of changes

in vital signs. These are excellent prediction tools for short-term mortality outcomes (24 or 48 hours), suitable in emergency settings since they can predict the outcome of 6 to 24 hours in advance by looking through the changes in vital signs.[34,35] There are several EWS score, such as the National Early Warning Score (NEWS) and its update NEWS2, Modified Early Warning Score (MEWS), Rapid Acute Physiology Score (RAPS), Rapid Emergency Medicine Score (REMS), and Simple Early Warning Score (SEWS).[36–38] NEWS2, the updated version of NEWS, aims to increase the specificity of patients with type 2 respiratory failure. Among the scores, NEWS/NEWS2 was the most accurate predictor, with NEWS sensitivity of 74% and specificity of 96% for short-term mortality,[38] with other measurements also having equal accuracy in predicting short-term mortality, but not for long-term 30-day mortality.[39] One study reported that the area under the curve (AUC) of NEWS/NEWS2 was 0.90 for predicting 24-hour mortality.[40,41] It is comparable to qSOFA and SIRS in predicting mortality and ICU transfer in patients with suspected infection or septic patients.[41–43]

Procalcitonin

More than 250 biomarkers have been identified, especially for sepsis and sepsis-like syndrome.[44] Procalcitonin (PCT) is a biomarker for presenting bacterial infection. Its level correlated with the severity of infection and sepsis. PCT is a prohormone precursor of calcitonin. It is produced by almost all organs and macrophages in response to bacterial infections and can decrease rapidly during recovery.[3,44] Some non-infectious conditions contribute to the elevation of procalcitonin, that might confound procalcitonin levels, such as trauma, surgery, burn, cardiogenic shock, autoimmune, and severe liver disease.[45]

The role of procalcitonin as a predictor tool of mortality remains controversial. Serial increase of PCT levels on serial examination is associated with unresolved or progressive infection. An elevated level of PCT was found to be associated with a higher risk of mortality with pooled relative risk (RR) of 2.60 (95% CI, 2.05-3.30), sensitivity of 0.76 (95% CI, 0.67-0.82), and specificity of 0.64 (95% CI, 0.52-0.74).[46] In addition, the persistent elevated PCT levels also showed a prognostic value with sensitivity and specificity for predicting mortality in septic patients of 0.72 (95% CI, 0.58-0.82) and 0.77 (95% CI, 0.55-0.90), respectively.[46] On the contrary, another study showed that procalcitonin has a poor predictor of mortality, with an AUC of 0.45 (95% CI, 0.36-0.54).[47] Therefore, procalcitonin should not be used as a single predictor for assessing mortality in septic patients.

Lactate

Serum lactate is a biomarker of systemic hypoperfusion or tissue hypoxia. Tissue hypoxia causes overproduction of lactate through anaerobic glycolysis. Lactate clearance mainly involves the liver and kidney, which are affected by septic shock as part of organ dysfunction. However, lactate is also found to be increased in other conditions such as dehydration, bleeding, heart failure, liver failure, and lactic acidosis.[47] Studies have shown that elevated lactate levels at admission predict sepsis mortality, with a sensitivity of 52.4% for 3-day mortality and 51% for 28-day mortality, and specificity of 91.4% and 75%, respectively.[48,49] A study comparing lactate serum level, SOFA score, and qSOFA found lactate as an independent prognostic predictor of mortality in patients with sepsis and has a superior discriminative power than qSOFA, similar to SOFA. However, the timing of lactate compared to SOFA and qSOFA was inconsistent.[50] Lactate clearance has also been found to be useful in predicting mortality.[51]

MOLECULAR MARKER IN SEPSIS PROGNOSIS

Cytokine

Cytokines have been studied for the diagnosis and prognosis of sepsis. Among the proinflammatory cytokines, Interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α) are the most frequently studied, while IL-10 is the most frequently studied for the anti-inflammatory cytokine.

IL-6 is an early-phase proinflammatory factor that induces multiple cells to synthesize and secrete

acute-phase proteins. During infection, IL-6 leads to the production and activation of neutrophils, proliferation, and differentiation of B and T-cells, and immunoglobulin production. Elevated IL-6 in the acute phase plays a role in early diagnosis of sepsis.[52] Its levels correlate with the worsening of organ dysfunction, especially in the early stages.[53] Some studies have identified IL-6 as a risk factor for 28-day mortality in septic patients, while others found no significant correlation.[52,54,55] However, its level can also be elevated in minor infections, remain high post-infection, and increases in non-infectious inflammatory conditions, such as trauma, tumorigenesis, or surgical interventions. TNF-α is another key proinflammatory mediator in sepsis. A meta-analysis found that TNF-α levels were associated with increased 28-day mortality in sepsis patients. However, the subgroup analyses did not show a relationship with the sepsis severity.[56] In contrast, IL-10, an anti-inflammatory cytokine, suppresses proinflammatory cytokines like IL-6 and TNF-α. IL-10 limits the severity of the immune response but can lead to immunosuppression and poor outcomes; however, studies on IL-10 are still limited.[57–59]

Some research combines cytokine and scoring systems. For instance, a study by Xie et al.[60] combined IL-6, PCT, and lactate levels to predict 28-day mortality in sepsis patients. Studies using the ratio of proinflammatory to anti-inflammatory cytokines (IL-10/IL-6 ratio) have also found correlations with patient mortality in sepsis.[61]

Omics Technique

In the last decade, various omics techniques have been developed for the molecular study of sepsis, including genomics, transcriptomics, proteomics, and metabolomics (Supplementary Table 2).[62]

Genomics requires large datasets from recombinant DNA methods, DNA sequencing, and bioinformatics to analyze the genome. Genetic polymorphisms occur regularly (>1%) with two or more alleles on a chromosome. Single nucleotide polymorphisms (SNPs) are the most common type of genetic polymorphism. Several SNPs are associated with sepsis prognosis, such as CTLA-4 genetic variants. Mewes et al.[63] found that SNPs of the CTLA-4 gene can predict 28-day and 90-day survival in sepsis patients. Genomic studies also use epigenetics. Various studies on microRNAs have been conducted, yielding different results. Studies have identified miR-27a and miR-451a have mortality prediction roles while other microRNAs such as miR-126 and miR-21 microRNAs have poor prognostic value.[64–67] A study by Wang et al.[68] combined seven microRNAs—miR-223, miR-15a, miR-16, miR-122, miR-193, and miR-483-5p—and found an AUC of 0.95, higher than APACHE, SOFA, and procalcitonin in predicting mortality. Further research is needed on the use of genomic techniques, particularly concerning the pathogenesis and heterogeneity of sepsis, with data and samples having broader characteristics.

Transcriptomic biomarkers examine gene expression. Davenport et al.[69] aimed to identify interindividual variations in the transcriptome of sepsis patients and correlate these with patient outcomes. The study performed a transcriptomic analysis, identifying two groups, termed Sepsis Response Signatures (SRS1 and SRS2). The sepsis SRS1 group identified immunosuppressive phenotype with higher 14-day mortality.[69] Future studies could focus on specific patient groups and clinical trials to benefit subsets of patients through immunomodulatory therapy.

