Early Diagnosis of Sepsis: The Role of Biomarkers and Rapid Microbiological Tests

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Abstract

Sepsis is a medical emergency resulting from a dysregulated response to an infection, causing preventable deaths and a high burden of morbidity. Protocolized and accurate interventions in sepsis are time-critical. Therefore, earlier recognition of cases allows for preventive interventions, early treatment, and improved outcomes. Clinical diagnosis of sepsis by clinical scores cannot be considered an early diagnosis, given that underlying molecular pathophysiological mechanisms have been activated in the preceding hour or days. There is a lack of a widely available tool enhancing preclinical diagnosis of sepsis. Sophisticated technologies for sepsis prediction have several limitations, including high costs. Novel technologies for fast molecular and microbiological diagnosis are focusing on bedside point-of-care combined testing to reach most settings where sepsis represents a challenge.

Keywords

- sepsis
- septic shock
- severe sepsis
- diagnosis
- biomarkers
- screening
- early diagnosis
- molecular diagnostic techniques
- molecular testing

Sepsis represents a medical condition associated with preventable deaths, a high burden of morbidity, and long-term sequelae. Global epidemiological data have shown that 48.9 million people develop sepsis yearly, and 11 million deaths are attributable to septic shock worldwide, accounting for almost 20% of all global deaths.[1] Consequently, the World Health Organization has urged for actions to improve sepsis prognosis. Delayed diagnosis and treatment of sepsis have consistently been considered independent risk factors for the progression of organ dysfunction and death, particularly in patients with septic shock.[2–5] According to the updated sepsis definition proposed by the last Surviving Sepsis Campaign (SSC) guidelines in 2021,[6] which defines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection, an arsenal of theragnostic tools has been developed to increase the specificity of sepsis detection.

Protocolized and accurate interventions are time-critical. These include early adequate empirical antimicrobial therapy, infection source control, and optimal hemodynamic resuscitation.[5,6] Current challenges in early detection of sepsis before clinical signs develop contribute to delays in implementing standard-of-care SSC recommendations for the early approach to sepsis and septic shock.[7,8] In some settings, evidence of the adverse outcomes of late-recognized cases has been insufficient to perceive sepsis as a medical emergency that requires prompt treatment.

There is a wide variety of other contributing factors or barriers to improving early diagnosis and treatment of sepsis.[9] Some studies have found barriers are often related to the lack of availability of some resources, such as microbiology laboratory that processes blood cultures and other microbiological detection tests. Still, advances in quality of care in sepsis and a better understanding of underlying pathobiological processes leading to organ dysfunction will aid in developing accurate, fast, and widely available point-of-care tests. Bedside accurate tools help the development of future quality improvements for the practical implementation of stand-of-care interventions, which have been consistently demonstrated to decrease mortality when implemented on time.[5]

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Over the last few years, sepsis biomarkers and rapid microbiological diagnostic tests (RDTs) have been considered a paradigm for novel strategies to improve earlier sepsis detection. Herein, we gathered the best available evidence on this topic. Biomarkers used for phenotyping, prognosis, and stratification of patients already diagnosed with sepsis, insights into machine-learning models, and other artificial intelligence tools are out of the scope of this review.

For this narrative review, we performed a comprehensive literature search in the Cochrane, PubMed, CINAHL, and Scopus databases from no start date to September 2023. The search criteria included the following Medical Subject Headings (MeSH) terms: *sepsis* OR *Septic shock* OR *Severe sepsis* AND *diagnosis* OR *biomarkers* OR *screening* OR *early diagnosis* OR *molecular diagnostic techniques* OR *molecular testing*. We reviewed articles written in Spanish and English. We obtained all full-text versions of the selected manuscripts. The first draft of the manuscript was reviewed and modified by all authors. All authors approved the final manuscript.

Sepsis Suspicion: Reasoning on a Case-by-Case Basis Is Crucial

When considering the pathophysiological events leading to sepsis, clinicians should acknowledge that clinical signs of sepsis are the ultimate consequence of complex underlying molecular and inflammatory derangements that culminate in measurable clinical signs. The main challenges when trying to diagnose sepsis in its early stages using clinical variables are the ability to differentiate sepsis from infection, the detection of occult organ dysfunction in the presence of infection, differentiating sepsis from local organ dysfunction as a consequence of specific infection (e.g., pneumonia), attributing a new-onset organ dysfunction to sepsis, organ dysfunction as the consequence of an unrecognized infection, and the variability of sepsis phenotypes (clinical and biological), which are influenced by recent interventions, and other noninfectious causes of inflammation with apparently close to similar clinical and biological host response (e.g., trauma, burns, autoimmune disease, pancreatitis, major surgery, comorbidities, age, gender, concurrent medications).[10]

The most appropriate workflow is the one that first rules out sepsis using objective data in the context of any infection to manage the patient accordingly. However, this is a real challenge with the available validated tools, and most cases are classified as "suspicious of sepsis" after a clinical evaluation. Recognition of sepsis cases before the occurrence of hypotension requires wise evaluations to prevent further organ dysfunction, given that a significant proportion of sepsis patients present subtle clinical signs and appear less sick at the time of presentation. The inadequate recognition of these cases and delayed treatment are associated with high mortality rates (up to 25% in some studies) due to the progression of illness to irreversible organ dysfunction.[11] New organ dysfunction or overt inflammatory response in the context of infection should prompt early evaluation to rule out sepsis. However, specific infectious conditions may lead to local organ dysfunction without causing a dysregulated systemic host response.

