Interference Journal
ISSN 2009-3578
DOI
A2 QUALIS SUCUPIRA 2017-2020

USE OF INFLAMMATORY AND MOLECULAR BIOMARKERS IN THE EARLY DIAGNOSTIC ASSESSMENT OF SEPSIS IN CRITICALLY ILL PATIENTS: LIMITS, ADVANCES, AND CLINICAL PERSPECTIVES

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https://doi.org/10.36557/2009-3578.2025v11n2p8163-8176
Artigo recebido em 2 de Outubro e publicado em 2 de Dezembro de 2025

REVISÃO INTEGRATIVA DA LITERATURA

ABSTRACT

Sepsis remains one of the most challenging syndromes in intensive care, marked by marked clinical heterogeneity, rapid hemodynamic deterioration, and high mortality. Traditional diagnostic approaches, based on clinical scores (SIRS, qSOFA, SOFA) and microbiological methods, frequently identify sepsis only after significant organ dysfunction is established and are limited by delayed results, false negatives, and the impact of prior antibiotic exposure. In this context, inflammatory and molecular biomarkers have emerged as promising tools to support earlier diagnostic approximation, risk stratification, and therapeutic decision-making in critically ill patients. This narrative review aimed to analyze the main inflammatory and molecular biomarkers used in the diagnostic approximation of sepsis in adult intensive care patients, discussing their accuracy, clinical applicability, and prognostic implications. The review was guided by the PICo strategy (Population, Interest, Context) and included original studies, systematic and narrative reviews, clinical trials, observational research, and translational investigations published between 2015 and 2025 in PubMed, Scopus, Web of Science, and SciELO, in Portuguese, English, and Spanish. The findings highlight that classical inflammatory biomarkers, such as C-reactive protein, procalcitonin, IL-6, and TNF-α, play a consolidated role in monitoring systemic inflammation, differentiating infectious from non-infectious processes, and supporting antimicrobial stewardship. Emerging molecular biomarkers, particularly presepsin and sTREM-1, together with transcriptomic, proteomic, and metabolomic approaches, expand the understanding of sepsis endotypes and suggest pathways toward precision intensive care. However, the lack of standardization, methodological variability, costs, and limited availability restrict their widespread implementation. Overall, biomarkers should be interpreted as complementary tools-integrated with clinical, hemodynamic, and microbiological assessment- to reduce diagnostic uncertainty and enable earlier, more individualized interventions in patients

with sepsis.

Keywords: Sepsis; Inflammatory biomarkers; Molecular biomarkers; Intensive care.

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1- INTRODUCTION

Sepsis is one of the most severe and complex conditions encountered in intensive care. It is defined as a dysregulated host immune response to infection capable of triggering organ dysfunction, hemodynamic instability, and high mortality rates (Cao; Wang; Xie, 2023). Despite advances in supportive care and antimicrobial strategies, the central clinical challenge remains unchanged: to identify septic patients early-prior to the escalation of the inflammatory cascade into irreversible physiological deterioration (Cajander *et al*., 2024).

Traditionally, diagnostic approaches have relied on clinical manifestations and syndromic criteria such as SIRS, qSOFA, and SOFA, which capture organ damage at later stages of the disease process. Microbiological testing, although indispensable for etiological confirmation, exhibits operational limitations in real-world intensive care settings: delayed results, transient false negatives, and interference from prior antibiotic exposure (Tjandra *et al*., 2022). Consequently, exclusive dependence on these tools often postpones therapeutic action, narrowing the therapeutic window and worsening clinical outcomes (Samuel, 2019).

Within this context, inflammatory and molecular biomarkers have emerged as key instruments for early diagnostic assessment. Classical biomarkers such as C-reactive protein and procalcitonin indicate immune activation, while cytokines like IL-6 and TNF-α reflect the magnitude and systemic spread of the inflammatory response (He *et al*., 2024). More recent tools-including presepsin and sTREM-1-enhance diagnostic discrimination between sterile inflammatory states and bacterial infection, while omics-based approaches aim to identify biological signatures associated with distinct immunological phenotypes (Özsoy; Moura; Ferreira; Pereira, 2025).

