Early Biomarkers in Sepsis: Can We Diagnose Before It's Too Late? – A Review on CRP, Procalcitonin, Presepsin, IL-6, and Novel Biomarkers

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ABSTRACT

Sepsis remains a leading cause of morbidity and mortality worldwide, with early diagnosis critical for improving outcomes. Conventional biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) aid in diagnosis but lack sufficient sensitivity and specificity, particularly in culture-negative cases. Emerging biomarkers, including interleukin-6 (IL-6), pentraxin 3 (PTX3), suPAR, and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), provide additional insight but are limited when used alone. Presepsin (sCD14-ST), a cleavage fragment of CD14, rises within 2–3 hours of infection and shows strong diagnostic and prognostic value. Evidence from emergency department studies demonstrates higher sensitivity and specificity for presepsin compared to PCT, especially in culture-negative sepsis. Combined use of presepsin with PCT enhances diagnostic yield and supports a multimarker strategy. Despite promising findings, assay variability and influence of renal dysfunction remain challenges. Future multicenter studies are needed to establish standardized cut-offs and validate its integration into clinical practice.

Keywords: Sepsis, Biomarkers, Presepsin, Procalcitonin, Early Diagnosis

INTRODUCTION

Sepsis is a life-threatening organ dysfunction resulting from a dysregulated host response to infection [1]. Despite advances in treatment, mortality remains between 30–50% [2]. The World Health Organization identifies sepsis as a major global health threat, causing approximately 49 million cases and 11 million deaths annually [3]. The pathophysiology involves activation of pattern recognition receptors [PRRs] by pathogen-associated molecular patterns [PAMPs], leading to cytokine release [TNF-α, IL-1β, IL-6] and endothelial dysfunction [4,5].

Pathophysiology and Clinical Challenges

Sepsis represents a biphasic immune disorder involving both hyperinflammation and immune paralysis [6]. Danger-associated molecular patterns [DAMPs] such as HMGB-1 and S100 proteins amplify the response [7]. The systemic inflammatory response syndrome [SIRS] and compensatory anti-inflammatory response syndrome [CARS] models describe this immunologic imbalance [8]. Despite improved awareness, diagnosis remains challenging due to nonspecific symptoms and up to 40% culture negativity [9]. Therefore, reliable biomarkers are needed for early diagnosis. The pathophysiology of sepsis involves an intricate interaction between pathogen-associated molecular patterns [PAMPs] and host pattern recognition receptors, including Toll-like, NOD-like, and RIG-I-like receptors. Activation of these receptors triggers macrophage and endothelial responses, resulting in the release of pro-inflammatory mediators such as tumor necrosis factor-alpha [TNF-α], interleukin [IL]-1β, and IL-6 [5]. These cytokines drive systemic inflammation and, if uncontrolled, can progress to septic shock and multi-organ dysfunction [MODS] [10]. Initially defined by the 1991 ACCP/SCCM consensus as infection plus

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systemic inflammatory response syndrome [SIRS] [6], the definition of sepsis evolved through Sepsis-2 [2001] and Sepsis-3 [2016], which emphasizes organ dysfunction quantified by SOFA and qSOFA scores [9].

Role of Biomarkers in Sepsis Diagnosis

Biomarkers are quantifiable biological indicators that reflect physiological or pathological processes. In sepsis, they play key roles in early diagnosis, risk stratification, prognostication, and therapeutic guidance [10]. Traditional biomarkers such as C-reactive protein [CRP] and procalcitonin [PCT] are well established but have limitations in sensitivity and specificity. CRP rises within 4–6 hours and peaks at 36–50 hours, but it can also be elevated in non-infectious inflammatory states such as surgery or autoimmune disease [11]. PCT rises faster—within 4 hours, peaking at 8–24 hours—and is more specific for bacterial infections [12].

However, both CRP and PCT may fail to differentiate sepsis from sterile inflammation or early infection stages. Consequently, new biomarkers, including presepsin, IL-6, soluble triggering receptor expressed on myeloid cells [sTREM-1], and circulating cell-free DNA, are being explored for better accuracy and clinical utility [13, 14].

Conventional and Novel Biomarkers for sepsis: A Comparison [22]

CRP [C-reactive protein]

Source: Liver [IL-6 mediated, acute-phase reactant]

Rise: 4–6h, peak at 36–50h

Strengths: Cheap, widely available, good for monitoring trends

Limitations: Nonspecific [also ↑ in trauma, surgery, autoimmune, etc.]

Clinical use: General inflammation marker, adjunct in infection

PCT [Procalcitonin]

Source: Precursor of calcitonin, extra-thyroid production during bacterial infection

Rise: 4–6h, peaks faster than CRP

Strengths: More specific for bacterial infections; useful for guiding antibiotic discontinuation

Limitations: False positives [surgery/trauma], false negatives [early or localized infection]

Clinical use: Bacterial infection marker, antibiotic stewardship

IL-6 [Interleukin-6]

Source: Early pro-inflammatory cytokine

Rise: Very early [within hours], short half-life

Strengths: Strong early diagnostic signal; correlates with severity

Limitations: Prognostic value inconsistent when used alone

Clinical use: Very early sepsis detection, adjunct to other markers

PTX3 [Pentraxin 3]

Source: Endothelial, epithelial, and immune cells [vascular inflammation]

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Rise: Early in vascular injury/inflammation

