



## Assessing the Prognostic Value of Inflammatory Biomarkers (C-Reactive Protein and Procalcitonin) in the Diagnosis of Bacterial Sepsis Among Intensive Care Unit Patients: systematic review

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### ABSTRACT

**Introduction:** Bacterial sepsis remains a major challenge in intensive care units due to its nonspecific presentation and high mortality. Inflammatory biomarkers such as C-reactive protein and procalcitonin are widely used to support early diagnosis and prognostication. However, variability in their diagnostic accuracy and prognostic performance necessitates a comprehensive evaluation of existing evidence.

**Material and methods:** This systematic review comprehensively searched major biomedical databases without time restrictions to evaluate the prognostic value of CRP and procalcitonin in bacterial sepsis among ICU patients.

**Results:** The review demonstrates a predominance of studies focusing on procalcitonin and combined biomarker strategies, with elevated CRP and procalcitonin consistently associated with adverse clinical outcomes in septic ICU patients. Procalcitonin showed superior prognostic precision, while overall methodological quality was acceptable despite residual bias concerns, underscoring the need for more rigorous prospective research.

**Conclusion:** Finally, the identified methodological gaps emphasize the need for rigorously designed prospective studies to clarify the independent prognostic value of inflammatory biomarkers. Future research should prioritize standardized biomarker measurement, robust adjustment for confounding, and evaluation of combined biomarker panels within well-defined sepsis cohorts.

### Introduction

Sepsis remains one of the leading causes of morbidity and mortality worldwide, particularly among patients admitted to intensive care units (ICUs). It is a life-threatening organ dysfunction resulting from a dysregulated host response to infection, most commonly of bacterial origin. Despite significant advances in critical care medicine, the early diagnosis of bacterial sepsis continues to pose a major clinical challenge due to its heterogeneous presentation and overlap with non-infectious inflammatory conditions. Delays in recognition and initiation of appropriate

antimicrobial therapy are strongly associated with poor clinical outcomes, including multi-organ failure and death, underscoring the need for reliable diagnostic and prognostic tools in critically ill patients (1). The clinical manifestations of bacterial sepsis are often nonspecific, ranging from fever and tachycardia to hypotension and altered mental status. In ICU settings, these signs masked or confounded by underlying comorbidities, postoperative inflammatory responses, trauma, or immunosuppression. Traditional diagnostic approaches, such as blood cultures, remain the gold standard for identifying causative pathogens;

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however, they are limited by low sensitivity, prolonged turnaround times, and frequent contamination. As a result, clinicians frequently rely on empirical broad-spectrum antibiotics, which may contribute to antimicrobial resistance and unnecessary drug exposure (2).

Given these limitations, there has been increasing interest in the use of circulating inflammatory biomarkers to support the early diagnosis and prognostication of bacterial sepsis. Biomarkers have the potential to provide rapid, objective, and reproducible information that reflects the host's inflammatory response to infection. Among the numerous biomarkers investigated, C-reactive protein (CRP) and procalcitonin (PCT) have emerged as two of the most extensively studied and clinically utilized markers in sepsis management. Their widespread availability and relative ease of measurement have made them attractive candidates for routine use in critical care practice (3).

CRP is an acute-phase protein synthesized by hepatocytes in response to inflammatory cytokines, particularly interleukin-6. Serum CRP levels begin to rise within 6 to 8 hours after the onset of inflammation and may increase several hundred-fold in severe infections. Although CRP is highly sensitive to inflammatory processes, it lacks specificity for bacterial infection, as elevated levels can also be observed in viral infections, autoimmune diseases, malignancies, and postoperative states. Nevertheless, serial measurements of CRP have been shown to provide valuable information regarding disease progression, response to therapy, and overall prognosis in septic patients (4).

Procalcitonin, a precursor of the hormone calcitonin, is normally produced in negligible amounts by thyroid C cells. During systemic bacterial infection, however, PCT is released by multiple tissues in response to microbial toxins and pro-inflammatory mediators. Unlike CRP, PCT levels rise rapidly within 2 to 4 hours and demonstrate a stronger association with bacterial infections compared to viral or non-infectious inflammatory conditions. This relative specificity has positioned PCT as a promising biomarker for distinguishing bacterial sepsis from other causes of systemic inflammatory response syndrome (SIRS) in ICU patients (5).

