Inflammatory Biomarkers in the Diagnosis and Prognosis of Severe Sepsis: An Integrative Review of Scientific Evidence

Biomarcadores Inflamatórios no Diagnóstico e Prognóstico da Sepse Grave: Revisão Integrativa da Evidência Científica

Biomarcadores Inflamatorios en el Diagnóstico y Pronóstico de la Sepsis Grave: Revisión Integrativa de la Evidencia Científica

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RESUMO

Objetivo: A sepse grave continua a ser uma das principais causas de mortalidade em unidades de cuidados intensivos, com taxas que podem chegar a 80% em países de baixa e média renda. O diagnóstico precoce é dificultado pela inespecificidade clínica e ausência de um padrão-ouro, tornando os biomarcadores ferramentas relevantes para auxiliar no diagnóstico, prognóstico e monitorização. Esta revisão integrativa analisou artigos publicados entre 2010 e 2025 que avaliaram biomarcadores inflamatórios na sepse grave. O objetivo foi identificar os marcadores mais utilizados e destacar novos potenciais para aplicação clínica. Os resultados mostraram que a proteína C-reativa (PCR) e a Procalcitonina (PCT) são amplamente utilizadas, embora com sensibilidade e especificidade inferiores a 90%. Níveis elevados de PCT associaram-se à maior mortalidade. Biomarcadores emergentes, como citocinas (TNF, IL-10), CD64, IP-10 e PLA2-II, demonstraram desempenho superior, com taxas acima de 90%. Destacaram-se ainda a pro-adrenomedulina (MR-proADM), com 77% de sensibilidade e 96% de especificidade, a Presepsina (PSEP), com AUC de 0,95, a pentraxin-3 (PTX-3), com AUC de 0,92, e a Calprotectina, com AUC de 0,90. Apesar dos avanços, nenhum biomarcador isolado mostrou ser definitivo. Assim, o futuro aponta para a combinação de múltiplos biomarcadores, permitindo maior precisão diagnóstica e prognóstica e abrindo caminho para a medicina personalizada na gestão da sepse grave.

Descritores: Biomarcadores; Sepse; Prognóstico

ABSTRACT

Objective: Severe sepsis remains one of the main causes of mortality in intensive care units, with rates reaching up to 80% in low- and middle-income countries. Early diagnosis is challenging due to nonspecific clinical manifestations and the absence of a gold standard. This integrative review analyzed studies published between 2010 and 2025 that evaluated inflammatory biomarkers in severe sepsis. The findings indicate that C-reactive protein (CRP) and procalcitonin (PCT) are the most widely used biomarkers. Elevated PCT levels were consistently associated with higher mortality. In contrast, emerging biomarkers such as cytokines (TNF, IL-10), CD64, IP-10, and PLA2-II demonstrated superior accuracy, particularly for early diagnosis. Other promising biomarkers include MR-proADM, with 77% sensitivity and 96% specificity, presepsin (AUC 0.95), pentraxin-3 (AUC 0.92), and calprotectin (AUC 0.90). Despite these advances, no single biomarker has proven definitive. Future strategies are expected to combine multiple biomarkers, improving diagnostic and prognostic precision and supporting the development of personalized medicine in the management of severe sepsis.

Descriptors: Biomarkers; Sepsis; Prognosis.

RESUMEN

Objetivo: La sepsis grave sigue siendo una de las principales causas de mortalidad en cuidados intensivos, con tasas de hasta el 80% en países de ingresos bajos y medios. El diagnóstico temprano se ve limitado por síntomas inespecíficos y la falta de un estándar de oro, lo que hace de los biomarcadores herramientas clave para el diagnóstico, pronóstico y seguimiento. Esta revisión integrativa analizó artículos (2010–2025) sobre biomarcadores inflamatorios en sepsis grave. La proteína C reactiva (PCR) y la procalcitonina (PCT) son ampliamente utilizadas, aunque con sensibilidad y especificidad inferiores al 90%; niveles elevados de PCT se asociaron con mayor mortalidad. Biomarcadores emergentes como citocinas (TNF, IL-10), CD64, IP-10 y PLA2-II mostraron alta precisión (>90%). Otros destacados fueron MR-proADM (77% sensibilidad, 96% especificidad), presepsina (AUC 0,95), pentraxina-3 (AUC 0,92) y calprotectina (AUC 0,90). Ningún marcador aislado es definitivo, pero la combinación de varios puede mejorar la precisión diagnóstica y pronóstica, impulsando la medicina personalizada en la sepsis.