Proteomic signatures are associated with patient outcomes in sepsis. Proteomic signatures improve the accuracy of sepsis diagnosis compared to traditional biomarkers, such as C-reactive protein (CRP) and PCT. They can identify specific panels of proteins related to organ dysfunction. Proteomics is also expected to aid precision medicine by identifying dynamic changes in protein expression associated with high mortality rates.[62] Sanmartin et al.[70] analyzed plasma proteins in sepsis patients, identifying 117 proteins, nine were associated with organ dysfunction and 22 were linked to patient mortality. However, larger multicenter studies are needed to further elucidate these proteins' role in the pathogenesis of sepsis.

Metabolomic biomarkers assess metabolites and their relationship with pathophysiological changes, particularly alterations in anabolism and metabolic consumption of the organism.

Jones et al.[71] found that patients with 14,15-dihydroxyeicosatrienoic acid (DHET), a breakdown product of cell membranes by endothelial cytochrome P450 epoxygenase, were associated with organ dysfunction and 28-day mortality in patients with sepsis.[71]

THE ROLE OF ENDOTYPE

Dysregulated immune response of septic patients differs individually. This heterogeneous condition makes the prediction and treatment of sepsis challenging. Studies are now attempting to examine patient endotypic factors for prognostic and therapeutic purposes. Genomic studies have been shown to identify septic patients subclass to address its heterogeneity.[69] Endotype studies refer to the differentiation of patient subgroups based on gene expression techniques or immunological profiles. Patient endotypes can be classified using various methods, such as gene expression analysis and protein biomarker profiling, which are associated with the risk of clinical outcomes.

Study from Baghela et al.[72] classified sepsis into 5 endotypes based on their gene expression. These endotypes are correlated with the prediction of the 28-day mortality outcome of sepsis patients both in the ED and ICU. This method had an AUC of 85%, sensitivity of 68%, and specificity of 70%. It was found that differences in endotype gene expression are correlated with the severity of organ dysfunction based on its SOFA score.[72] Another study from Chenoweth G. J. et al.[74] classified four subtypes of sepsis relevant in stratifying high mortality groups. A group with low mortality exhibited molecular markers indicating a functional adaptive immune response. In contrast, the three high-mortality groups showed more severe clinical manifestations, often associated with multiple organ dysfunction. The immunosuppressed group demonstrated signs of an impaired immune response, the acute-inflammation group was characterized by molecular markers related to the innate immune response, and the immunometabolic group was defined by metabolic processes such as heme biosynthesis. This study result aligns with other studies showing mortality prediction using endotypes.[75,76] All of the studies showed reduced mortality and less severe clinical manifestation in endotype with immunocompetent adaptive immune response. While the endotype having altered adaptive immune response and coagulopathic showed increased mortality.

The role of endotype in outcome prediction showed benefits in predicting mortality of heterogeneous septic patients. It is a promising precision medicine approach for individualized outcome prediction and intervention.

OUTCOME PREDICTION IN SPECIAL POPULATION

Elderly

Studies have developed tools to predict mortality in this group of populations (Supplementary Table 3). Sepsis mortality increases correlated to age;[75] hence, early identification of high-risk patients in this group may improve their prognosis. The diverse clinical manifestation of atypical signs of this population may hinder its identification.[77]

Modification of qSOFA, the geriatric-quickSOFA, is proposed due to the incapability of assessing GCS as an alteration of mental status in this subset group, particularly in elderly people with pre-existing cognitive disorders. Geriatric-qSOFA includes the presence of delirium instead of abnormal GCS. It was shown to predict short-term mortality risk for elderly patients with sepsis.[78] Frailty Index (FI) is another tool that is also used for elderly patients. Frailty is a condition of multisystem physiological reserve decline and inability to maintain homeostasis associated with accumulated age-related deficits.[79,80] The FI is characterized by three or more of the following criteria: unintentional weight loss (10 lbs in the past year), self-reported exhaustion, weakness (grip strength), slow walking velocity, and low physical activity.[81] It is a significant predictor of mortality for both in-hospital and 3-month mortality in elderly patients with sepsis.[79,80,82]

Malignancy

Many patients with malignancy have fulfilled SIRS criteria without existing infection. Thus, it was found that SOFA was more sensitive

Supplementary Table 1. Accuracy of conventional and biomarker sepsis mortality predicting tools

Author/ Year	Outcome prediction tools	Population	Sepsis definitio	Settings	Design	Sensitivity (%)	Specificity (%)	AUC in predicting mortality	Measured mortality	Conclusion
Conventional scoring tools										
Wang/ 2022	SIRS, qSOFA, NEWS	62,338 patients (26 studies) with sepsis/ suspected sepsis	Sepsis-3	ED	Meta-Analysis	qSOFA: 82; SIRS: 46; NEWS 82	qSOFA: 24; SIRS:24	qSOFA: 0.63	In-hospital mortality, 30-day,60-day	qSOFA is more accurate than SIRS and NEWS in the ED, all these scoring systems have limitations in balancing sensitivity and specificity
Seymour/2016	SOFA	352 patients with suspected infection	N/A	ED, HW, ICU	Prospective cohort study	NR	NR	ICU: SIRS:0.64, SOFA: 0.74. Non-ICU qSOFA: 0.81; SOFA:0.79 and SIRS: 0.76 (SIRS;SOFA)	In-hospital mortality	SOFA is highly effective for predicting mortality in ICU patients, while qSOFA is more effective than SOFA and SIRS in non-ICU settings
Raith/ 2017	SOFA, SIRS qSOFA	184,875 patients with suspected infection	Sepsis-3	ICU	Retrospective cohort study	NR	NR	SOFA: 0.753 SIRS: 0.58; qSOFA: 0.60	In-hospital mortality	For adults with suspected infections in the ICU, the SOFA score provides a more accurate prediction of in-hospital mortality compared to SIRS criteria or the qSOFA.
Grissom/2010	modified SOFA	1,770 patients admitted	NR	ICU, HW	Retrospective cohort study	NR	NR	1-day: 0.83; 0.84 3-day: 0.79; 0.78 5-day: 0.74; 0.72 (MSOFA;SOFA)	1-day, 3-day, 5-day	The MSOFA predicts mortality similarly to the SOFA but it is more feasible to be implemented in resource-limited settings.
Wang/ 2022	qSOFA, SIRS, NEWS	62,338 patients (26 studies) with sepsis or suspected sepsis	Sepsis-3	ED	Meta-Analysis	0.46	0.82	0.69	In-hospital mortality, 28-day, 30-day, 60-day	qSOFA was superior compared to SIRS and NEWS. None exhibits both high sensitivity and specificity.
Goulden/2018	qSOFA, SIRS, NEWS	1,818 patients with suspected and treated sepsis	Sepsis-3	ED	Retrospective cohort study	NEWS: 75; SIRS 80; qSOFA 37	NEWS: 43; SIRS: 21; qSOFA: 79	NEWS: 0.65; qSOFA: 0.62; SIRS: 0.49	In-hospital mortality	NEWS exhibits comparable or superior performance compared to SIRS and qSOFA.
Park/ 2017	qSOFA, SIRS	1,009 patients with suspected infection	NR	ED	Retrospective cohort study	qSOFA: 53	qSOFA: 84	qSOFA: 0.73; SIRS: 0.599	In-hospital mortality	The qSOFA score is more accurate than the SIRS criteria at predicting organ failure and mortality.
Moskowitz/2017	qSOFA, SIRS	22,164 patients with suspected infection	Sepsis-3	ED	Retrospective cohort study	qSOFA: 39; SIRS: 80	qSOFA: 87; SIRS: 44	qSOFA: 0.74; SIRS: 0.66	In-hospital mortality	ED patients with suspected infections with low qSOFA scores are often still misclassified as 'low risk,' with low sensitivity.
Tusgul/ 2017	qSOFA, SIRS	886 patients with suspected or proven infection	Sepsis-3	Pre-hospital, ED	Retrospective cohort study	Pre-hospital: (60, 64, <60); ED:(60; 80: 60) (qSOFA, SIRS, Sepsis-3)	NR	NR	48-hour	qSOFA, SIRS, and sepsis-3 definition have low sensitivity in selecting septic patients in the pre-hospital or the ED at risk of complication.

