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Presepsin and Interleukin-6 as Early Diagnostic Biomarkers of Sepsis: A Scoping Review

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Abstract

Sepsis is a life-threatening medical condition with high morbidity and mortality, making early detection very important to improve patient outcomes. Conventional biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) have limitations in sensitivity and specificity, so more accurate biomarkers are needed. This study aims to analyze the role of presepsin and interleukin-6 (IL-6) as early diagnostic biomarkers of sepsis using a scoping review approach. The method used was a literature review of articles published between 2016–2026 from PubMed, ScienceDirect, and other sources based on specific inclusion and exclusion criteria. A total of 10 articles were included in this study. The results show that presepsin has high diagnostic accuracy, with AUC values ranging from 0.76 to 0.94, and is strongly associated with disease severity and patient mortality. Meanwhile, IL-6 acts as an inflammatory biomarker that significantly increases in severe cases and has good prognostic value for mortality. In addition, the combination of presepsin and IL-6 improves diagnostic accuracy and prediction compared to using a single biomarker. In conclusion, presepsin and IL-6 are complementary biomarkers in the diagnosis and prognosis of sepsis. Presepsin is more specific to bacterial infection, while IL-6 reflects the inflammatory response. Their combination has strong potential to improve early detection, risk assessment, and clinical decision-making in sepsis management.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection and remains a major global health problem with high morbidity and mortality rates. It is estimated that sepsis affects nearly 49 million people worldwide annually and is responsible for approximately 11 million deaths, representing a significant burden on healthcare systems (Piccioni et al., 2025). Despite advances in critical care and antimicrobial therapy, early diagnosis of sepsis remains a major clinical challenge due to its heterogeneous presentation and overlap with non-infectious inflammatory conditions (Da, 2022; He et al., 2024).

Timely identification of sepsis is crucial, as delayed diagnosis and treatment are strongly associated with increased mortality and poor clinical outcomes (Husabø et al., 2020). Current diagnostic approaches rely on clinical assessment, scoring systems such as the Sequential Organ Failure Assessment (SOFA), and conventional biomarkers including C-reactive protein (CRP) and procalcitonin (PCT). However, these markers have limitations in sensitivity and specificity, as they may also be elevated in non-infectious inflammatory states such as trauma, surgery, or autoimmune diseases (Xing et al., 2025). Therefore, there is an urgent need for more reliable and early-detection biomarkers that can improve diagnostic accuracy and guide clinical decision-making.

Among emerging biomarkers, presepsin (soluble CD14 subtype, sCD14-ST) has gained increasing attention as a promising diagnostic and prognostic indicator of sepsis. Presepsin is released into the circulation following activation of monocytes and macrophages during bacterial infection, reflecting innate immune response activation (Zhang et al., 2015). Several studies have demonstrated that presepsin levels rise early in the course of infection and correlate with disease severity, organ dysfunction, and mortality (Lee et al., 2022; Memar & Baghi, 2019). Meta-analyses have reported high diagnostic accuracy for presepsin, with pooled sensitivity and specificity of approximately 0.86 and 0.78, respectively, and an area under the curve (AUC) of approximately 0.89 (Zhang et al., 2015). Furthermore, elevated presepsin levels have been consistently associated with higher mortality rates in septic patients, underscoring its prognostic value (Yang et al., 2018).

In parallel, interleukin-6 (IL-6), a pro-inflammatory cytokine, has also been extensively studied as an early biomarker of sepsis. IL-6 is rapidly released during the systemic inflammatory response and can rise earlier than traditional biomarkers such as CRP and PCT. Elevated IL-6 levels have been associated with disease severity, organ dysfunction, and mortality in septic patients (Gamarra-Morales et al., 2024). Clinical studies have shown that IL-6 is an independent predictor of sepsis and may enhance diagnostic performance when combined with other clinical parameters (Yu et al., 2022). Additionally, IL-6 has demonstrated strong prognostic capability, particularly within the first 72 hours of intensive care unit (ICU) admission, making it a valuable marker for early risk stratification.