Descriptores: Biomarcadores; Sepsis; Pronóstico

REVISÃO

Introduction

Sepsis is a complex state characterized by systemic inflammation, coagulation, complement system activation, apoptosis, and organ dysfunction. It is one of the main causes of death in critically ill patients, reaching up to 80% in low- and middle-income countries, despite modern interventional technologies and significant associated costs. Compounding its severity, the diagnosis of sepsis is hindered by the nonspecific nature of its signs and symptoms; that is, there is no gold standard for its diagnosis, given that the host response is highly individual. [1,2]

It is in this context that biomarkers play an important role, as they can indicate the presence, absence, or severity of sepsis, in addition to differentiating the nature of the infection, and guiding antibiotic therapy and the clinical path to be followed. [3,4]

In the current scenario, the most widely used biomarker is C-reactive protein (CRP), but its specificity is still considered low. Another widely used biomarker is procalcitonin (PCT), a calcitonin precursor peptide that usually has extremely low serum levels in healthy individuals. In cases of sepsis, these proteins substantially increase, which can be used to determine prognoses within the first 24 to 48 hours of treatment. Furthermore, studies analyze the possibility of expanding the use of MR-proADM (pro-adrenomedullin), which, although not highly sensitive, has very high specificity, in conjunction with presepsin (PSEP) and pentraxin-3 (PTX-3). [1,5,6,7,8,9,10]

Thus, the objective of this integrative review is to investigate the development of early sepsis biomarkers capable of identifying the infection, monitoring the patient's metabolic status, predicting the prognosis, and guiding therapeutic treatment.

Method

This is an integrative literature review, aimed at gathering, analyzing, and synthesizing information about the use of inflammatory and endothelial biomarkers in the prognosis of severe sepsis. The guiding research question was: "What are the main inflammatory and endothelial biomarkers associated with the prognosis of severe sepsis according to recent scientific literature?". The literature search was carried out between July and August 2025, covering articles published from February 2010 to June 2025, ensuring a comprehensive view of the topic. The methodological system used began with the selection of descriptors, found in the Health Sciences Descriptors (DeCS) dictionary, such as "Sepsis," which was combined, using the Boolean operator "AND," with the descriptor: "Biomarkers." This systematization strategy allowed for the finding of 21 articles published in databases such as the National Library of Medicine (PubMed). In the screening phase, three researchers independently selected and excluded the articles. Six were excluded for duplication and 5 for not addressing severe sepsis or prognostic biomarkers, resulting in 10 final selected articles. The selection and exclusion of studies followed the PRISMA flowchart criteria, and the critical analysis focused on three main axes: general and specific objectives of the studies; type of methodology applied; results and discussions about traditional and emerging biomarkers. The evaluation followed a

qualitative approach, seeking to identify convergences and divergences between the studies, as well as research gaps. All included articles fully provided data and were available in Portuguese and/or English. The limitations of this review include the temporal restriction and the reduced number of studies; the contributions involve the critical systematization of recent literature and the identification of gaps for future research. Regarding ethical aspects, as this is an integrative review based exclusively on already published secondary data, submission to the Research Ethics Committee was not required.

Results

In order to facilitate the synthesis of the studies present in the analysis, the information was categorized in Table I, including: author, title, objective, methodology, and main results found.

Tabela I - categorização dos estudos.

Author	**Title**	**Methodology**	**Results**
Pierrakos C, Vincent JL. [1]	Sepsis biomarkers: a review.	Literature review on sepsis biomarkers used in clinical or experimental studies, with the aim of better assessing their utility.	178 different biomarkers were analyzed in sepsis. Of these, 5 showed sensitivity and specificity values greater than 90%: TNF, IL-10, CD64, IP-10, and PLA2-II.
Azevedo JRA de, Torres OJM, Czeczko NG, Tuon FF, Nassif PAN, Souza GD de. [2]	Procalcitonin as a prognostic biomarker for severe sepsis and septic shock.	Observational prospective cohort study including patients with severe sepsis and septic shock.	28 PCT determinations were performed at the time of sepsis diagnosis in 28 different patients. Of these, 5 died, 3 from septic shock. The concentration of PCT after 24 and 48 hours was higher in the survivor group.
Julián-Jiménez A, Yañez MC, González-Del Castillo J, *et al.* [3]	Prognostic power of biomarkers for short-term mortality in the elderly patients seen in Emergency Departments due to infections.	Prospective, observational, multicenter, and analytical study, with 136 patients aged 75 years or older treated for infection, from 8 participating hospitals.	MR-proADM has a sensitivity of 77% and a specificity of 96%, being the best at predicting death within 30 days.
Lanziotti VS, Póvoa P, Soares M, Silva JRL e, Barbosa AP,	Use of biomarkers in pediatric sepsis: a literature	A literature review was conducted searching for the uniterms biomarkers AND children AND pediatric AND sepsis in	The combined use of biomarkers can increase the sensitivity and specificity of diagnosis and prognosis in sepsis, when compared to the use of a single