Askim/ 2017	qSOFA, RETTS	1,535 admitted patients with infection and sepsis symptoms	Sepsis-2	ED	Prospective cohort study	7-day: (16.62) 30-day: (13.66) (qSOFA, RETTS)	7-day: (96.53) 30-day: (96.54) (qSOFA, RETTS)	7-day qSOFA: 0.57; 30-day qSOFA: 0.54	7-day, 30-day	The qSOFA score was ineffective as a risk stratification tool due to its low sensitivity in predicting 7-day and 30-day mortality
Covino/ 2023	NEWS, NEWS2, MEWS, RAPS, REMS, and SEWS	225,369 patients in the ED	N/A	ED	Retrospective cohort study	NEWS 81.5; NEWS2 82.9; MEWS 84.1 RAPS 48.4 REMS 64,5	NEWS 88.9 NEWS2 87.5 MEWS 86.8 RAPS 94.7 REMS 90.4	NEWS 0.904; NEWS2 0.901; MEWS 0.088 RAPS 0.821, REMS 0.874	24-hour	NEWS is the most precise early warning system for predicting the risk of death or ICU admission within 24 hours of arrival at the emergency department.
Liu/2020	NEWS, BTF, qSOFA, SIRS	773,477 hospitalized patients with and without infection	Sepsis 3	ED, HW	Retrospective cohort study	NEWS ≥ 6: 87-89, SIRS ≥ 2: 86-87	NEWS ≥ 8: 72-74, qSOFA ≥ 2: 59-63%	NEWS: 0.86-0.87; MEWS: 0.83; qSOFA: 0.78 ; SIRS 0.76; BTF 0.73-0.74	In-hospital mortality	NEWS may be particularly effective for inpatient risk stratification in identifying patients at high risk of mortality, regardless of infection status.
Churpek/2017	qSOFA, SIRS, MEWS, NEWS	30,677 patients were admitted for suspicion of infection in the ED	Sepsis-3	ED, HW	Retrospective cohort study	SIRS:91, qSOFA: 54, MEWS:59, NEWS: 67	SIRS 13, qSOFA 67, MEWS 70, NEWS 66	NEWS 0.77; MEWS 0.73; qSOFA 0.69; SIRS 0.65	In-hospital mortality	EWS is more precise than the qSOFA score in predicting death and ICU transfer for non-ICU patients.
Biomarkers										
Liu/2015	Procalcitonin	23 studies with 3,994 patients	Sepsis 1,2	ED, HW, ICU	Systematic review and meta-analysis	Elevated PCT: 76, PCT non-clearance: 72	Elevated PCT: 64, PCT non-clearance: 77	Elevated PCT: 0.77, PCT non-clearance: 0.79		Elevated PCT concentrations and PCT non-clearance are strongly associated with all-cause mortality in septic patients
Schuetz/2017	Procalcitonin	646 patients with severe sepsis or septic shock were admitted to the ICU	Sepsis 1,2	ICU	Prospective multicentre observational clinical trial	77	39	NR	28-day	A reduction of procalcitonin by less than 80% serves as a major independent predictor of mortality.
Effendi/2022	Procalcitonin	128 patients with sepsis due to Gram-negative bacteria	Sepsis 3	ED, HW, ICU	Retrospective cohort study	40	50	0.45	28-day	Procalcitonin has poor performance in predicting mortality in patients with sepsis caused by Gram-negative bacteria
Villar/2019	Lactate	Admitted patient with or without sepsis	Sepsis-3	ED, HW, ICU	Retrospective cohort study	3-day: 52;	3-d: 91	NR	3-day, 30-day, 1-year	Lactate increases mortality risk for all patients; Lactate showed a higher risk of 30-day (OR:2.6) and 1-year (OR:1.8) mortality.

BTF, Between the Flags; ED, Emergency Department; HW, Hospital Ward; ICU, Intensive Care Unit; mSOFA, Modified Sequential Organ Failure Assessment; MEWS, Modified Early Warning Score; NEWS, National Early Warning Score; NR, Not Reported; N/A, Not Applicable; PCT, Procalcitonin; RAPS, Rapid Acute Physiology Score; REMS, Rapid Emergency Medicine Score; RETTS, Rapid Emergency Triage and Treatment System; SEWS, Standardized Early Warning Score; SIRS, Systemic Inflammatory Response Syndrome; qSOFA, Quick Sequential Organ Failure Assessment.