Before discussing the potential biomarkers available for clinical purposes, we should define "early" when discussing sepsis diagnosis. The literature has no valid and widely accepted definition of early sepsis. Most studies have considered *early sepsis* before septic shock develops, for cases in which clinical signs are evident and the infection is not confirmed, or during the early (reversible) stages of organ dysfunction. In our view, those considerations are inaccurate and should be considered "sepsis diagnosis" or, more precisely, late sepsis diagnosis. Some studies define early sepsis when sepsis-3 criteria are present (infection + sequential organ failure assessment [SOFA] score ≥ 2), but septic shock is not present yet.[12] All tools detecting sepsis after clinical data are present should be considered diagnostic tools if organ dysfunction is already present, or there is a clinically evident process possibly linked to infection progressing to organ dysfunction (e.g., systemic inflammatory response syndrome [SIRS], SOFA score 0–1). For the purpose of this review, we will consider prediction of sepsis to any preclinical condition in which there is an infection in a host in whom different pathophysiological pathways, particularly immunological status, will irreversibly lead to organ dysfunction if untreated. All screening tools detecting sepsis in this phase are *predictors* of sepsis (see ►**Fig. 1**).

Sepsis as a Clinical Syndrome: Delayed Recognition of a Time-Dependent Condition

Interestingly, clinical scores are currently recommended as the best widely available tools in our arsenal for sepsis screening.[6] However, studies in prehospital settings have shown that up to one-third of patients with documented infection who develop sepsis have normal vital signs.[13] Sepsis results from complex host interactions and dysregulated response, amplified by endogenous factors, to a given pathogen. Therefore, recognizing sepsis from parameters that reflect its clinical consequences can be considered as a delayed strategy for detection. Clinical scores may not be ideal for sepsis prediction before organ dysfunction is clinically overt. However, an accurate clinical assessment remains the core strategy to detect potential sepsis cases in some low-resource settings.[14]

The lack of validity of SIRS as a tool for the early detection of sepsis has been demonstrated. The classic systemic SIRS criteria for diagnosing sepsis focus only on bedside clinical variables and laboratory parameters. The need for two or more SIRS criteria excludes 12.5% of sepsis cases with the same organ dysfunction and mortality risk as cases that fulfill SIRS criteria.[15] In the same study, the authors found SIRS criteria failed to define the transition point in the overall risk of death.

Sepsis-3 criteria have not proven beneficial to decrease overall mortality or to improve sepsis recognition and screening. Adding lactate, procalcitonin (PCT), or other