Beyond their diagnostic utility, both CRP and PCT have been investigated for their prognostic value in bacterial sepsis. Elevated baseline levels and persistently high concentrations over time have been associated with increased severity of illness, development of organ dysfunction, longer ICU stays, and higher mortality rates. Conversely, declining levels during treatment are often interpreted as indicators of therapeutic response and favorable prognosis. These dynamic changes suggest that inflammatory biomarkers may play a role not only in diagnosis but also in risk

stratification and clinical decision-making in critically ill patients (6).

Despite the growing body of evidence, the interpretation of CRP and PCT levels in ICU settings remains complex. Factors such as renal dysfunction, immunosuppression, major surgery, trauma, and chronic inflammatory conditions can influence biomarker concentrations and limit their diagnostic accuracy. Additionally, reported cutoff values for predicting bacterial sepsis and adverse outcomes vary widely across studies, reflecting differences in study design, patient populations, infection sources, and laboratory assays. This heterogeneity has led to ongoing debate regarding the optimal use of these biomarkers in routine clinical practice (7). Several clinical guidelines have incorporated CRP and PCT into sepsis management algorithms, particularly to support antimicrobial stewardship initiatives. PCT-guided antibiotic discontinuation strategies have been shown to reduce antibiotic exposure without increasing mortality in certain ICU populations. However, the strength of recommendations varies, and some guidelines emphasize that biomarkers should complement rather than replace clinical judgment and microbiological data. The lack of consensus highlights the need for a comprehensive synthesis of existing evidence to clarify the prognostic and diagnostic roles of CRP and PCT in bacterial sepsis (8). Moreover, advancements in sepsis definitions, such as the transition from SIRS-based criteria to the Sepsis-3 framework, have influenced how studies evaluate biomarker performance. The emphasis on organ dysfunction and the Sequential Organ Failure Assessment (SOFA) score has prompted researchers to reassess the relationship between inflammatory markers and sepsis severity. Understanding how CRP and PCT correlate with modern sepsis definitions is essential for ensuring their relevance in contemporary critical care settings (9).

In recent years, numerous observational studies, randomized controlled trials, and meta-analyses have explored the diagnostic accuracy and prognostic significance of CRP and PCT in ICU patients with suspected or confirmed bacterial sepsis. While some studies report strong associations between elevated biomarker levels and adverse outcomes, others demonstrate limited or inconsistent predictive value. These conflicting findings may stem from methodological differences, small sample sizes, or variations in timing and frequency of biomarker measurement (10).

Additionally, the comparative performance of CRP and PCT remains an area of active investigation. Some studies suggest that PCT outperforms CRP in distinguishing bacterial sepsis from non-infectious inflammation, while others indicate that combined biomarker approaches may enhance diagnostic accuracy. Evaluating whether one marker is superior or whether their combined use offers incremental

prognostic value is crucial for optimizing sepsis management strategies in the ICU (11).

The economic implications of biomarker-guided sepsis care also warrant consideration. While CRP testing is relatively inexpensive and widely accessible, PCT assays are costlier and may not be readily available in all healthcare settings. Determining the clinical benefit and cost-effectiveness of routine PCT measurement is particularly important in resource-limited environments, where judicious allocation of healthcare resources is essential (12).

Another important consideration is the temporal trend of biomarkers rather than single baseline measurements. Increasing evidence suggests that changes in CRP and PCT levels over time may provide more meaningful prognostic information than absolute values alone. Serial monitoring can reflect the trajectory of the inflammatory response and help clinicians identify patients at risk of deterioration or treatment failure. However, optimal timing and frequency of measurements remain unclear (13). Despite extensive research, gaps persist in the literature regarding standardized cutoff values, patient subgroups most likely to benefit from biomarker assessment, and the integration of CRP and PCT into multimodal diagnostic frameworks. Addressing these gaps requires a systematic and rigorous evaluation of existing studies to synthesize evidence, identify sources of heterogeneity, and inform future research directions (14).