Supplementary Table 2. Accuracy of molecular sepsis mortality predicting tools

Author/ Year Molecular biomarker	Outcome prediction tools	Population	Sepsis definition	Settings	Design	Sensitivity (%)	Specificity (%)	AUC in predicting mortality	Measured mortality	Conclusion
Yu/ 2022	IL-6	128 septic patients in ED	Sepsis 3	ED	Prospective cohort study	68	82	0.76	28-day	IL-6 is not significantly correlated with 28-day mortality in patients with sepsis
Song/ 2019	IL-6, Pentraxin 3	142 patients (51 sepsis, 46 septic shock, 45 control)	Sepsis 3	ED	Prospective controlled study	IL-6: 63; PTX3:56; IL-6+PTX: 82	IL-6: 78; PTX3: 76; IL-6+PTX3: 76	IL-6: 0.79; PTX3: 0.7; IL-6+PTX3: 0.8	30-day	IL-6 is an independent risk factor for 28-day mortality and superior to PTX3 and PCT for sepsis and septic shock.
Suhua/ 2019	PCT, hs-CRP, IL-6	66 patients with sepsis	Sepsis-3	ED, ICU	Prospective cohort study	PCT: 94; hs-CRP: 83; IL-6 82	PCT: 73; hs-CRP: 64; IL-6: 71	PCT: 0.88; hs-CRP: 0.76; IL-6: 0.77	28-day	Serum level of PCT, hs-CRP, and IL-6 associated with sepsis patients 28-day mortality
Matera/ 2013	IL-10, soluble CD25, and interferon-γ	52 patients admitted with criteria of sepsis	Sepsis 1	ED, HW, ICU	Prospective cohort study	24-hour:IL-10: 91, sCD25: 83, IFN- γ: 50, PCT: 83, SOFA: 83. 7-day : IL-10: 100, sCD25: 91, IFN- γ: 66, PCT: 75, SOFA: 100	24-hour: IL-10: 86, sCD25: 83, IFN- γ: 86, PCT: 69, SOFA: 83. 7-day:IL-10: 95, sCD25: 91, IFN- γ: 95, PCT: 95, SOFA: 86	24-hour: IL-10: 0.94, sCD25: 0.79, IFN-γ: 0.59, PCT: 0.76, SOFA: 0.87. 7-day: IL-10: 0.97, IFN-γ: 0.81, PCT: 0.90, SOFA: 0.94	24-hour, 7-day	sCD25 and IL-10 are independent predictors of a poor outcome during the first day of hospital admission
Xie/ 2023	IL-6, PCT, lactate	367 septic patients	Sepsis-3	ED	Retrospective cohort study	NR	NR	0.849	28-day	Combined serial IL-6, lactate, PCT of IL-6D1, IL-6D3, PCTD1, PCTD3, and LACcD3 best model in predicting mortality
Ou/ 2022	MiR-27a	23 septic patients and 25 patients without sepsis	Sepsis 3	ED	Retrospective cohort study	80	64	0.73	28-day	Circulating miR-27a correlated with mortality in patients with sepsis.
Geng/ 2022	MiR-451a, Th1/ Th2	117 septic patients and 50 controls	Sepsis 3	NR	Prospective cohort study	NR	NR	miR-451:0.77; Th1/Th2: 0.76	28-day	MiR-451a and Th1/Th2 ratio correlated with mortality risk in patients with sepsis.
Lin/ 2020	miRNA-126	208 sepsis patients and 210 healthy controls	Sepsis 2	NR	Prospective cohort study	81	44	0.61	28-day	miR-126 was able to predict mortality in sepsis with poor AUC
Na/2020	miRNA-21	219 septic patients	Sepsis-3	NR	Prospective cohort study	NR	NR	0.58	28-day	miR-21 exhibited a poor predictive value for 28-day mortality risk in sepsis patients
Wang/ 2012	miR-223, 15a,16,122,193, and 5p	214 septic patients	Sepsis 1	NR	Prospective cohort study	88	90	0.95	28-day	The six miRNAs were found to be valuable predictors of sepsis mortality
Sanmartin/ 2022	Proteomic	141 patients with sepsis	Sepsis 3	ED, HW, ICU	Prospective cohort study	81	84	0.82	In-hospital mortality	Proteomic patterns associated with organ dysfunction and mortality.
Baghela/ 2022	Classified five endotype	348 patients in ED and ICU, and 44 healthy controls	Sepsis 1,3	ED, ICU	Prospective cohort study	68	70	0.75	28-day	The severity and endotype signatures indicate distinct immune signatures precede the onset of severe sepsis and lethality
Chenowth/ 2024	Classified four sepsis endotype	494 patients with sepsis	Sepsis 1	ED, HW	Prospective cohort study	NR	NR	0.812	28-day	Molecular endotypes in sepsis that support immunotherapeutic intervention and predict outcomes in these groups.

ED, Emergency Department; HW, Hospital Ward; ICU, Intensive Care Unit; IFN, Interferon; IL, Interleukin; hs-CRP, High-sensitivity C-reactive Protein; MiR, MicroRNA; NR, Not Reported; N/A, Not Applicable; PCT, Procalcitonin; PTX, Pentraxin; RAPS, Rapid Acute Physiology Score; REMS, Rapid Emergency Medicine Score; RETTS, Rapid Emergency Triage and Treatment System; SEWS, Standardized Early Warning Score; SIRS, Systemic Inflammatory Response Syndrome; SOFA, Sequential Organ Failure Assessment; sCD25, Soluble CD25; Th1/Th2, T-helper 1/T-helper 2.

Supplementary Table 3. Accuracy of mortality predicting tools in special populations and machine learning

Author/ Year	Outcome prediction tools	Population	Sepsis definition	Settings	Design	Sensitivity (%)	Specificity (%)	AUC in predicting mortality	Measured mortality	Conclusion
Prognostic tools in specific populations										
Remelli/ 2021	geriatric-quickSOFA	165 elderly patients with sepsis or septic shock	Sepsis-3	HW	Retrospective Cohort Study	Geriatric-qSOFA:92, qSOFA: 73	Geriatric qSOFA: 50; qSOFA: 40	Geriatric qSOFA: 0.8, qSOFA 0.48	30-day	Geriatric-qSOFA is significantly associated with short-term mortality in older patients with sepsis than traditional quick-SOFA.
Murldharan/ 2022	Frailty index, SOFA, qSOFA, SIRS	50 elderly patients with suspected sepsis	NR	ED, HW, ICU	Prospective cohort study	FI: 88	SOFA: 95	In-hospital: (0.88; 0.76; 0.53; 0.54) 3-month: (0.84; 0.54; 0.51; 0.50) (FI, SOFA, qSOFA, and SIRS)	In-hospital mortality, 3-month	The frailty index had greater sensitivity among other scores in predicting in-hospital mortality, whereas SOFA had higher specificity in predicting in-hospital mortality. The frailty index was superior to SOFA in predicting 3-month mortality
Costa/ 2018	SOFA,qSOFA, SIRS	450 cancer patients admitted to ICU with suspected infection	Sepsis-2, 3	ICU, HW	Retrospective cohort study	ICU mortality: (65, 78, 96) Hospital mortality: (67, 72, 95) (SIRS, qSOFA, SOFA)	ICU mortality: (52, 52, 13). Hospital mortality: (44, 59, 15) (SIRS, qSOFA, SOFA)	ICU mortality: 0.62; 0.71; 0.76; Hospital mortality: 0.58; 0.69; 0.69 (SIRS, qSOFA, SOFA)	In-hospital mortality	SOFA and qSOFA were more sensitive and accurate than SIRS in predicting ICU and hospital mortality for critically ill cancer patients with suspected infection
Probs/ 2019	SOFA,qSOFA, SIRS	450 patients with haematological cancer	Sepsis 3	ICU, HW	Multicentre retrospective cohort study	SIRS, SOFA, and qSOFA score: 79, 76, 45	SIRS, SOFA, and qSOFA score: 19, 69, 85	SIRS, SOFA, and qSOFA score: 0,49, 0,69, 0,67	In-hospital mortality	An increase in SOFA score of ≥ 2 had better prognostic accuracy for both diagnosis and in-hospital mortality in haematological patients with sepsis
Guarino/2021	qSOFA, modified qSOFA	1,001 patients with sepsis and septic shock	NR	ED	Retrospective cohort study	MqSOFA, qSOFA: 77, 61	MqSOFA, qSOFA: 67, 72	MqSOFA, qSOFA: 0.805, 0.712	In-hospital mortality	MqSOFA provided a better predictive score than qSOFA regarding patient outcomes.
Sinto/ 2020	Lactate-qSOFA	1,213 patients with suspected bacterial infection	Sepsis 3	ED	Prospective cohort study	SOFA, qSOFA, qSOFA-lactate, SIRS: 89, 78, 55, 2	SOFA, qSOFA, qSOFA-lactate, SIRS: 49, 47, 92, 11	SOFA qSOFA,qSOFA-lactate, SIRS: 0.75; 0.70; 0.74; 0.54	28-day	The prognostic accuracy of the qSOFA-lactate criteria is as good as SOFA criteria in the emergency department of a hospital with limited resource
Wright/ 2022	Lactate-qSOFA	4,980 patients with suspected infection	Sepsis-3	ED, HW, ICU	Cohort prospective study	92	35	qSOFA, lactate, qSOFA-lactate, mSOFA: 0.68; 0.76; 0.78; 0.77	28-day	POCT lactate combined with qSOFA can identify mortality risk with greater accuracy than qSOFA score alone, and with similar accuracy to mSOFA score.
Liu/ 2020	Lactate-qSOFA	821 mixed sepsis patients	Sepsis-3	ED	Retrospective cohort study	NR	NR	LqSOFA,qSOFA, SIRS, MEWS, MEDS:0.75; 0.71; 0.70; 0.68; 0.67	28-day	LqSOFA is a superior prognostic tool for predicting mortality in the hospital