Strengths: Adds prognostic/vascular information

Limitations: Less discriminative than IL-6, limited clinical availability

Clinical use: Adjunct marker for endothelial activation

sTREM-1

Source: Released from activated neutrophils/monocytes

Rise: Moderate during infection

Strengths: Improves accuracy when combined with IL-6/PCT

Limitations: Limited utility alone, not standardized

Clinical use: Combination biomarker panels, research

suPAR

Source: Marker of immune activation

Rise: Stable and reproducible

Strengths: Strong correlation with mortality, good prognostic marker

Limitations: Not specific for bacterial infection

Clinical use: Risk stratification in ED/ICU

Presepsin [sCD14-ST]

Source: Cleavage fragment of CD14 after bacterial activation

Rise: 2–3h [earlier than CRP/PCT], half-life ~5h, influenced by renal function

Strengths: High sensitivity/specificity; especially useful in culture-negative sepsis; dynamic trends predict mortality

Limitations: Affected by renal dysfunction [needs adjusted cutoffs], not yet universal

Clinical use: Early sepsis detection [esp. ED], prognostic monitoring, best in panels

Presepsin: A Promising Biomarker for Early Sepsis Detection

Presepsin [soluble CD14 subtype or sCD14-ST] has emerged as a novel biomarker reflecting monocyte and macrophage activation during bacterial and fungal infections [15]. It is a fragment of the CD14 receptor that binds to lipopolysaccharide [LPS]-lipopolysaccharide binding protein complexes, directly linking it to the pathogenesis of sepsis [16]. Presepsin levels rise within 2–3 hours of infection onset, peak around 3 hours, and have a half-life of approximately 5 hours [17]. Elevated presepsin levels have been shown to correlate with sepsis severity, organ dysfunction, and mortality risk [18].

In comparison with other biomarkers, presepsin demonstrates higher specificity in distinguishing sepsis from non-infectious systemic inflammatory conditions [18]. It has been found to outperform CRP and PCT in predicting septic shock, acute respiratory distress syndrome [ARDS], and renal complications [19].

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Evidence from Emergency Department Studies on Presepsin

A prospective observational cohort study conducted at Policlinico Agostino Gemelli, Rome [May 2023–Oct 2024], evaluated 216 adult patients admitted to the Emergency Department [ED] with clinical suspicion of sepsis [20]. Alongside standard diagnostics, presepsin was measured using a chemiluminescent immunoassay. Patients were followed with culture results and discharge diagnoses for sepsis classification.

RESULTS showed that 86 patients were culture-positive and 130 were culture-negative; of the latter, 36 were diagnosed clinically with sepsis. Elevated presepsin [>165 pg/mL] was found in 89.5% of culture-positive and 94.4% of culture-negative sepsis cases, compared with procalcitonin [PCT] elevation [>0.5 ng/mL] in 65.1% and 86.1%, respectively. Presepsin demonstrated higher sensitivity [91%] and diagnostic accuracy than PCT [71%], with ROC analysis showing AUC 0.946 vs. 0.905 [$p < 0.001$] [20].

The combination of presepsin and PCT improved diagnostic yield, particularly in culture-negative sepsis, supporting a multimarker strategy for early detection. Discordant biomarker levels reflected infection stage: elevated presepsin with low PCT indicated early infection, whereas elevated PCT with low presepsin suggested later systemic progression [21].

Presepsin levels also correlated with disease severity, septic shock, acute kidney injury, and mortality risk. However, renal dysfunction influenced levels, with adjusted cut-offs [>1000 pg/mL if creatinine >1.5 mg/dL] recommended [22]. The study concluded that presepsin had greater sensitivity and specificity than PCT for early sepsis detection in the ED. Rapid point-of-care tests enable results within 15 minutes, making presepsin practical for emergency triage and antibiotic stewardship [22].

Expanded Evidence: Comparing Biomarkers & Combinations

Because no single marker perfectly identifies sepsis, multi‑marker panels are under study. In ICU cohorts, presepsin combined with PCT and IL‑6 improved discrimination compared with each marker alone. Studies integrating presepsin with endothelial and coagulation markers [Ang‑1/2, soluble thrombomodulin] further enhanced accuracy. In molecular approaches, combining presepsin with microbial DNA sequencing [mNGS] also improved bacterial detection in culture‑negative sepsis [21,22].

DISCUSSION

The clinical diagnosis of sepsis remains hindered by nonspecific symptoms and delayed culture results. Biomarkers such as CRP and PCT are valuable but insufficient for early-stage differentiation. The inclusion of presepsin offers enhanced diagnostic sensitivity, especially in culture-negative or ambiguous cases. Its rapid kinetic response provides a window for early therapeutic intervention, reducing time to antibiotic initiation and improving outcomes [22].

Moreover, combining presepsin with established biomarkers forms a robust diagnostic panel, reflecting different aspects of the host response. This multimarker approach aligns with the precision medicine paradigm, allowing stratified treatment decisions and antibiotic stewardship [22]. Despite promising evidence, limitations include small sample sizes, single-center data, and variable assay standardization. Future multicenter trials should validate cut-offs and explore serial monitoring to assess prognostic trends.

CONCLUSION

Presepsin represents a valuable addition to the panel of sepsis biomarkers, offering higher sensitivity and specificity than traditional markers like CRP and PCT. Its rapid rise after infection onset makes it suitable for early diagnosis in the Emergency Department setting. When combined with PCT, presepsin provides superior diagnostic accuracy, aiding timely recognition and risk stratification of septic patients. Further multicentric validation and integration into clinical guidelines may pave the way for routine use, ultimately improving survival and optimizing resource utilization in sepsis management [22].

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