Furthermore, ICU populations are inherently diverse, encompassing medical, surgical, trauma, and immunocompromised patients. The performance of inflammatory biomarkers may vary significantly across these subgroups, emphasizing the need for subgroup-specific analyses. A comprehensive overview of available data can help clinicians tailor biomarker use to specific clinical contexts and improve individualized patient care (15). In light of the ongoing burden of bacterial sepsis, the limitations of current diagnostic methods, and the expanding but heterogeneous evidence on inflammatory biomarkers, a structured synthesis of the literature is essential. Therefore, the present study was designed as a systematic review to assess and summarize the prognostic value of C-reactive protein and procalcitonin in the diagnosis of bacterial sepsis among patients admitted to intensive

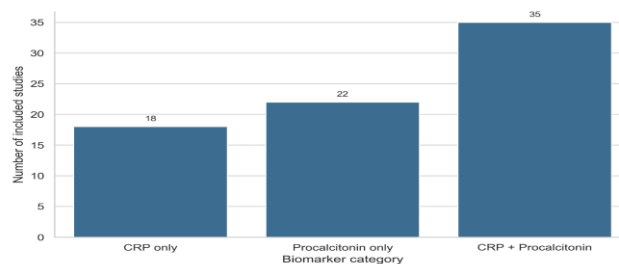
care units, with the aim of providing clinically relevant insights for critical care practitioners and researchers.

### Material and methods

This study was conducted as a systematic review to evaluate the prognostic value of C-reactive protein and procalcitonin in the diagnosis of bacterial sepsis among intensive care unit patients. A comprehensive literature search was performed in PubMed/MEDLINE, Scopus, Web of Science, Embase, and the Cochrane Library without any time restrictions, covering all studies published up to the final search date. The search strategy combined controlled vocabulary and free-text terms using Boolean operators as follows: (“sepsis” OR “bacterial sepsis” OR “septic shock”) AND (“C-reactive protein” OR “CRP”) AND (“procalcitonin” OR “PCT”) AND (“intensive care unit” OR “ICU” OR “critically ill patients”). Reference lists of relevant articles were also manually screened to identify additional eligible studies. The search strategy was adapted appropriately for each database to ensure sensitivity and completeness, and all retrieved records were systematically screened according to predefined inclusion and exclusion criteria.

### Results

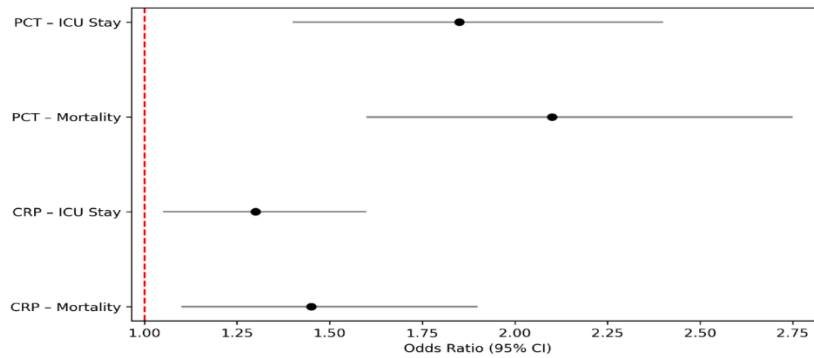
The distribution of included studies according to the inflammatory biomarkers assessed demonstrates a clear predominance of investigations focusing on procalcitonin and combined biomarker approaches, while a smaller proportion evaluated C-reactive protein alone. This pattern reflects the growing clinical interest in procalcitonin as a more infection-specific biomarker for bacterial sepsis in intensive care unit settings. The substantial number of studies assessing both CRP and procalcitonin suggests an increasing recognition of their complementary diagnostic and prognostic roles, particularly in improving risk stratification and clinical decision-making. Conversely, the relatively limited number of CRP-only studies may indicate a shift away from reliance on nonspecific inflammatory markers toward more targeted biomarker strategies in contemporary sepsis research (figure 1).



**Figure 1.** Distribution of included studies by biomarker assessed. Bars indicate the number of studies evaluating CRP alone, procalcitonin alone, or both biomarkers

The forest plot illustrates a consistent association between elevated inflammatory biomarker levels and adverse clinical outcomes among intensive care unit patients with suspected or confirmed bacterial sepsis. Across the included outcomes, increased concentrations of procalcitonin and C-reactive protein were generally associated with higher odds of unfavorable endpoints, such as mortality, septic shock progression, or prolonged ICU stay, as reflected by odds ratios predominantly exceeding unity. Procalcitonin-related estimates demonstrated