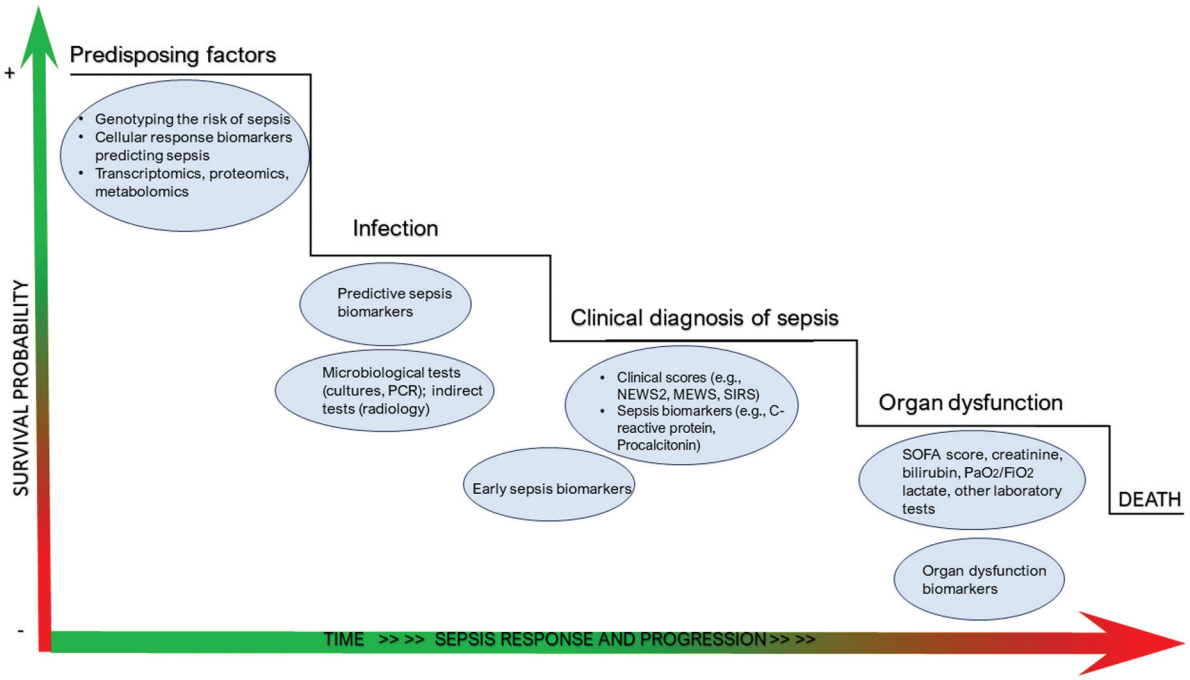

Fig. 1 The potential usefulness of currently available biomarkers and rapid microbiological tests for prediction, early diagnosis, and diagnosis of sepsis. MEWS, Modified Early Warning Score; NEWS2, National Early Warning Score-2; PCR, polymerase chain reaction; SIRS, systemic inflammatory response syndrome; SOFA score, Sequential Organ Failure Assessment score.

clinical variables improves its sensitivity. In the study of Machado et al,[16] the authors conducted a prospective study of two cohorts, with mortality as the primary outcome. They included patients with suspected infection but without sepsis and patients with sepsis. The predictive accuracy of quick sequential organ failure assessment (qSOFA) score was assessed, considering the worst values prior to the suspicion of infection or sepsis. One cohort had 5,460 patients, 78.3% had a qSOFA score $\leq$1, and crude mortality was of 14%. The sensitivity of qSOFA score $\geq$2 for predicting mortality was 53.9% (95% confidence interval [CI]: 50.3–57.5). The sensitivity was higher for a qSOFA $\geq$1 (85%), a qSOFA score $\geq$1 or lactate $\geq$2 mmol/L, and SIRS plus organ dysfunction. The second cohort included 4,711 patients, and 62.3% had a qSOFA score $\leq$1, and a mortality rate of 17.3%. In public hospitals, the mortality rate was higher, 39.3%. In a previous study, approximately one-quarter of infected patients had a qSOFA score $\geq$2, with 70% of them having poor outcomes.[17] When using sepsis-3 criteria to detect sepsis, patients in the early phase of sepsis are missed. The SOFA score performs better in diagnosing sepsis later in clinical stages and predicting intensive care unit (ICU) admission.[12,16,18,19]

As previously mentioned, the qSOFA score is far from being a predictive tool, as clinical repercussions of sepsis should be evident for a positive score. The frequency of patients having hyperlactatemia who are still normotensive can be as common as 26% of sepsis cases.[20] Different studies have demonstrated that qSOFA is less sensitive than SIRS to identify organ dysfunction due to sepsis.[21–23] Despite the National Early Warning Score (NEWS; and the updated version NEWS2) and the Modified Early Warning Score (MEWS) being better tools than qSOFA[24,25] and recommended by the current SSC guidelines,[6] clinicians still lack a specific bedside tool to differentiate sepsis from other conditions in patients with unclear medical history or to predict sepsis in some subsets of patients prone to develop sepsis in the following hours after infection. Clinical scores are more useful for predicting mortality in sepsis than early predictors of the risk for developing sepsis.

In-hospital quality-of-care programs often use automated sepsis screening tools in electronic health records, which have been studied to detect sepsis early. However, their accuracy is variable, given that some studies have shown low predictive values while others show improvements in sepsis care processes.[26–28] There are studies showing no mortality benefits from sepsis screening tools.[29–31] In many settings, improvements in sepsis screening have been made by developing and implementing performance improvement programs, which have been shown to standardize and improve the standards of care for the management of sepsis patients. These programs generally focus on sepsis screening, sepsis bundle performance metrics, health care staff education and adherence to sepsis bundles, patient outcomes, and actions for identified opportunities.[9,32–36] Parameters reflecting the underlying pathophysiology of sepsis are not included in this type of clinical screening tools.