Dadeh/ 2022	NEWS-lactate	92 patients with sepsis	Sepsis 3	ED	Prospective cohort study	NEWS-L and NEWS 24-h mortality: 100, 67	NEWS-L and NEWS 24-h mortality: 56, 91	NEWS-L 14-hour, 48-hour, 28-day, and in-hospital mortality: 0.86; 0.90; 0.81; 0.83; and 0.837	14-hour, 48-hour, 28-day, in-hospital mortality	NEWS-L is an accurate predictor for 24-hour mortality in septic patients in the ED. NEWS–L performed better than NEWS for each outcome.
Machine-Learning										
Selcuk/ 2022	Eight ML methods	200 patients admitted to ICU with sepsis or septic shock	Sepsis-3	ICU	Retrospective cohort study	MLP APACHE II vs SAPS II vs SOFA: 77,77,58	MLP APACHE II vs SAPS II vs SOFA: 88, 93, 85	MLP APACHE II, SAPS II, SOFA: 0.84; 0.85; 0.73	In-hospital mortality	There is a potential use of ML methods in predicting ICU mortality superior to traditional scores APACHE II, SAPS II, and as good as SOFA
Karlsson/2021	Machine learning model	445 septic patients	Sepsis 2	ED	Retrospective cross-sectional	7-day :84; 30-day :87	7-day: 67; 30-day: 64	7-day: 0.83. 30-day: 0.80	7-day, 30-day	Six specific variables were predictive of 7- and 30-day mortality with good accuracy among septic patients presenting to the ED
Park/ 2022	Four ML model	923,759 patients with sepsis	N/A	HW, ICU	Retrospective cohort study	70- 83	72-79	0.78- 0.89	In-hospital mortality	ML approaches can improve sensitivity, and specificity in predicting in-hospital mortality in patients with sepsis.

ED, Emergency Department; FI, Frailty Index; HW, Hospital Ward; ICU, Intensive Care Unit; ML, Machine Learning; NEWS, National Early Warning Score; NR, Not Reported; N/A, Not Applicable; qSOFA, Quick Sequential Organ Failure Assessment; SIRS, Systemic Inflammatory Response Syndrome; SOFA, Sequential Organ Failure Assessment.

and accurate than SIRS in predicting ICU and hospital mortality in cancer patients with suspected infection.[83,84] Performance status (PS) score reflects cancer patients' functional ability. PS showed a mortality predictive value in cancer patients, including patients with sepsis.[85–87]

Immunocompromised

Patients who are immunocompromised, including patients with the use of high-dose steroids, organ transplants, and HIV/AIDS, are more prone to develop sepsis. This population will also benefit from the early identification and prompt treatment of sepsis. However, the recognition of sepsis is more intricate due to the altered immune response. Studies on outcome predictions in these populations are still limited. In the study of septic patients using high-dose steroids, NEWS was found to be better than qSOFA in predicting short-term mortality.[88] In patients with allogeneic hematopoietic cell transplant, NEWS also outperformed qSOFA and SIRS in short-term mortality prediction.[89] While in HIV patients, proinflammatory cytokine biomarkers like IL-6 and IL-10 are associated with predicting mortality in septic patients.[90]

THE USE OF MULTIPLE PREDICTOR

None of the scoring systems that are easy to perform in the emergency department, such as qSOFA, SIRS, and NEWS, demonstrated both high sensitivity and specificity. Many studies tried to combine predictors to enhance the sensitivity and specificity in predicting mortality for septic patients.

QSOFA-Lactate

Studies have found that the use of qSOFA combined with lactate will increase its performance. It only requires simple bedside lactate testing. It is a promising prognostic tool for hospitals with limited resources.[91] Lactate-qSOFA (LqSOFA) studies showed an increased AUROC, while the sensitivity and specificity differed between studies. Studies indicating increased sensitivity resulted in decreased specificity, whereas those showing increased specificity demonstrated the opposite effect.[92] The combined LqSOFA prognostic accuracy was significantly higher than SIRS and qSOFA alone.[91,93,94] However, the confounding factors of lactate are still applied to this modality. The lactate cut-off and timing of lactate measurement also influence its predictive performance. Lastly, the use of venous lactate point-of-care compared to arterial lactate is still debatable.[92]

NEWS-Lactate

A study showed the use of NEWS with lactate also improves its predicting ability of septic patients for 24-hour, 28-hour, and 48-hour mortality, and ICU admission. In this study, the addition of lactate increases the sensitivity of NEWS in early mortality prediction.[95] However, the size of the study was still limited. To date, the study of NEWS-L in septic patients is still limited.

Future clinical studies that combine predictors to increase prognostic ability performance may be beneficial.

ROLE OF MACHINE-LEARNING MODEL

In recent years, machine-learning algorithms have been developed (**Supplementary Table 3**). This model needs a large subject with big data to develop create and validate models. Machine learning builds a predictive model for outcome prediction. Variable that predictive models used are diverse, such as patients' demographics, clinical manifestation, vital signs, hematology parameters, renal function, electrolyte, enzyme, albumin, liver function, bilirubin, lipids, protein gene expression, and others.[96] Studies found that machine learning to be superior to conventional scoring systems in predicting sepsis mortality.[97–99] It showed good sensitivity and specificity in predicting septic patient mortality.[96,100,101] However, further studies and more extensive datasets are needed for the validation of machine-learning models to be adopted in real hospital settings.[102]

PROGNOSTIC TOOLS IN PRECISION MEDICINE

All septic patients should receive standard sepsis therapy, including the one-hour bundle protocol, which is essential for management. Despite this, sepsis mortality rates remain high. Precision medicine addresses the heterogeneity of sepsis by providing personalized treatment

options based on individual characteristics, such as genetic profiles, biomarkers, and omics data. This approach enables the identification of factors associated with high mortality risks and allows for targeted therapies, particularly for those unresponsive to conventional treatments. For example, septic patients with a high mortality risk due to immunoparalysis endotype, specific hemodynamic phenotypes, or hypercytokinemia, could benefit from interventions such as immunoadjuvants, customized resuscitation, and cytokine hemoadsorption. These tailored approaches help manage the individual variations in disease manifestation.[103–106]

CONCLUSION

Sepsis is a heterogeneous condition with disparities and different outcomes. Early identification of this life-threatening condition is beneficial. The NEWS/NEWS2, SOFA, SIRS, SOFA, and other scoring systems provide valuable insights into patient status and prognosis, though their effectiveness can vary depending on patient demographics and specific conditions. Biomarkers like procalcitonin and lactate, alongside advanced techniques, such as omics and genotyping, offer additional layers of precision in sepsis management. Emerging technologies, particularly artificial intelligence, hold great potential for enhancing predictive accuracy and personalized treatment. However, to fully integrate these advanced methods into clinical practice, further large-scale studies and data validations are essential to fully integrate these advanced methods into clinical practice.