Although both presepsin and IL-6 have demonstrated promising diagnostic and prognostic potential, evidence regarding their comparative performance and combined utility as early biomarkers of sepsis remains fragmented. Some studies suggest that presepsin may offer superior specificity for bacterial infection, while IL-6 may reflect the magnitude of the systemic inflammatory response more sensitively. Moreover, recent evidence indicates that combining multiple biomarkers may significantly improve diagnostic accuracy compared to the use of a single marker alone (Piccioni et al., 2025).

Given the growing body of literature and the need for comprehensive evidence mapping, a scoping review represents an appropriate methodological approach to explore the roles of presepsin and IL-6 as early diagnostic biomarkers of sepsis. This review aims to systematically identify, summarize, and analyze current evidence regarding their diagnostic performance, prognostic value, and potential clinical applications in the early detection of sepsis. The anticipated benefit of this study is both theoretical and practical. Theoretically, it may enrich the scientific literature on emerging biomarkers in sepsis diagnosis and prognosis. Practically, it may provide clinicians and healthcare practitioners with evidence-based guidance in selecting more accurate biomarkers to support early diagnosis, risk stratification, and clinical decision-making in sepsis management.

METHOD

This study employed a scoping review design using a literature-based approach and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines to ensure transparency and methodological rigor. Data collection was conducted through reviewing, identifying, and synthesizing relevant scientific literature from previously published studies. Therefore, this study utilized secondary

data derived from existing research articles and scientific journals related to presepsin and interleukin-6 (IL-6) as early diagnostic biomarkers of sepsis.

The research question was structured using the PICO framework (Population, Intervention, Comparison, Outcome). The Population (P) included patients with sepsis or suspected sepsis. The Intervention (I) was the use of presepsin and interleukin-6 (IL-6) as early diagnostic biomarkers. The Comparison (C) involved comparisons between presepsin and IL-6 or with conventional biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT). The Outcome (O) focused on diagnostic accuracy, early detection capability, and prognostic value in sepsis. The literature search was conducted in March 2026 using three electronic databases: PubMed, ScienceDirect, and Google Scholar. The search strategy used a combination of keywords including "presepsin" AND "interleukin-6" AND "sepsis" AND "diagnosis" AND "biomarker" AND "early detection", which were connected using Boolean operators to refine the results.

The inclusion criteria for literature selection were: (1) articles discussing presepsin and/or interleukin-6 as diagnostic biomarkers of sepsis; (2) studies evaluating diagnostic accuracy or prognostic value; (3) articles published in English; (4) articles published between 2016 and 2026; (5) original research articles with observational or clinical study designs; and (6) full-text articles available. The exclusion criteria included: (1) review articles, systematic reviews, meta-analyses, and scoping reviews; (2) articles not directly related to the study topic; and (3) studies with incomplete data.

Using the three databases, a total of 198 articles were identified during the initial search stage, consisting of 52 articles from PubMed, 71 from ScienceDirect, and 75 from additional sources. After removing 16 duplicate records, 182 articles remained. The screening stage involved reviewing titles and abstracts to assess relevance, resulting in 68 articles considered relevant and 114 articles excluded. The eligibility stage involved full-text assessment of the remaining articles based on the predefined criteria. Studies that did not meet the criteria were excluded, resulting in 20 eligible articles. Finally, 10 articles were excluded due to incomplete data or lack of relevance, leaving 10 studies included in the final analysis. The study selection process followed the PRISMA-ScR flow and is presented in a flow diagram.

Data extraction was carried out systematically using a standardized approach. The extracted data included the author and year of publication, study design, study population, type of biomarker assessed (presepsin and/or IL-6), diagnostic performance indicators such as area under the curve (AUC), sensitivity and specificity, as well as prognostic outcomes including disease severity and mortality. Although a formal critical appraisal was not conducted, only peer-reviewed articles published in reputable scientific journals were included to ensure the reliability and credibility of the evidence. The article selection process is illustrated in a flow diagram (Figure 1).