Nonetheless, clinical applicability requires prudence: the immune response in critically ill patients is heterogeneous, modulated by comorbidities, previous therapies, and metabolic status. Biomarkers do not replace clinical reasoning; rather, they complement it when interpreted longitudinally and integrated with physiological, hemodynamic, and microbiological data (Wong, 2019; He *et al*., 2024). This narrative review aims to analyze the principal inflammatory and molecular biomarkers used in the early diagnostic assessment of sepsis in critically ill patients, examining their accuracy,

clinical utility, and prognostic implications.

2- METHOD

This study is a Narrative Literature Review developed to integrate and critically interpret the scientific evidence related to the use of inflammatory and molecular biomarkers in the early diagnostic assessment of sepsis in critically ill patients. The choice of this review format stems from the multifactorial nature of sepsis and the heterogeneity of its clinical, pathophysiological, and immunological manifestations, allowing for the articulation of findings originating from intensive care, immunology, molecular biology, and related fields. The narrative approach enables a broad, interpretative, and contextual analysis, fostering an integrated understanding of the phenomena that modulate the host's response to infection, as well as the methodological limitations inherent to different biomarkers (Rother, 2007; Green *et al*., 2006).

To guide the search and selection of studies, the PICo strategy was adopted as follows: P (Population): adult patients hospitalized in intensive care units with suspected or confirmed sepsis; I (Interest): scientific evidence related to inflammatory and molecular biomarkers-such as C-reactive protein, procalcitonin, IL-6, TNF-α, presepsin, sTREM-1, and omics-based approaches-used for early detection, prognostic stratification, and monitoring of sepsis; Co (Context): clinical and laboratory settings in intensive care, including translational research, observational studies, clinical trials, consensus statements, and guidelines relevant to clinical practice (Stern; Jordan; McArthur, 2014; Lockwood; Munn; Porritt, 2015).

Based on this framework, the guiding question was formulated: What is the current scientific evidence on the use of inflammatory and molecular biomarkers in the early diagnostic assessment of sepsis in critically ill patients, and what are their clinical and prognostic implications?

The bibliographic search was conducted in PubMed, Scopus, Web of Science, and SciELO, considering publications in Portuguese, English, and Spanish from 2015 to 2025. Controlled descriptors (MeSH/DeCS) and free terms related to the central theme were

used, including: “sepsis,” “biomarkers,” “procalcitonin,” “C-reactive protein,” “IL-6,” “TNF-alpha,” “presepsin,” “TREM-1,” “omics,” “critical care,” “intensive care unit,” and “diagnostic accuracy.”

Original studies, narrative and systematic reviews, clinical trials, observational research, and translational investigations addressing the use of biomarkers for diagnosis, stratification, or monitoring of sepsis were included. Opinion articles, duplicate reviews, exclusively pediatric or neonatal studies, research focused solely on pharmacological treatment without biomarker discussion, and publications not directly related to the intensive care context were excluded.

After critical reading and comparative analysis, eligible studies were organized into interpretative thematic axes to identify convergences, gaps, and controversies in contemporary sepsis literature. This systematization enabled the synthesis of advances, limitations, and potential clinical applications of inflammatory and molecular biomarkers, fostering an integrated understanding of their diagnostic and prognostic role in the care of critically ill patients.

3- RESULTS

The studies analyzed demonstrate significant progress in understanding the inflammatory dynamics of sepsis, showing that innate immune activation occurs rapidly and disproportionately. Biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), IL-6, and TNF-α emerge as central indicators of systemic inflammatory response, correlating with the severity of organ dysfunction (He *et al*., 2024; Xu *et al*., 2025). CRP, traditionally used for inflammatory monitoring, exhibits high sensitivity but delayed kinetics; PCT, in contrast, shows a more intrinsic association with bacterial infections and proves useful for severity stratification and guiding initiation or discontinuation of antimicrobial therapy, particularly in intensive care settings (Schuetz *et al*., 2017; Pierrakos *et al*., 2020).