Improved Understanding of Sepsis Pathobiology for Earlier Detection

The early diagnosis of sepsis should be based on the early diagnosis of an infection, along with the identification of a dysregulated response that may subsequently lead to organ dysfunction.[6,37] Sepsis involves the early activation of pro-

and anti-inflammatory molecular responses and other non-immunologic pathways triggered by a pathogen (e.g., neuronal, cardiovascular, metabolic, bioenergetic, autonomic, hormonal, and coagulation) with outstanding prognostic significance.[38] According to this framework, the ideal biomarker should have enough sensitivity to rule out sepsis early during the triage of suspicious cases presenting to the emergency department (ED) and enough specificity to differentiate sepsis from other conditions. Accurate tools that improve clinical judgment are the game changer for improving sepsis diagnosis, management, and prognosis. Host response biomarkers have been extensively studied, as they play a critical role in diagnosis, early detection, phenotyping, risk of organ dysfunction and death, personalized patient management, and antibiotic stewardship.

Biomarkers for "Early" Sepsis Diagnosis

Early diagnosis of sepsis based on biomarkers has evolved to enhance the accuracy of our clinical assessments. Acceptable reliability of early diagnosis of sepsis using only clinical scores is not feasible, as they have low sensitivity and specificity for sepsis detection in the absence of a severe illness or organ dysfunction and have important limitations to predicting the mortality risk.[39] Diagnostic biomarkers should add value and be able to change the pretest probability and reclassify patients when there is diagnostic uncertainty, increasing specificity and providing a high negative predictive value. Ideal biomarkers should be able to detect sepsis even before clinical suspicion (predictive biomarkers), enabling presymptomatic diagnosis. In real life, most clinicians use a combination of widely available laboratory biomarkers to diagnose sepsis (e.g., white blood cell and neutrophil count, lactate, C-reactive protein [CRP]), more than clinical scores; only 36% use the Sepsis-3 definition alone, 34.2% still calculate the qSOFA, and 44.7% use the SOFA score.[40]

PCT has been extensively studied as a diagnostic tool for sepsis. Three meta-analyses evaluating the diagnostic utility of PCT reported a pooled sensitivity and specificity of 77 to 85% and 75 to 83%, respectively.[41–43] Of note, most studies reporting a lack of PCT usefulness for sepsis diagnosis have included patients with a low pretest probability for sepsis of bacterial origin, and international guidelines do not support the use of PCT to initiate antibiotics in sepsis.[6,44,45] PCT is thought to be more accurate than CRP for detecting patients with suspected sepsis; however, studies have shown PCT is not beneficial to early diagnose sepsis cases with a less severe clinical condition.

Illness severity and pretest probability for sepsis influence the usefulness and cut-off of PCT as a diagnostic tool.[46] A reliable cut-off value of 1.1 ng/mL with sensitivity and specificity of 77% and 79%, respectively (area under the receiver operating characteristic curve [AUROC] of 0.85, 95% CI: 0.81–0.88) can be used to support sepsis diagnosis,[43] depending on pretest probability, the presence of clinical criteria, and severity of illness.[12,18] In an interesting retrospective study by Kim et al, PCT was a useful biomarker for sepsis and septic shock diagnosis in the ED when used in patients who fulfilled sepsis-3 criteria.[12] In other words, it was useful to enhance the diagnosis of sepsis when clinical repercussions and organ dysfunction are already established, with a proposed cut-off of 0.41 ng/dL for sepsis (sensitivity and specificity of 74.8% and 63.8%, respectively; AUROC: 0.745), and 4.7 ng/dL for septic shock (sensitivity and specificity of 66.1% and 79.0%, respectively; AUROC: 0.784). The lack of effectiveness of PCT to rule out or *predict* early sepsis has been recognized, and the current SSC guidelines do not recommend its use to start antibiotics.[6]

Consequently, early diagnosis or prediction of sepsis using PCT is unreliable.[12] The less severe the condition, the less likely sepsis will be diagnosed early before overt clinical signs or organ dysfunction develop. Previous studies on this matter have assessed PCT usefulness compared to clinical criteria as the gold standard.[47] International guidelines do not recommend using PCT in ventilator-associated pneumonia, a common condition related to sepsis in critically ill patients.[48–50] There is no agreed PCT cut-off value for diagnosis of infection regardless of the presence of sepsis; some studies used PCT values from 0.5 to 2 μg/L, as previous studies of community-acquired pneumonia (CAP).[51] A recent meta-analysis of patients with diverse etiologies of CAP showed that PCT has low sensitivity during early CAP and cannot reliably distinguish viral from bacterial pneumonia.[52] A previous study on PCT kinetics in patients with bacteriemia showed poor diagnostic accuracy and a low PCT reliability to guide the initiation of therapy.[53] Moreover, PCT is not specific to sepsis; it increases in other conditions often confused with sepsis, such as trauma, pancreatitis, or autoimmune disease.[46,54] The most widely accepted applicability of PCT in the context of sepsis is antimicrobial stewardship and prognosis assessment.[46,55–57]