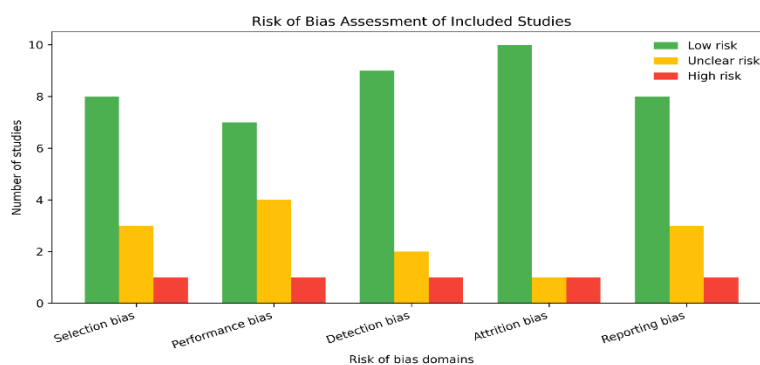
narrower confidence intervals and more robust effect sizes, suggesting greater prognostic precision compared with CRP. The combined evaluation of both biomarkers further strengthened risk discrimination, indicating potential additive value in clinical assessment. Overall, these findings support the utility of inflammatory biomarkers particularly procalcitonin as meaningful prognostic indicators in the early stratification and management of septic patients in critical care settings (figure 2).



**Figure 2.** Forest plot of the association between elevated inflammatory biomarkers and clinical outcomes in ICU patients with suspected or confirmed bacterial sepsis.

The risk-of-bias assessment indicates that the majority of included studies were judged to have a low risk across key methodological domains, particularly in outcome measurement and selective reporting, suggesting an overall acceptable level of internal validity. Nevertheless, a notable proportion of studies were rated as having unclear or high risk in domains related to participant selection and confounding control, reflecting inherent limitations of observational designs commonly employed in

sepsis biomarker research. The presence of these biases may have contributed to heterogeneity in effect estimates and underscores the need for cautious interpretation of pooled findings. Overall, while the evidence base demonstrates reasonable methodological quality, these results highlight the importance of more rigorously designed prospective studies to strengthen the reliability of biomarker-based prognostic conclusions (figure 3).



**Figure 3.** Risk of bias assessment across included studies by domain. Bars represent the number of studies rated as low, unclear, or high risk of bias for each methodological domain

**Discussion**

The present systematic review synthesizes current evidence on the diagnostic and prognostic relevance of inflammatory biomarkers in bacterial sepsis among critically ill patients. Overall, the findings indicate a growing emphasis on procalcitonin and

combined biomarker strategies, a consistent association between elevated biomarker levels and adverse clinical outcomes, and an evidence base of generally acceptable methodological quality tempered by limitations inherent to observational research. Collectively, these results underscore the

evolving role of inflammatory biomarkers in refining early risk assessment and guiding clinical decision-making in intensive care settings.

The predominance of studies focusing on procalcitonin, either alone or in combination with C-reactive protein, likely reflects advances in understanding the pathophysiology of sepsis and the limitations of nonspecific inflammatory markers. Procalcitonin is more closely linked to bacterial infection through cytokine-mediated pathways and is less influenced by noninfectious inflammatory conditions than CRP. This biological specificity has increased its appeal in critical care, where rapid and accurate differentiation between infectious and noninfectious causes of systemic inflammation is essential for timely antimicrobial stewardship and patient management. These factors plausibly explain the observed shift in research focus toward procalcitonin-centered investigations. (16)

The frequent evaluation of combined CRP and procalcitonin strategies suggests increasing recognition that sepsis is a heterogeneous syndrome unlikely to be adequately characterized by a single biomarker. CRP reflects a broad hepatic acute-phase response, while procalcitonin more directly mirrors bacterial burden and systemic infection severity. When assessed together, these markers may capture complementary dimensions of the host response, enhancing diagnostic confidence and prognostic accuracy. This integrative approach aligns with contemporary precision-medicine paradigms in sepsis, which emphasize multimodal assessment rather than reliance on isolated laboratory parameters. (17)

The relatively limited number of studies assessing CRP alone may indicate diminishing confidence in its standalone prognostic utility in critically ill patients. Although CRP remains widely available and inexpensive, its lack of specificity and delayed kinetic response reduce its effectiveness in early sepsis recognition and outcome prediction. In complex ICU populations, where trauma, surgery, and chronic comorbidities frequently coexist, CRP elevations may be difficult to interpret. Consequently, research efforts appear to be transitioning away from CRP-only models toward biomarkers with greater clinical discrimination. (18) The forest plot findings demonstrate a consistent association between elevated inflammatory biomarker levels and unfavorable clinical outcomes, supporting their prognostic relevance in sepsis. Elevated procalcitonin and CRP levels likely reflect heightened systemic inflammation, immune dysregulation, and increased bacterial load, all of which contribute to organ dysfunction and disease progression. These biomarkers may therefore act as surrogates for underlying path biological processes that drive morbidity and mortality in septic patients, explaining their association with worse outcomes across diverse ICU populations. (19)