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CONFLICT OF INTEREST

All authors declare no competing interests.

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REFERENCES

1. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis. JAMA. 2016;315(8):762.
2. Datta D, Conway Morris A, Antonelli J, et al. Early PREdiction of Severe Sepsis (ExPRES-Sepsis) study: protocol for an observational derivation study to discover potential leucocyte cell surface biomarkers. BMJ Open. 2016 Jul 1;6(8):e011335.
3. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021;49(11):e1063–143.
4. Bassetti D, Bassetti M, Mantero E. Strategies for antibiotic selection in empirical therapy. Clin Microbiol Infect. 2000;6:98–100.
5. Javed A, Guirgis FW, Sterling SA, et al. Clinical predictors of early death from sepsis. J Crit Care. 2017;42:30–4.
6. Schertz AR, Lenoir KM, Bertoni AG, et al. Sepsis prediction model for determining sepsis vs SIRS, qSOFA, and SOFA. JAMA Netw Open. 2023;6(8):e2329729.
7. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest. 1992;101(6):1644–55.
8. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med. 2003;31(4):1250–6.
9. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis. JAMA [Internet]. 2016;315(8):762. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2016.0288
10. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801.
11. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new clinical criteria for septic shock. JAMA. 2016;315(8):775.
12. Jarczak D, Kluge S, Nierhaus A. Sepsis—pathophysiology and therapeutic concepts. Front Med. 2021;8.
13. Liu D, Huang SY, Sun JH, et al. Sepsis-induced immunosuppression: mechanisms, diagnosis and current treatment options. Mil Med Res. 2022;9(1):56.
14. Darden DB, Kelly LS, Fenner BP, et al. Dysregulated immunity and immunotherapy after sepsis. J Clin Med. 2021;10(8):1742.
15. Lelubre C, Vincent JL. Mechanisms and treatment of organ failure in sepsis. Nat Rev Nephrol. 2018;14(7):417–27.
16. van der Poll T, Shankar-Hari M, Wiersinga WJ. The immunology of sepsis. Immunity. 2021;54(11):2450–64.
17. Delano MJ, Ward PA. Sepsis-induced immune dysfunction: can immune therapies reduce mortality?

J Clin Investig. 2016;126(1):23–31.
18. Marshall JC, Vincent JL, Guyatt G, et al. Outcome measures for clinical research in sepsis: A report of the 2nd Cambridge Colloquium of the International Sepsis Forum. Crit Care Med. 2005;33(8):1708–16.
19. Wang C, Xu R, Zeng Y, et al. A comparison of qSOFA, SIRS and NEWS in predicting the accuracy of mortality in patients with suspected sepsis: A meta-analysis. Rostami A, editor. PLOS ONE. 2022;17(4):e0266755.
20. Kaukonen KM, Bailey M, Pilcher D, et al. Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis. N Engl J Med. 2015;372(17):1629–38.
21. Ferreira FL. Serial Evaluation of the SOFA Score to Predict Outcome in Critically Ill Patients. JAMA. 2001;286(14):1754.
22. Jain A, Palta S, Saroa R, et al. Sequential organ failure assessment scoring and prediction of patient's outcome in Intensive Care Unit of a tertiary care hospital. J Anaesthesiol Clin Pharmacol. 2016;32(3):364.
23. Raith EP, Udy AA, Bailey M, et al. Prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. JAMA. 2017;317(3):290.
24. Pölkki A, Pekkarinen PT, Takala J, et al. Association of Sequential Organ Failure Assessment (SOFA) components with mortality. Acta Anaesthesiol Scand. 2022;66(6):731–41.
25. Capan M, Hoover S, Ivy JS, et al. Not all organ dysfunctions are created equal – Prevalence and mortality in sepsis. J Crit Care. 2018;48:257–62.
26. Raschke RA, Agarwal S, Rangan P, et al. Discriminant accuracy of the SOFA score for determining the probable mortality of patients with COVID-19 pneumonia requiring mechanical ventilation. JAMA. 2021;325(14):1469.
27. Grissom CK, Brown SM, Kuttler KG, et al. A modified sequential organ failure assessment score for critical care triage. Disaster Med Public Health Prep. 2010;4(4):277–84.
28. Williams JM, Greenslade JH, McKenzie J V., et al. Systemic inflammatory response syndrome, quick sequential organ function assessment, and organ dysfunction. Chest. 2017;151(3):586–96.
29. Goulden R, Hoyle MC, Monis J, et al. qSOFA, SIRS and NEWS for predicting inhospital mortality and ICU admission in emergency admissions treated as sepsis. Emerg Med J. 2018;35(6):345–9.
30. Park HK, Kim WY, Kim MC, et al. Quick sequential organ failure assessment compared to systemic inflammatory response syndrome for predicting sepsis in emergency department. J Crit Care. 2017;42:12–7.
31. Moskowitz A, Patel P V., Grossestreuer A V., et al. Quick sequential organ failure assessment and systemic inflammatory response syndrome criteria as predictors of critical care intervention among patients with suspected infection*. Crit Care Med. 2017;45(11):1813–9.
32. Tusgul S, Carron PN, Yersin B, et al. Low sensitivity of qSOFA, SIRS criteria and sepsis definition to identify infected patients at risk of complication in the prehospital setting and at the emergency department triage. Scand J Trauma Resusc Emerg Med. 2017;25(1):108.
33. Askim Å, Moser F, Gustad LT, et al. Poor performance of quick-SOFA (qSOFA) score in predicting severe sepsis and mortality – a prospective study of patients admitted with infection to the emergency department. Scand J Trauma Resusc Emerg Med. 2017;25(1):56.
34. Burgos-Esteban A, Gea-Caballero V, Marín-Maicas P, et al. Effectiveness of early warning scores for early severity assessment in outpatient emergency care: A systematic review. Front Public Health. 2022;10.
35. Holland M, Kellett J. A systematic review of the discrimination and absolute mortality predicted by the National Early Warning Scores according to different cut-off values and prediction windows. Eur J Intern Med. 2022;98:15–26.
36. Royal college of physicians. National Early Warning Score (NEWS) standardising the assessment of acute-illness severity in the NHS. London: RCP; 2012.
37. Royal college of physicians. National Early Warning Score (NEWS) 2 standardising the assessment of acute-illness severity in the NHS. London: RCP; 2017.
38. Covino M, Sandroni C, Della Polla D, et al. Predicting ICU admission and death in the Emergency Department: A comparison of six early warning scores. Resuscitation. 2023;190:109876.
39. Hoikka M, Silfvast T, Ala-Kokko TI. Does the prehospital national early warning score predict the short-term mortality of unselected emergency patients? Scand J Trauma Resusc Emerg Med. 2018;26(1):48.
40. Burgos-Esteban A, Gea-Caballero V, Marín-Maicas P, et al. Effectiveness of early warning scores for early severity assessment in outpatient emergency care: A systematic review. Front Public Health. 2022;10.
41. Loisa E, Kallonen A, Hoppu S, et al. Ability of the national early warning score and its respiratory and haemodynamic subcomponents to predict short-term mortality on general wards: a prospective three-centre observational study in Finland. BMJ Open. 2022;12(4):e055752.
42. Liu VX, Lu Y, Carey KA, et al. Comparison of early warning scoring systems for hospitalized patients with and without infection at risk for in-hospital mortality and transfer to the intensive care unit. JAMA Netw Open. 2020;3(5):e205191.
43. Churpek MM, Snyder A, Han X, et al. Quick sepsis-related organ failure assessment, systemic inflammatory response syndrome, and early warning scores for detecting clinical deterioration in infected patients outside the intensive care unit. Am J Respir Crit Care Med. 2017;195(7):906–11.
44. Póvoa P, Coelho L, Dal-Pizzol F, et al. How to use