In parallel, the literature highlights the growing adoption of emerging molecular biomarkers capable of capturing earlier and more specific aspects of septic physiology. Presepsin (sCD14-ST) demonstrates strong performance in distinguishing sterile inflammation from bacterial infection and presents superior correlations with mortality

and clinical progression compared to traditional markers in selected contexts (Chen; Zhu, 2020; Moura; Ferreira; Pereira, 2025). sTREM-1, expressed in activated myeloid cells, stands out for amplifying inflammatory signaling and for its prognostic value in pulmonary and abdominal infections. These biomarkers, particularly when assessed in combined panels, enhance diagnostic accuracy and early detection sensitivity (Yu *et al.*, 2024; Moura; Ferreira; Pereira, 2025).

Furthermore, recent investigations demonstrate the relevance of omics-based approaches-including transcriptomics, proteomics, and metabolomics-in characterizing immunological phenotypes of sepsis. The identification of molecular signatures capable of differentiating hyperinflammatory and immunoparalytic endotypes has enabled more nuanced interpretations of disease evolution and suggests pathways toward individualized prognostic stratification (Pandey, 2024). However, these advancements also reveal substantial challenges: operational costs, lack of laboratory standardization, methodological variability across studies, and limited applicability in real-world ICU environments, where treatment decisions must occur within narrow therapeutic windows (Antcliffe *et al.*, 2025; Chang *et al.*, 2023).

To synthesize the key findings of this section, a summary table will be inserted, gathering the main identified biomarkers, their diagnostic contributions, limitations, and potential prognostic implications in the context of sepsis.

Table 1: Key inflammatory and molecular biomarkers and challenges in the early diagnostic assessment of sepsis

Thematic Axis / Modality	**Main Findings**	**Key Evidence (Authors/Year)**
Classical inflammatory biomarkers (CRP, PCT)	CRP shows high sensitivity but late kinetics; PCT exhibits stronger association with bacterial infection, supports severity stratification and antibiotic stewardship.	He et al. (2024); Schuetz et al. (2017); Pierrakos et al. (2020).
Pro-inflammatory cytokines (IL-6, TNF-α)	Early immune activation markers reflecting systemic inflammatory burden; associated with endothelial injury, microcirculatory dysfunction and multiorgan failure.	He et al. (2024); Vella et al. (2025); Liu et al. (2022).
Serial biomarker assessment & composite panels	Temporal trends (rise–decline–response) enhance diagnostic reliability; integrated panels (CRP + PCT + IL-6) improve clinical decision-making and early deterioration detection.	Wirz et al. (2018); Mathew et al. (2024); Xu et al. (2025).
Molecular biomarkers (presepsin)	Strong discriminatory performance between sterile inflammation and bacterial sepsis; robust prognostic association with mortality and sepsis-associated complications.	Chen & Zhu (2020); Xing et al. (2025); Moura; Ferreira; Pereira (2025).

Innate immune receptor biomarkers (sTREM-1)	Amplifies inflammatory signaling; high value in abdominal and pulmonary infections; improves diagnostic precision when combined with inflammatory markers.	Moor et al. (2021); Formenti et al. (2024); Özsoy et al. (2024).
Omics-based approaches (transcriptomics, proteomics, metabolomics)	Identification of endotypes (hyperinflammatory vs. immunoparalytic) enables personalized risk stratification; elucidates mitochondrial and metabolic dysfunction in sepsis.	Pandey (2024); Antcliffe et al. (2025); Chang et al. (2023).
Clinical implications & precision intensive care	Biomarkers support anticipatory medicine; integrate laboratory profiles with clinical scoring to reduce empiricism and accelerate therapeutic decisions.	Cajander et al. (2024); He et al. (2024); Pierrakos et al. (2020).
Challenges and limitations	Lack of standardization, cost, accessibility, and methodological variability; biomarkers should not replace clinical judgment or microbiological confirmation.	Samuel (2019); Wong (2019); Moor et al. (2021).