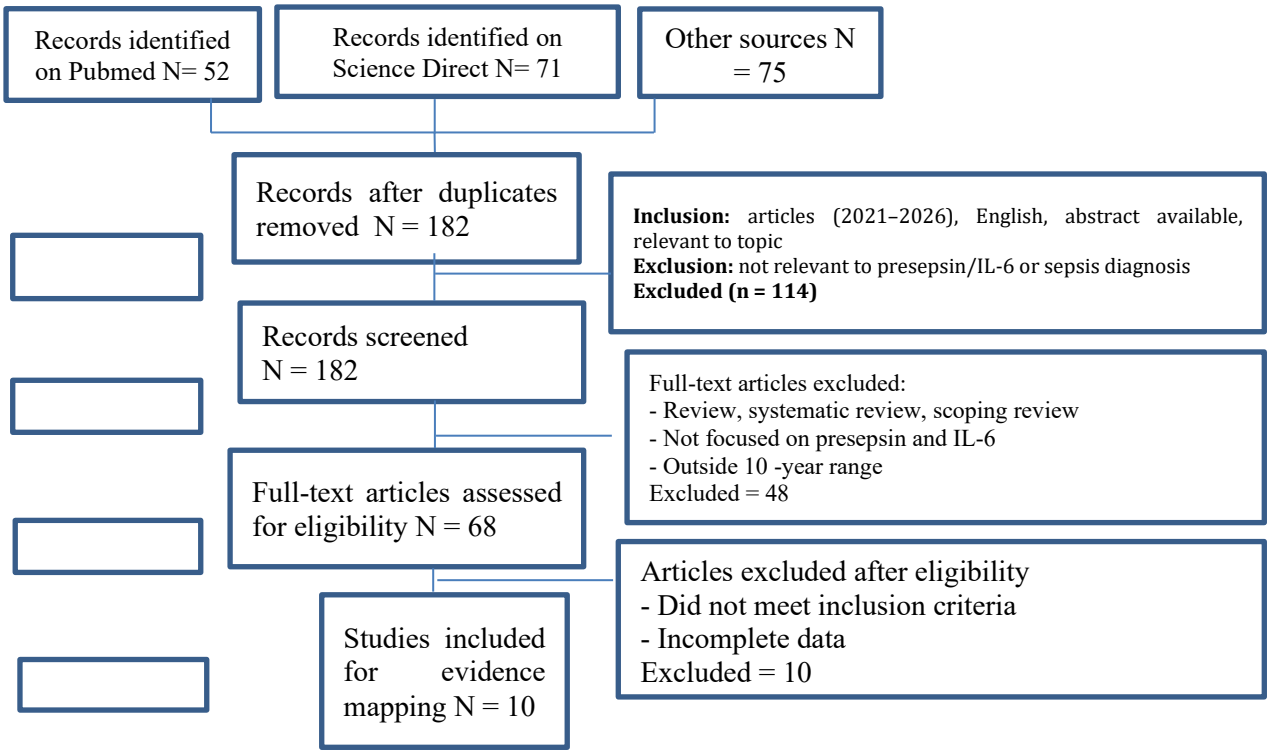

Figure 1. PRISMA-based flow diagram

Source: Processed by the authors based on literature search results, 2026

Table 1. Presepsin and Interleukin-6 as Early Diagnostic Biomarkers of Sepsis A Scoping Review

No	Author, Title	Aim	Results	Conclusion
1	Kim et al.,(2023) Presepsin levels for discriminating sepsis and predicting mortality among organ failure patients stratified by hypercreatinemia	To evaluate the diagnostic accuracy and prognostic value of presepsin in diagnosing sepsis and predicting mortality in patients with organ failure	Presepsin levels were significantly higher in septic patients compared to non-septic patients across all groups. The biomarker demonstrated high diagnostic accuracy with AUROC values of 0.884 in patients with hypercreatinemia and 0.854 in those without. Presepsin levels also correlated with disease severity and were associated with increased 30-day mortality. Optimal cutoff values varied depending on renal function, indicating that kidney impairment influences presepsin levels.	Presepsin is a reliable biomarker for diagnosing sepsis and predicting mortality. Its diagnostic and prognostic performance remains strong regardless of renal function, although different cutoff values should be considered based on creatinine levels.
2	Akkoç et al., (2020) Efficacy of presepsin as a biomarker of sepsis and its	To assess the diagnostic and prognostic	Presepsin levels were significantly elevated in septic shock patients	Presepsin is an effective biomarker for both