Salluh JIF. [4]	review.	the MEDLINE/PubMed database up to May 1, 2016, with no language limits.	biomarker.
Kim MH, Choi JH. [5]	An Update on Sepsis Biomarkers.	Literature search on biomarkers measured in septic patients, comparing AUC, sensitivity, and specificity.	The highlighted biomarkers were: Presepsin (PSEP), with an AUC of 0.95; Pentraxin-3 (PTX-3), a biomarker from the CRP family, but more sensitive, with an AUC of 0.92; and Calprotectin, with an AUC of 0.90.
Bedate-Núñez M, Moreno-Racionero F, de Andrés-Asenjo B, *et al.* [6]	Importancia de los parámetros clínicos y analíticos de la sepsis grave en la uropatía obstructiva.	Observational and prospective study with 65 patients in emergency. A predictor model for SS was constructed and a multivariate risk analysis was performed.	At admission, the variable that best predicted severe sepsis was the increase in procalcitonin.
Pierrakos C, Velissaris D, Bisdorff M, Marshall JC, Vincent JL.[7]	Biomarkers of sepsis: time for a reappraisal.	Literature review in the PubMed database, from 2009 until September 2019, with the terms "Biomarker" AND "Sepsis".	Forty biomarkers were compared to PCT and/or CRP for diagnostic value; 9 showed better diagnostic performance than one or both.
He RR, Yue GL, Dong ML, Wang JQ, Cheng C.[8]	Sepsis Biomarkers: Advancements and Clinical Applications – A Narrative Review.	Narrative review of the literature, updating the state-of-the-art on sepsis biomarkers, with the aim of identifying and evaluating emerging biomarkers.	Recent studies identified new biomarkers with greater sensitivity and specificity, including circular RNAs, HOXA distal antisense RNA, microRNA-486-5p, protein C, triiodothyronine, and prokineticin 2.
Wejnaruemarn S, Susantitaphong P, Komolmit P, *et al.* [9]	Procalcitonin and presepsin for detecting bacterial infection and spontaneous bacterial peritonitis in cirrhosis: A systematic review and meta-analysis.	A systematic search was performed in the MEDLINE, EMBASE, and Scopus databases for studies that evaluated the diagnostic role of PCT and presepsin, from their creation until June 2024.	PCT and presepsin show high sensitivity and specificity in detecting bacterial infections in patients with cirrhosis (PCT: sensitivity of 0.73 and specificity of 0.83; presepsin: sensitivity of 0.75 and specificity of 0.80).

Yoon SH, Eun S. [10]	Neutrophil CD64 as a prognostic biomarker for mortality in sepsis: A systematic review and meta-analysis.	Systematic review and meta-analysis, including patients aged ≥ 16 years, diagnosed with sepsis according to Sepsis-1, Sepsis-2, or Sepsis-3 criteria.	Although neutrophil CD64 has an AUC ≥ 0.80, suggesting good prognostic performance, its relatively low specificity may lead to false positives, limiting its role as a standalone tool. nCD64 may be more useful as a screening test, aiding in the early identification of septic patients at high risk of mortality who require strict monitoring.

Source: Personal collection (2025).

Discussion

Of the most commonly used current biomarkers, two can be mentioned: procalcitonin (PCT) and C-reactive protein (CRP), which present a limitation: sensitivity and specificity below 90%. Elevated plasma procalcitonin levels were associated with high mortality in patients with severe sepsis and septic shock. Of those that show sensitivity and specificity greater than this rate, there are cytokines, such as TNF and IL-10, CD64 receptor expression, IP-10, and PLA2-II, which showed promising results especially for early sepsis diagnosis. There are also those with high negative predictive value, useful for sepsis exclusion, such as PCT, aPTT waveform, and fibrin degradation products. Another highlight was MR-proADM (pro-adrenomedullin), having 77% sensitivity (chance of correctly identifying who will not survive) and 96% specificity (chance of correctly identifying who will survive), in addition to Presepsin (PSEP), with an AUC ("Area Under the Curve," referring to the relationship between sensitivity and specificity or, also, between true positives and false positives) of 0.95; Pentraxin-3 (PTX-3), a biomarker from the CRP family, but more sensitive, with an AUC of 0.92; and Calprotectin, with an AUC of 0.90. The future of using potential biomarkers for sepsis will likely involve a combination of multiple markers, given the multifactorial and heterogeneous nature of sepsis. Furthermore, the integration of these biomarkers into predictive algorithms can significantly increase prognostic accuracy. The use of artificial intelligence for the combined analysis of multiple clinical and laboratory parameters has proven to be a growing trend, allowing for a dynamic and personalized assessment of sepsis evolution in real-time.

Final Considerations

Although there is currently no single biomarker capable of predicting a specific outcome for each patient with complete certainty, the future is promising: in addition to the discovery of new biomarkers, and new strategic applications for existing ones, there is also risk stratification involving multiple biomarkers. This proves the prognostic value of this system and the importance of creating strategies for the use of multi-biomarkers, in addition to segmenting personalized medicine in sepsis management, allowing for therapies more directed to the immunological and inflammatory profile of each patient. Thus, it is essential that future multicenter

clinical studies, with larger samples and standardized methodologies, be conducted to validate the most promising biomarkers and define their ideal cutoff points. Only with the consolidation of this evidence will it be possible to effectively implement multi-marker panels in clinical practice, promoting earlier, more assertive, and cost-effective interventions in the treatment of sepsis.

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