Various individual biomarkers are developed to enhance the clinical diagnosis of sepsis. In a recent meta-analysis, soluble urokinase plasminogen activator receptor (suPAR) was observed to have an AUROC of 0.83 for predicting sepsis (95% CI: 0.80–0.86).[58] In addition, AUROC for differentiating sepsis from non-sepsis SIRS was 0.81 (95% CI: 0.77–0.84), and the sensitivity and specificity were 0.67 (95% CI: 0.58–0.76) and 0.82 (95% CI: 0.73–0.88), respectively. Soluble triggering receptor expressed on myeloid cells (sTREM-1) is expressed in innate immune cells (e.g., monocytes and neutrophils). This protein reflects important processes of the inflammatory and cytotoxic response to sepsis, such as the synergic activation of Toll-like receptors and the augmented production of pro-inflammatory cytokines.[59] Serum levels of sTREM-1 have been studied as a biomarker for early sepsis.[60] Previous studies have shown an AUROC of 0.78 (95% CI: 0.69–0.86) to differentiate sepsis from other causes of SIRS,[61] and an AUROC of 0.95 for septic shock diagnosis. In a study of 90 patients with SIRS due to sepsis and other etiologies,[61] a PCT cut-off value of 1.57 ng/mL and sTREM-1 cut-off value $\geq$133 pg/mL yielded a sensitivity of 71.1 and 67.33%, and specificity of 73.3 and 65.79%, respectively, for the differentiation of sepsis from other causes of SIRS.

Biomarker-enhanced clinical scores may improve specificity of diagnosis, though sensitivity remained low.[12] Other

biomarkers have been more beneficial in predicting prognosis in sepsis, such as pro-MR-adrenomedullin.[62–64]

Sepsis often presents a hyperinflammatory response pattern followed by an immunosuppressive state, during which multiple organ dysfunction develops.[65,66] A biomarker or a combination of biomarkers could be a new alternative to predict, identify, or provide new approaches to manage sepsis patients. In some settings, the combination of biomarkers has been used as a strategy to increase the sensitivity for early diagnosis and improved outcomes.[63,67] The combination of two or more biomarkers increases the diagnostic accuracy of sepsis diagnosis in some studies.[68] Seeking more accurate therapeutic interventions and patient outcomes in this condition should be the goal of any combination of biomarkers.

Still, association of different biomarkers reflecting the same pathophysiological pathway may have no added value in terms of diagnostic accuracy. An important study of ICU patients with SIRS showed no combination of biomarkers performed better than CRP alone to diagnose sepsis.[69] Increased costs, complexities in interpreting results, lack of validation studies, and inadequate training in the obtention and implementation in different settings are other disadvantages of combining biomarkers. Standardization of sample collection, analysis, and processing are needed for their reliability regardless of the laboratory performing the tests. Combining point-of-care inflammatory biomarkers would solve all those issues related to the usual measurement of biomarkers. This innovative strategy needs to be further validated in clinical studies.[70]

Machine learning tools and biomarker-enhanced scores that involve the combination of laboratory and clinical biomarkers have been overwhelming in recent years. Machine-learning models using artificial intelligence have been studied over the last few years to improve the usefulness of clinical and laboratory biomarkers by combining them for early sepsis detection.[30,31,71] The performance of these models has been variable, and some limitations have been identified due to the lack of availability of some biomarkers or clinical measurements. Electronic alerts are more useful in emergency settings to reduce hospital length of stay, improve time to treatment, and reduce mortality, though sometimes they are poorly generalizable.[72]

Prediction of Sepsis: Detecting Occult Processes Leading to Sepsis and Organ Dysfunction

As we have discussed before, even machine learning models that use clinical variables and relevant host factors with characteristics that progress over time are not sufficiently accurate to diagnose early sepsis, as they rely on clinical consequences and common laboratory tests resulting from underlying molecular derangements leading to an aberrant or dysregulated host response and organ dysfunction. The logical pathway would be to find preclinical biomarkers of systems that accurately predict the risk of sepsis once the infection is established (or before) and combine microbiological and inflammatory panels. This review will not discuss biomarkers that have been studied as predictors of organ dysfunction in sepsis and increased mortality.

Novel Molecular Biomarkers for Prediction or Early Diagnosis

Extensive research in the field of biomarkers is being performed to validate new molecules detecting sepsis underlying processes at early stages, with the intention to facilitate effective sepsis prediction at the time of infection, allowing for preventive rather than early interventions and ultimately reducing the number of deaths. Interesting studies on earlier biomarkers, including serial measurements of pancreatic stone protein, demonstrated an increase of this marker 3 days preceding the onset of signs necessary to diagnose sepsis clinically.[73] As discussed above, some studies propose using panels of biomarkers to predict or diagnose sepsis early as the most pragmatic strategy, so far, to improve clinical diagnosis of sepsis.[68] ►**Table 1** gathers a summary of novel predictive biomarkers in sepsis; PCT was added to the table as a comparator.