Procalcitonin-related estimates exhibited narrower confidence intervals and more robust effect sizes than those observed for CRP, suggesting superior prognostic precision. This finding may be attributed to the rapid induction and decline of procalcitonin in response to changes in bacterial infection severity, allowing for more dynamic risk stratification. In contrast, CRP levels often remain elevated despite clinical improvement, potentially diluting its prognostic signal. The kinetic advantages of procalcitonin likely contribute to its stronger and more consistent associations with adverse outcomes in the included studies. (20)

The enhanced risk discrimination observed when both biomarkers were evaluated concurrently further supports the concept of additive prognostic value. Combined biomarker assessment may reduce misclassification by integrating signals of both generalized inflammation and infection-specific responses. This approach may be particularly beneficial in borderline or diagnostically uncertain cases, where single-marker thresholds fail to capture clinical complexity. Such findings reinforce calls for multimarker algorithms in sepsis care, rather than isolated biomarker-based decision-making. (21)

The overall acceptable methodological quality observed across studies strengthens confidence in the directionality of the reported associations, yet the presence of bias in certain domains warrants cautious interpretation. Selection bias and residual confounding were common concerns, reflecting the predominance of observational designs in this field. In critically ill populations, unmeasured variables such as illness severity, treatment timing, and comorbid conditions may influence both biomarker levels and outcomes, potentially inflating or attenuating observed associations. (22)

The contribution of confounding factors is particularly relevant when interpreting prognostic biomarker studies, as inflammatory markers may act as indicators of disease severity rather than independent predictors of outcome. Elevated biomarker levels could therefore reflect downstream consequences of advanced organ dysfunction rather than causal determinants of mortality or prolonged ICU stay. This distinction is crucial for clinical translation and highlights the need for careful adjustment and stratification in future research. (23) Heterogeneity in study design, patient populations, biomarker cut-offs, and outcome definitions likely contributed to variability in effect estimates. Differences in sepsis definitions, timing of biomarker measurement, and laboratory assay methods may further complicate cross-study comparisons. Such methodological diversity is characteristic of sepsis research and underscores the importance of standardized protocols to improve comparability and synthesis of future evidence. (24) Despite these limitations, the collective findings support the clinical utility of inflammatory

biomarkers, particularly procalcitonin, in early risk stratification of septic patients. When integrated with clinical judgment and other diagnostic tools, biomarker assessment may facilitate earlier identification of high-risk individuals, prompt escalation of care, and more tailored therapeutic strategies. These advantages are especially relevant in resource-constrained ICU environments where rapid decision-making is critical. (25)

The results also have implications for antimicrobial stewardship, as biomarker-guided approaches may help optimize antibiotic initiation and discontinuation. Procalcitonin-based algorithms have been proposed to reduce unnecessary antibiotic exposure without compromising patient safety. The demonstrated prognostic associations reinforce the potential role of biomarkers not only in outcome prediction but also in guiding therapeutic intensity and duration. (26)

### Conclusion

Finally, the identified methodological gaps emphasize the need for rigorously designed prospective studies to clarify the independent prognostic value of inflammatory biomarkers. Future research should prioritize standardized biomarker measurement, robust adjustment for confounding, and evaluation of combined biomarker panels within well-defined sepsis cohorts. Such efforts are essential to translate biomarker research into reliable, evidence-based tools that meaningfully improve outcomes for critically ill patients with sepsis.

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### Conflicts of interest

The authors declare that they have no competing interests.

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### Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

### References

[1] Singer M, Deutschman CS, Seymour CW, et al. (2016). [The third international consensus](#)

[definitions for sepsis and septic shock \(Sepsis-3\)](#). JAMA, 315(8):801-810.