biomarkers of infection or sepsis at the bedside: guide to clinicians. Intensive Care Med. 2023;49(2):142–53.
45. Hatzistilianou M. Diagnostic and prognostic role of procalcitonin in infections. Scientific World Journal. 2010;10:1941–6.
46. Liu D, Su L, Han G, et al. Prognostic value of procalcitonin in adult patients with sepsis: A systematic review and meta-analysis. In: Stover CM, editor. PLOS ONE. 2015;10(6):e0129450.
47. Effendi B, Pitoyo CW, Sinto R, et al. Procalcitonin prognostic value in predicting mortality among adult patients with sepsis due to Gram-negative bacteria. Med J Indones. 2022;31(1):50–5.
48. Villar J, Short JH, Lighthall G. Lactate predicts both short- and long-term mortality in patients with and without sepsis. infectious diseases: Research and treatment. 2019;12:117863371986277.
49. Mikkelsen ME, Miltiades AN, Gaieski DF, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. Crit Care Med. 2009;37(5):1670–7.
50. Liu Z, Meng Z, Li Y, et al. Prognostic accuracy of the serum lactate level, the SOFA score and the qSOFA score for mortality among adults with Sepsis. Scand J Trauma Resusc Emerg Med. 2019;27(1):51.
51. Zhang Z, Xu X. Lactate clearance is a useful biomarker for the prediction of all-cause mortality in critically ill patients. Crit Care Med. 2014;42(9):2118–25.
52. Yu B, Chen M, Zhang Y, et al. Diagnostic and prognostic value of interleukin-6 in emergency department sepsis patients. Infect Drug Resist. 2022;15:5557–66.
53. Bozza FA, Salluh JI, Japiassu AM, et al. Cytokine profiles as markers of disease severity in sepsis: a multiplex analysis. Crit Care. 2007;11(2):R49.
54. Song J, Park DW, Moon S, et al. Diagnostic and prognostic value of interleukin-6, pentraxin 3, and procalcitonin levels among sepsis and septic shock patients: a prospective controlled study according to the Sepsis-3 definitions. BMC Infect Dis. 2019;19(1):968.
55. Suhua Z, Lefeng Z, Qingli C, et al. The prognostic value of serum PCT, hs-CRP, and IL-6 in patients with sepsis. Open Life Sci. 2017;12(1):425–8.
56. Gharamti AA, Samara O, Monzon A, et al. Proinflammatory cytokines levels in sepsis and healthy volunteers, and tumor necrosis factor-alpha associated sepsis mortality: A systematic review and meta-analysis. Cytokine. 2022;158:156006.
57. Yin J, Chen Y, Huang J ling, et al. Prognosis-related classification and dynamic monitoring of immune status in patients with sepsis: A prospective observational study. W J Emerg Med. 2021;12(3):185.
58. Abe R, Hirasawa H, Oda S, et al. Up-regulation of interleukin-10 mRNA expression in peripheral leukocytes predicts poor outcome and diminished human leukocyte antigen-dr expression on monocytes in septic patients. J Surg Res. 2008;147(1):1–8.
59. Matera G, Puccio R, Giancotti A, et al. Impact of interleukin-10, soluble CD25 and interferon-γ on the prognosis and early diagnosis of bacteremic systemic inflammatory response syndrome: a prospective observational study. Crit Care. 2013;17(2):R64.
60. Xie Y, Zhuang D, Chen H, et al. 28-day sepsis mortality prediction model from combined serial interleukin-6, lactate, and procalcitonin measurements: a retrospective cohort study. Eur J Clin Microbiol Infect Dis. 2023;42(1):77–85.
61. Xiao L, Ran X, Zhong Y, et al. A combined ratio change of inflammatory biomarkers at 72 h could predict the severity and prognosis of sepsis from pulmonary infections. Immunobiology. 2022;227(6):152290.
62. Miao H, Chen S, Ding R. Evaluation of the molecular mechanisms of sepsis using proteomics. Front Immunol. 2021 Oct 21;12.
63. Mewes C, Büttner B, Hinz J, et al. CTLA-4 genetic variants predict survival in patients with sepsis. J Clin Med. 2019;8(1):70.
64. Ou Y, An R, Wang H, et al. Oxidative stress-related circulating miRNA-27a is a potential biomarker for diagnosis and prognosis in patients with sepsis. BMC Immunol. 2022;23(1):14.
65. Geng F, Liu W, Yu L. MicroRNA-451a and Th1/Th2 ratio inform inflammation, septic organ injury, and mortality risk in sepsis patients. Front Microbiol. 2022;13.
66. Lin R, Hu H, Li L, et al. The potential of microRNA-126 in predicting disease risk, mortality of sepsis, and its correlation with inflammation and sepsis severity. J Clin Lab Anal. 2020;34(9).
67. Na L, Ding H, Xing E, et al. The predictive value of microRNA-21 for sepsis risk and its correlation with disease severity, systemic inflammation, and 28-day mortality in sepsis patients. J Clin Lab Anal. 2020;34(3).
68. Wang H, Zhang P, Chen W, et al. Serum MicroRNA signatures identified by solexa sequencing predict sepsis patients' mortality: A prospective observational study. In: Moormann AM, editor. PLoS ONE. 2012;7(6):e38885.
69. Davenport EE, Burnham KL, Radhakrishnan J, et al. Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. Lancet Respir Med. 2016;4(4):259–71.
70. Ruiz-Sanmartín A, Ribas V, Suñol D, et al. Characterization of a proteomic profile associated with organ dysfunction and mortality of sepsis and septic shock. In: Jacobs JM, editor. PLOS ONE. 2022;17(12):e0278708.
71. Jones TN, Janani L, Gordon AC, et al. A novel role for cytochrome P450 epoxygenase metabolites in septic shock. Crit Care Explor. 2022;4(1):e0622.
72. Baghela A, Pena OM, Lee AH, et al. Predicting sepsis severity at first clinical presentation: The role of endotypes and mechanistic signatures. EBioMedicine.