Advances in the understanding of the genetic basis for sepsis activation of the innate immune response,[74] the release of acute phase reactants, knowledge of biomarkers involved in the pathophysiology of sepsis, and the serum levels of glycoproteins on cell membranes have allowed for the study of different molecules and genes encoding those molecules (e.g., proteins, cytokines, soluble receptors, chemokines) as sepsis-predictive biomarkers. Of note, newer potentially predictive biomarkers have been validated in comparison with the gold standard for screening in sepsis (clinical scores), though others have been studied prospectively as predictors of sepsis risk, which correlate with mortality risk.[75]

More recent advances in gene expression and transcriptomics have led to the identification of new classes of biomarkers, such as microRNAs, long-noncoding RNAs, or the human microbiome. Noncoding RNAs have been studied as early predictive sepsis biomarkers. The expression of the LncMALAT1/miR-125a axis discriminates between sepsis patients and healthy controls and is associated with an excellent diagnostic yield (AUROC of 0.931, 95% CI: 0.908–0.954).[76]

Given that a significant proportion of patients with early sepsis do not show clinical signs but do develop an immunopathogenic phenotype leading to dysregulated organ dysfunction and increased mortality, the most sophisticated prediction models have proposed the use of clinical parameters with a panel of genes encoding inflammatory biomarkers.[105] The most important disadvantages of these models are the high cost and difficulties in sample processing, laboratory testing, and lack of availability for all hospital (or prehospital) settings. Predictive biomarkers have been studied compared to clinical scores rather than in prospective cohorts of infected patients and their clinical trajectories.

Novel technologies are poorly affordable in middle- or low-resource settings, which account for 85% of sepsis cases.[1] Their lack of validity in prehospital settings or ED is outstanding. In such settings, an objective and quick tool is

Table 1 Brief summary of potentially applicable biomarkers for sepsis prediction or early diagnosis

Biomarker	Clinical applicability
PCT	Classic biomarker, not useful for sepsis prediction or early diagnosis of sepsis. Diagnosis of bacterial sepsis or infection. More accurate in more severe illness.[61] PCT cut-off for sepsis, 1.1 ng/mL[43]; 1.57 ng/mL[61] • ↑ Concentrations in patients with sepsis and infection[77] • Distinction between patients with sepsis and patients without sepsis in the ICU ↑ values in septic shock, sepsis, and controls (17.1, 1.8, and 0.04 ng/mL, respectively)[78]
sTREM-1	Sepsis indicator.[61,79,80] An early distinction between sepsis and SIRS predictive of septic shock.
Pancreatic stone protein (PSP)	C-type lectin protein that triggers polymorphonuclear cell activation. Serial measurements are potentially useful to predict sepsis 3 days before clinical diagnosis.[73]
sPD-L1	Indicates sepsis-associated immunoparalysis (immunosuppression)[81,82] Cut-off of 0.16 ng/mL, ↑ sPD-L1 immunosuppression phenotype.[82]
IL-10	Levels correlate with the hypoinflammatory phenotype.[82,83]
IL-1β and IL-6	Levels increase in the acute phase of sepsis.[84,85]
Pentraxin-3	Predicts the risk of sepsis in patients with suspected infection in the emergency department.[86] Sepsis versus SIRS.[87]
Calprotectin	Better distinction between sepsis versus nonsepsis patients in the ICU than PCT. Distinction between sepsis and trauma patients.[88]
Bio-adrenomedullin	Useful to distinguish sepsis, septic shock, and nonsepsis patients (74, 107, and 29 pg/mL, respectively).[89]
Resistin (and eNamp)	Early sepsis biomarkers.[90,91]
suPAR	Risk of patients with suspected infection.[92]
LDL-C	Protective effect against sepsis.[93] Low values can reflect a risk of sepsis and admission to the ICU. Risk of sepsis (OR: 0.86) and admission to the ICU (OR: 0.85). The lower quartile had a greater risk of sepsis (OR: 1.48) and admission to the ICU (OR: 1.45) vs. the highest quartile, considering other comorbidities.
Presepsin	Plasma levels are considered a biomarker of the activation of innate immune effector cells in response to invasive organisms. Biomarker of phagocytosis.[94,95] High accuracy (AUROC 0.954) for prediction of sepsis risk, an early diagnosis.[96,97] ↑ Presepsin in sepsis patients compared to nonsepsis SIRS.
CD64	High-affinity Fcγ receptor I in neutrophils upregulated in the early stages of activation of the innate immune response. AUROC 0.879 of nCD64 for diagnosis of bacterial infection.[78]
↑CD68	Increased in the hippocampus, putamen, and cerebellum in patients with sepsis.[98]
VLA-3 (a3β1)	Indicative of sepsis.[99,100] Discrimination of sepsis and SIRS. Increased α3β1 (VLA-3, CD49c/CD29) on neutrophils of septic patients. ↑ β1 (CD29), on neutrophils of sepsis patients.[100]
↑ sTNFR-1	Distinguish sepsis from nonsepsis SIRS.[101]
↓ miR-125	Good predictive values for sepsis risk.[102]
↑lnc-ANRIL/miR-125a axis	Determine the risk for sepsis.[103]
miR-125a and miR-125b	Useful to distinguish sepsis from other SIRS states.[103]
↑ Lnc-MALAT1/miR-125a	Increased levels in sepsis and risk of sepsis.[76]
Lnc-MALAT1/miRNA-125a	Discriminates sepsis patients from healthy controls. Reflects inflammation level.[76]
lnc-MEG3	Increased values are predictive of sepsis risk. Lnc-MEG3 is a potential biomarker for the prediction of sepsis via interacting with miR-21.[104]
Genetic polymorphisms	The expressions of inflammatory mediators, microRNA expression, and other mechanisms have been described as a tool for predicting sepsis responses in infected patients.[74]