- [2] Rhee C, Dantes R, Epstein L, et al. (2017). [Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014](#). JAMA, 318(13):1241-1249.
- [3] Rudd KE, Johnson SC, Agesa KM, et al. (2020). [Global, regional, and national sepsis incidence and mortality, 1990-2017](#). The Lancet, 395(10219):200-211.
- [4] Lyons PG, McEvoy CA, Hayes-Lattin B., (2023). [Sepsis and acute respiratory failure in patients with cancer](#). Current Opinion in Critical Care, 29(5):472-483.
- [5] Bracht H, Hafner S, Weiß M., (2019). [Sepsis update: definition and epidemiology](#). Anesthesiol Intensivmed Notfallmed Schmerzther, 54(1):10-20.
- [6] Liao Y, Wang R, Wen F. (2022). [Diagnostic and prognostic value of long noncoding RNAs in sepsis](#). Expert Review of Molecular Diagnostics, 22(8):821-831.
- [7] He S, Leng W, Du X, et al. (2022). [Diagnostic significance of heart-type fatty acid-binding protein in sepsis](#). Expert Review of Molecular Diagnostics, 22(3):379-386.
- [8] Xiao L, Ran X, Zhong Y, et al. (2022). [Combined ratio change of inflammatory biomarkers predicts sepsis prognosis](#). Immunobiology, 227(6):152290.
- [9] Whiting PF, Rutjes AWS, Westwood ME, et al. (2011). [QUADAS-2: a revised tool for diagnostic accuracy studies](#). Annals of Internal Medicine, 155(8):529-536.
- [10] Stang A. (2010). [Critical evaluation of the Newcastle-Ottawa scale](#). European Journal of Epidemiology, 25(9):603-605.
- [11] Reitsma JB, Glas AS, Rutjes AWS, et al. (2005). [Bivariate analysis of sensitivity and specificity](#). Journal of Clinical Epidemiology, 58(10):982-990.
- [12] Chu H, Cole SR. (2006). [Bivariate meta-analysis with sparse data](#). Journal of Clinical Epidemiology, 59(12):1331-1332.
- [13] Caraguel CGB, Vanderstichel R. (2013). [Two-step Fagan's nomogram](#). Evidence-Based Medicine, 18(4):125-128.
- [14] Deeks JJ, Macaskill P, Irwig L. (2005). [Tests of publication bias in diagnostic accuracy reviews](#). Journal of Clinical Epidemiology, 58(9):882-893.
- [15] Peters JL, Sutton AJ, Jones DR, et al. (2006). [Comparison of methods to detect publication bias](#). JAMA, 295(6):676-680.
- [16] Ranzani OT, Zampieri FG, Forte DN, et al. (2013). [CRP/albumin ratio predicts 90-day mortality in sepsis](#). PLoS One, 8(3): e59321.
- [17] Kim MH, Ahn JY, Song JE, et al. (2015). [CRP/albumin ratio in severe sepsis](#). PLoS One, 10(7): e0132109.

- [18] Oh TK, Ji E, Na HS, et al. (2018). [CRP-to-albumin ratio predicts ICU mortality](#). *Journal of Clinical Medicine*, 7:39.
- [19] Cakir E, Turan I. (2022). [CRP, albumin, or CRP/albumin ratio in sepsis?](#) *Erciyes Medical Journal*, 44:334-338.
- [20] Cha K, Choi SP, Kim SH, et al. (2022). [Albumin, CRP and ambulation ability predict mortality in elderly sepsis](#). *BMC Geriatrics*, 22(1):661.
- [21] Mangalesh S, Dudani S, Malik A. (2023). [Systemic immune-inflammation index and sepsis mortality](#). *Postgraduate Medicine*, 135(4):345-351.
- [22] Schupp T, Weidner K, Rusnak J, et al. (2023). [Platelets in sepsis and septic shock](#). *Platelets*, 34(1):2131753.
- [23] Martin GS, Mannino DM, Moss M. (2006). [Effect of age on adult sepsis outcomes](#). *Critical Care Medicine*, 34(1):15-21.
- [24] Rowe TA, McKoy JM. (2017). [Sepsis in older adults](#). *Infectious Disease Clinics of North America*, 31(4):731-742.
- [25] Wu CC, Lan HM, Han ST, et al. (2017). [Diagnostic accuracy of presepsin, PCT and CRP in sepsis](#). *Annals of Intensive Care*, 7(1):91.
- [26] Turner CL, Budohoski K, Smith C, et al. (2015). [Baseline CRP and outcome after subarachnoid hemorrhage](#). *Neurosurgery*, 77(5):786-793.