2022;75:103776.
73. Churpek MM, Snyder A, Han X, et al. Quick sepsis-related organ failure assessment, systemic inflammatory response syndrome, and early warning scores for detecting clinical deterioration in infected patients outside the intensive care unit. Am J Respir Crit Care Med [Internet]. 2017;195(7):906–11. Available from: https://www.atsjournals.org/doi/10.1164/rccm.201604-0854OC
74. Chenoweth JG, Brandsma J, Striegel DA, et al. Sepsis endotypes identified by host gene expression across global cohorts. Commun Med. 2024;4(1):120.
75. Sweeney TE, Azad TD, Donato M, et al. Unsupervised analysis of transcriptomics in bacterial sepsis across multiple datasets reveals three robust clusters. Crit Care Med. 2018;46(6):915–25.
76. Scicluna BP, van Vught LA, Zwinderman AH, et al. Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study. Lancet Respir Med. 2017;5(10):816–26.
77. Mohamed AS, Mehta A, James P. Predictors of mortality of severe sepsis among adult patients in the medical Intensive Care Unit. Lung India. 2017;34(4):330.
78. Remelli F, Castellucci F, Vitali A, et al. Predictive value of geriatric-quickSOFA in hospitalized older people with sepsis. BMC Geriatr. 2021;21(1):241.
79. Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: a systematic review and meta-analysis. Age and Ageing. 2018;47(2):193–200.
80. Li X, Ploner A, Karlsson IK, et al. The frailty index is a predictor of cause-specific mortality independent of familial effects from midlife onwards: a large cohort study. BMC Med. 2019;17(1):94.
81. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–57.
82. Murlidharan A, Dhar M, Pathania M, et al. Predictive value of frailty index in comparison to traditional markers of sepsis in predicting mortality among elderly admitted in tertiary care hospital. J Assoc Physicians India. 2022;70(9):32–6.
83. Costa RT, Nassar AP, Caruso P. Accuracy of SOFA, qSOFA, and SIRS scores for mortality in cancer patients admitted to an intensive care unit with suspected infection. J Crit Care. 2018;45:52–7.
84. Probst L, Schalk E, Liebregts T, et al. Prognostic accuracy of SOFA, qSOFA and SIRS criteria in hematological cancer patients: a retrospective multicenter study. J Intensive Care. 2019;7(1):41.
85. Costa RT, Zampieri FG, Caruso P, et al. Performance status and acute organ dysfunction influence hospital mortality in critically ill patients with cancer and suspected infection: a retrospective cohort analysis. Rev Bras Ter Intensiva. 2021;33(2):52–7.
86. López R, Pérez-Araos R, Baus F, et al. Outcomes of sepsis and septic shock in cancer patients: Focus on Lactate. Front Med (Lausanne). 2021 Apr 26;8.
87. Guarino M, Gambuti E, Alfano F, et al. Predicting in-hospital mortality for sepsis: a comparison between qSOFA and modified qSOFA in a 2-year single-centre retrospective analysis. Eur J Clin Microbiol Infect Dis. 2021;40(4):825–31.
88. Boekhoud L, Schaap HMEA, Huizinga RL, et al. Predictive performance of NEWS and qSOFA in immunocompromised sepsis patients at the emergency department. Infection. 2024 Apr 12.
89. Lind ML, Phipps AI, Mooney S, et al. Predictive value of 3 clinical criteria for sepsis (quick sequential organ failure assessment, systemic inflammatory response syndrome, and national early warning score) with respect to short-term mortality in allogeneic hematopoietic cell transplant recipients with suspected infections. Clin Infect Dis. 2021;72(7):1220–9.
90. Amancio RT, Japiassu AM, Gomes RN, et al. The innate immune response in hiv/aids septic shock patients: A comparative study. In: Salluh JI, editor. PLoS ONE. 2013;8(7):e68730.
91. Sinto R, Suwarto S, Lie KC, et al. Prognostic accuracy of the quick sequential organ failure assessment (qSOFA)-lactate criteria for mortality in adults with suspected bacterial infection in the emergency department of a hospital with limited resources. Emerg Med J. 2020;37(6):363–9.
92. Gill A, Ackermann K, Hughes C, et al. Does lactate enhance the prognostic accuracy of the quick sequential organ failure assessment for adult patients with sepsis? A systematic review. BMJ Open. 2022;12(10):e060455.
93. Wright SW, Hantrakun V, Rudd KE, et al. Enhanced bedside mortality prediction combining point-of-care lactate and the quick sequential organ failure assessment (qSOFA) score in patients hospitalised with suspected infection in southeast Asia: a cohort study. Lancet Glob Health. 2022;10(9):e1281–8.
94. Liu S, He C, He W, et al. Lactate-enhanced-qSOFA (LqSOFA) score is superior to the other four rapid scoring tools in predicting in-hospital mortality rate of the sepsis patients. Ann Transl Med. 2020;8(16):1013–1013.
95. Dadeh AA, Kulparat M. Predictive performance of the news–lactate and news towards mortality or need for critical care among patients with suspicion of sepsis in the emergency department: A prospective observational study. Open Access Emerg Med. 2022;14:619–31.
96. Wang D, Li J, Sun Y, et al. A machine learning model for accurate prediction of sepsis in ICU patients. Front Public Health. 2021;9.
97. Selcuk M, Koc O, Kestel AS. The prediction power of machine learning on estimating the sepsis mortality in the intensive care unit. Inform Med Unlocked. 2022;28:100861.
98. Karlsson A, Stassen W, Loutfi A, et al. Predicting mortality among septic patients presenting to the

emergency department–a cross sectional analysis using machine learning. BMC Emerg Med. 2021;21(1):84.
99. Valik JK, Ward L, Tanushi H, et al. Predicting sepsis onset using a machine learned causal probabilistic network algorithm based on electronic health records data. Sci Rep. 2023;13(1):11760.
100. Park JY, Hsu TC, Hu JR, et al. Predicting sepsis mortality in a population-based national database: machine learning approach. J Med Internet Res. 2022;24(4):e29982.
101. Goh KH, Wang L, Yeow AYK, et al. Artificial intelligence in sepsis early prediction and diagnosis using unstructured data in healthcare. Nat Commun. 2021 Jan 29;12(1):711.
102. Deng HF, Sun MW, Wang Y, et al. Evaluating machine learning models for sepsis prediction: A systematic review of methodologies. iScience. 2022;25(1):103651.
103. Rosenbloom AJ, Linden PK, Dorrance A, et al. Effect of granulocyte-monocyte colony-stimulating factor therapy on leukocyte function and clearance of serious infection in nonneutropenic patients. Chest. 2005;127(6):2139–50.
104. Vacheron CH, Lepape A, Venet F, et al. Granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients presenting sepsis-induced immunosuppression: The GRID randomized controlled trial. J Crit Care. 2023;78:154330.
105. Friesecke S, Stecher SS, Gross S, et al. Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study. J Artif Organs. 2017;20(3):252–9.
106. Kattan E, Bakker J, Estenssoro E, et al. Hemodynamic phenotype-based, capillary refill time-targeted resuscitation in early septic shock: The ANDROMEDA-SHOCK-2 randomized clinical trial study protocol. Rev Bras Ter Intensiva. 2022;34(1):96–106.