Source: Prepared by the author (2025) based on the reviewed literature.

4- DISCUSSION

Recent advances in clinical immunology and molecular biology have expanded the understanding of sepsis beyond a reductionist view centered solely on pathogen presence, revealing its multifactorial, dynamic, and immunometabolically complex nature. The findings of this review reinforce that sepsis arises from a breakdown in immunological homeostasis, in which defense mechanisms and tissue-injury processes coexist, leading to divergent responses even among patients with similar clinical presentations. The integration of basic science, laboratory technologies, and bedside practice has facilitated more refined approaches to diagnostic stratification, positioning biomarkers as key elements for early diagnostic approximation and risk assessment. In light of this evidence, the discussion is organized into two analytical categories: (1) inflammatory biomarkers and pathophysiological mechanisms in sepsis, and (2) emerging molecular biomarkers and perspectives for precision intensive care.

4.1 Inflammatory biomarkers and pathophysiological mechanisms in sepsis

The reviewed literature shows that the set of classical inflammatory biomarkers-such as CRP, procalcitonin, IL-6, and TNF-α-reflects distinct dimensions of the immune response to infectious insult. Although sensitive, CRP presents delayed kinetics, representing more established inflammatory processes. Procalcitonin, in contrast,

demonstrates greater specificity for bacterial infections, correlating with disease severity and adverse clinical outcomes, in addition to supporting antimicrobial stewardship decisions (Mathew *et al*., 2024; Wirz *et al*., 2018). Cytokines such as IL-6 and TNF-α express the degree of early immune activation and are associated with microcirculatory and organ dysfunction, functioning as relevant indicators of pathophysiological progression. These findings support the view of sepsis as a heterogeneous systemic inflammatory syndrome, whose intensity and trajectory vary according to the patient's biological susceptibility (He *et al*., 2024; Vella *et al*., 2025).

Beyond systemic inflammatory response, the pathophysiology of sepsis involves profound endothelial alterations, microvascular dysfunction, and metabolic dysregulation. Experimental and clinical evidence demonstrates that imbalance between pro- and anti-inflammatory mediators contributes to immunoparalysis phenomena, predisposing patients to secondary infections and progressive organ failure (McMullan *et al*., 2024; Liu *et al*., 2022). Intense cytokine release, combined with endothelial injury, compromises regional blood flow, accelerates the generation of reactive species, and triggers mitochondrial bioenergetic shifts that impact cellular metabolism. In this scenario, inflammatory biomarkers cease to be mere laboratory indicators and instead act as physiological sensors capable of translating states of systemic instability (Srdić *et al*., 2024).

Another relevant aspect highlighted in the studies concerns the timing of use and serial monitoring of these biomarkers. The isolated interpretation of single values often produces imprecise clinical conclusions, particularly in critically ill patients with multiple comorbidities and overlapping diagnoses (He *et al*., 2024; Xu *et al*., 2025). Temporal analysis, integrating patterns of elevation, decline, and treatment response, enables recognition of disease trajectories and early identification of deterioration, consistent with evidence supporting procalcitonin-guided antibiotic decision-making (Mathew *et al*., 2024; Wirz *et al*., 2018). In this regard, the development of integrative biomarker panels (e.g., CRP + PCT + IL-6) emerges as a promising strategy to form more reliable physiopathological profiles, reducing uncertainty and informing therapeutic decision-making (Pierrakos *et al*., 2020; Vella *et al*., 2025).