Abbreviations: ICU, intensive care unit; OR, odds ratio; PCT, procalcitonin; SIRS, systemic inflammatory response syndrome.

highly needed for the early triage of patients. Important studies exist on the potential immune response biomarkers for the prediction of sepsis. However, they have been performed preferably in hospitalized patients or later in the ICU.[82,88]

Heterogeneity in critically ill patients with sepsis involves a new paradigm with clinical applications, as it has contributed to the challenging task of finding a perfect combination of biomarkers. Novel genetic studies may enable better characterization of different panels of biomarkers at the

time of a specific infection to predict the risk of sepsis. Identifying unique biological signatures in patients could enhance selected enrollment in clinical trials and strengthen our diagnosis and early detection approaches.[106] Most importantly, the clinical applicability of new discoveries is a *sine qua non* to revolutionize sepsis management and reduce deaths.

Rapid Microbiological Diagnosis as an Element for Sepsis Prediction

Early identification of causative microorganisms in suspected sepsis is needed to optimize antimicrobial use and patient survival. However, current culture-based pathogen identification often takes at least 24 to 48 hours to give meaningful results, weakening their usefulness in decision-making to start antimicrobial treatment, thus, broad-spectrum antibiotics are often used to ensure coverage of all potential organisms, implying risks of overtreatment, toxicity, and selection of multidrug-resistant bacteria. Furthermore, previous or current antimicrobial treatment decreases these tests' sensitivity. Empirical broad-spectrum antimicrobial treatment leads to overtreatment in 60 to 70% of conditions that mimic sepsis, such as other inflammatory states, or secondary to less severe viral or susceptible bacterial infections.[107]

The clinical need for a faster microbiological approach to target treatments early in the course of infections potentiated the therapeutic advantages of new microbiological technologies, such as RDT.[108] Pathogen molecular diagnostic tests speed up the time to identification of pathogens and their susceptibility to antibiotic and eventually targeted treatment.[109] There is a lack of evidence on the clinical impact of RDT in sepsis patients. Most data have been extracted from studies performed in infections, such as bacteremia or pneumonia, that could lead to sepsis.

Previous studies of matrix-associated laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) have been successful in the management of bloodstream infections.[110–112] A previous meta-analysis and other studies showed that antimicrobial stewardship programs are associated with reduced mortality, time to optimal treatment and length of stay, and are cost-effective.[112–114] Patients with sepsis and gram-negative bacteremia may benefit from RDT due to the wide range of possible infecting pathogens and the implications of inappropriate treatment in the context of drug resistance. Previous studies of patients with drug-resistant gram-negative bacteremia have shown earlier initiation of appropriate therapy, shortened length of stay, and reduced 30-day mortality.[115] MALDI-TOF MS has been studied for rapid identification of antimicrobial susceptibility; however, some misclassifications have been observed, and the accuracy of this method needs to be improved.[108,116] There is a lack of studies evaluating MALDI-TOF MS in sepsis. In the study of Verroken et al,[117] the authors assessed the impact of MALDI-TOF MS results in the management workflow of antimicrobial stewardship in sepsis patients with positive blood cultures to *Enterobacteriaceae*, *Pseudomonas aeruginosa,* and *Staphylococcus aureus*. The mean time to pathogen identification was reduced by 61 to 65% (10.8 hours). The mean time to optimal treatment was decreased significantly. The impact on mortality was not assessed.

Multiplex polymerase chain reaction (PCR) has been previously studied for the rapid identification of *S. aureus* and its resistance patterns. The FilmArray Blood Culture ID Panel (BCID), which can identify 24 different bacteria, fungi, and common antimicrobial resistance genes (KPC, mecA, and vanA/B) within 1 hour of organism growth in blood cultures, was evaluated in the randomized Blood Culture Identification trial.[118] In this study, the molecular technique reduced the time to targeted treatment, decreased the use of broad-spectrum antibiotics, and contributed to antimicrobial de-escalation.

There is a paucity of evidence on gram-negative pathogen identification in sepsis using PCR.[118–122] In the study of Vincent et al,[123] the use of culture-independent PCR/electrospray ionization-mass spectrometry technology resulted in rapid pathogen identification in critically ill patients. The authors tested different sources of infection (e.g., pneumonia: 185 cases, blood stream: 616 cases, sterile fluid: 110 cases, and tissue infection: 529 cases) in critically ill patients. The study reported the effectiveness of PCR to rule out infection within 6 hours compared with standard culture-based microbiological testing, with a sensitivity of 81%, a specificity of 69%, and a negative predictive value of 97%. In a study of 617 patients with positive Gram stains in blood cultures, BCID resulted in faster pathogen identification than standard blood cultures and usual susceptibility testing, which improved antimicrobial de-escalation. The T2Bacteria Panel (including the identification of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus faecium,* and *S. aureus*), identified the causative pathogen in whole blood samples at a mean of 3.6 to 7.7 hours compared with almost 72 hours with standard blood cultures.[122]

Ideally, RDT should provide pathogen species and data on antimicrobial susceptibility, such as Accelerate Pheno system (APS; Accelerate Diagnostics, Denver, CO), an automated system that reduces the time to pathogen identification and gives susceptibility data (at 27 and 40 hours, respectively) compared with conventional cultures.[124] This system has been approved by the Food and Drug Administration in 2017 for testing in blood.

There are some drawbacks regarding the use of RDT. These tests are not specific to sepsis and are *not useful* for making a differential diagnosis between three conditions: colonization, infection, and sepsis. Likewise, RDTs have led to overdiagnosis and overtreatment.[125] Data on clinical benefit and cost-effectiveness are still emerging. Costs and microbiology lab expertise in molecular techniques are also seen as a barrier to their widespread use, particularly in low-resource settings. None of these technologies have approached the point of care, nor can they be described as genuinely culture-independent diagnostic tests. Evidence on their effectiveness in improving mortality is conflicting and should be further

studied.[121] A recent systematic review of RDT in sepsis[126] reported improvements in appropriate antimicrobial therapy, nonsignificant change in time to targeted therapy, decreased length of stay in two studies, and a significant decrease in antimicrobial cost in six studies. The impact on mortality was unclear. This study has important limitations on the number of studies included and high heterogeneity.

RDTs per se are not useful for diagnosing a specific immunopathogenic state that predisposes patients to a significant risk of death, such as sepsis. More specific biomarkers recently identified reflect the immunopathologic state leading to sepsis, which is triggered by the interaction of infectious agents and the innate immune system.

Inflammatory biomarker-enhanced RDT will aid in very early diagnosis or *prediction* of sepsis before overt clinical consequences, differentiating sepsis from other acute inflammatory conditions, identifying and quantifying the causative organism, determining resistance patterns early to target treatments from time zero, improving antimicrobial stewardship practices, and monitoring patient progression. Combining point-of-care RDT tests and more specific inflammatory biomarkers is a novel strategy to enhance biomarkers' availability and affordability for earlier sepsis diagnosis in ED. This can improve time to diagnosis (up to 10 times faster when compared with the gold standard),[73] faster detection of pathogens,[127] quick resistance profiles, and detection and rapid monitoring of specific biomarkers. Precision medicine has developed tools to identify new cases, predict prognosis, and target treatments according to their clinical and molecular phenotypes.[128,129] Multiplex point-of-care devices and other theragnostic approaches are integrated approaches that gather data for early diagnosis and classification of sepsis (e.g., inflammatory and organ dysfunction biomarkers and microbiological diagnosis).[130]

Monitoring different biomarkers gives a holistic view of patients' clinical status and prognosis. Integrated point-of-care biomarkers are promising for democratizing novel theragnostic tools and developing precision medicine elsewhere. To improve their applicability in different settings, further clinical studies assessing the effectiveness of these innovative techniques are needed. Widely available and affordable combinations of RDT and predictive biomarkers (e.g., predictive biomarker-enhanced RDT point-of-care tests) should be further studied and clinically validated and promise to be the game changer in sepsis diagnosis.

Conclusion

Early sepsis prediction is still in its first stages, and it remains a complex field for clinicians and researchers. In recent years, an increasing interest has evolved in techniques to improve sepsis definition, prediction, early diagnosis, classification of patients, defining prognosis, and personalizing treatment. Novel developments and deep study of point-of-care biomarkers have been promising to enhance the accuracy of near-patient diagnoses. The continuous developments of point-of-care tools using widely applicable and affordable combinations of biomarkers and faster techniques for accurate microbiological information have driven new insights for sepsis management.

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R.F. and J.C.R. have received honoraria from Biomerieux. E. P.P. has shares in Loop Diagnostics. However, the authors do not recommend any specific product or brand in this review.

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