4.2 Emerging molecular biomarkers and perspectives for precision intensive care

The expansion of molecular biomarkers has broadened the diagnostic landscape of sepsis. Presepsin (sCD14-ST), associated with monocyte activation, demonstrates consistent performance in distinguishing non-infectious inflammation from bacterial infections, in addition to showing meaningful correlation with mortality and complication rates (Xing *et al*., 2025; Moura; Ferreira; Pereira, 2025). sTREM-1, expressed on activated myeloid cells, exhibits particular prognostic relevance in pulmonary and abdominal sepsis, especially when combined with classical inflammatory markers (Moor *et al*., 2024; Formenti *et al*., 2024; Özsoy *et al*., 2024). These findings support the hypothesis that combined biomarker interpretation enhances early diagnostic detection and improves recognition of clinical patterns that, when assessed in isolation, remain opaque at the bedside (He *et al*., 2024; Pierrakos *et al*., 2020; Xu *et al*., 2025).

From a practical standpoint, the incorporation of emerging biomarkers signals a conceptual shift in sepsis management: from reactive medicine to anticipatory medicine (Cajander *et al*., 2024). Molecular profiles capable of differentiating hyperinflammatory phenotypes from immunosuppressed states pave the way for personalized interventions, preventing both excessive antibiotic exposure and delays in the initiation of essential therapies (Antcliffe *et al*., 2025; Pandey, 2024; Liu *et al*., 2022; Mathew *et al*., 2024; Wirz *et al*., 2018). The convergence of laboratory data, clinical scores, and serial trends may shorten the time to appropriate therapeutic decision-making-one of the most critical windows in the ICU (Pierrakos *et al*., 2020; He *et al*., 2024). Such an approach aligns with the principles of precision intensive care, particularly relevant in settings where clinical heterogeneity hinders uniform recommendations (Cajander *et al*., 2024).

Despite promising advances, substantial challenges remain for meaningful implementation of these biomarkers in clinical practice. Methodological variability across studies, lack of standardized reference ranges, operational costs, and laboratory access limitations reduce their generalizability (Pierrakos *et al*., 2020; Moor *et al*., 2024). Moreover, no biomarker should be interpreted in isolation, as sepsis is a multifactorial phenomenon influenced by comorbidities, previous therapies, and contextual

conditions (Wong, 2019; Formenti *et al*., 2024). Integrating biomarkers with clinical, hemodynamic, and microbiological assessment remains essential to support ethical and safe therapeutic decisions, in accordance with the principles of comprehensive critical care (Cajander *et al*., 2024; Moor *et al*., 2024).

5- CONCLUSION

Sepsis remains one of the most critical challenges in intensive care medicine, characterized by heterogeneous clinical trajectories, rapid hemodynamic deterioration, and high mortality. Although scoring systems and prognostic criteria provide support for severity assessment, they capture only later manifestations of the syndrome, when organ injury is already established. In this context, inflammatory and molecular biomarkers emerge as tools capable of anticipating the identification of septic patients, translating early biological events into laboratory indicators that precede systemic failure and supporting clinicians in timely decision-making.

The findings of this review demonstrate that classical biomarkers-such as C-reactive protein, procalcitonin, IL-6, and TNF-α-have a consolidated role in risk stratification, therapeutic response monitoring, and differentiation between infectious and inflammatory processes. However, more recent advances, including presepsin, sTREM-1, and transcriptomic and metabolomic approaches, broaden the understanding of the diverse immunological profiles of sepsis and highlight the potential of precision intensive care. This model is grounded in the integration of combined biomarker panels, longitudinal trend interpretation, and alignment with clinical, laboratory, and microbiological parameters, moving clinical practice away from empiricism and toward mechanisms-based decision-making that reduces diagnostic uncertainty and improves targeted interventions.

Nevertheless, the systematic incorporation of these biomarkers requires caution. The lack of standardization across studies, operational costs, variability related to comorbidities, and the risk of isolated interpretations remain significant barriers. Thus, the use of biomarkers should be understood as a complementary strategy-not a substitute-for clinical judgment and traditional diagnostic methods. Advancing multicenter validation, developing rapid and accessible testing platforms, and

consolidating multimodal diagnostic algorithms are essential steps for biomarkers to move beyond academic promise and become effective instruments in the critical care of septic patients.

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