No	Author, Title	Aim	Results	Conclusion
	prognostic value for prediction of mortality	performance of presepsin in sepsis and septic shock	compared to those with SIRS. The biomarker showed superior diagnostic performance compared to conventional markers such as CRP and PCT, and was associated with increased mortality risk	diagnosis and prognosis of sepsis
3	Liu et al., (2021) Mortality prediction using a novel combination of biomarkers in the first day of sepsis in intensive care units	To identify biomarkers associated with mortality in septic patients	IL-6 levels were significantly higher in non-survivors compared to survivors. Elevated IL-6 levels were strongly associated with increased mortality and disease severity, demonstrating its role as an early inflammatory marker	IL-6 is a strong predictor of mortality and disease severity in sepsis
4	Baik et al., (2022) Validation of Presepsin Measurement for Mortality Prediction	To evaluate the predictive value of presepsin for mortality in septic patients	Presepsin levels were significantly higher in non-survivors, with moderate diagnostic accuracy (AUC = 0.764). The biomarker showed a clear association with disease severity and clinical outcomes	Presepsin can be used as a prognostic biomarker for mortality in sepsis
5	Iskandar et al.,(2025) Presepsin and Mortality Risk in Sepsis: A Valuable Tool for Predicting Patient Survival	To evaluate the prognostic significance of presepsin in predicting mortality among sepsis patients	Presepsin levels were significantly higher in non-survivors compared to survivors (median 17,503 vs 4,331.5 pg/mL). ROC analysis showed excellent predictive performance with an AUC of 0.939. Patients with presepsin levels ≥17,085 pg/mL had a significantly higher mortality risk, with a hazard ratio of 3.654. Mortality reached 96.9% in patients with high presepsin levels compared to 36.4% in those with lower levels. Elevated presepsin was strongly associated with reduced survival time (median 3 vs 9 days).	Presepsin is a highly effective biomarker for predicting mortality and disease severity in sepsis and can support early risk stratification and clinical decision-making
6	Ragán et al., (2023) Presepsin: gelsolin ratio, as a promising marker of sepsis-related organ	To evaluate the effectiveness of combined biomarkers in sepsis	The combination of presepsin with other biomarkers (including IL-6) significantly improved diagnostic	Combined biomarker strategies are more effective than single biomarker use in sepsis evaluation

No	Author, Title	Aim	Results	Conclusion
	dysfunction: a prospective observational study	diagnosis and prognosis	accuracy and prognostic performance. Multi-biomarker approaches provided better discrimination of sepsis severity compared to single biomarkers	
7	Gamarra-Morales et al.,(2024) Efficiency of IL-6 in Early Prognosis and Follow-Up in Critically Ill Patients with Septic Shock	To assess the role of IL-6 in predicting outcomes in septic shock patients	IL-6 levels were significantly elevated at ICU admission in septic shock patients and were strongly associated with mortality. The biomarker showed good predictive accuracy (AUC = 0.826) and correlated with disease severity	IL-6 is an important biomarker for early prognosis and severity assessment in sepsis
8	Sater et al.,(2025) Potentials of Presepsin as a Novel Sepsis Biomarker in Critically Ill Adults: Correlation Analysis with the Current Diagnostic Markers	To evaluate presepsin and other biomarkers in critically ill septic patients	Both presepsin and IL-6 levels were significantly elevated in septic patients and were able to differentiate between types and severity of sepsis. Their combined use improved diagnostic and prognostic performance	Presepsin and IL-6 are valuable biomarkers for diagnosis and prognosis in sepsis
9	Piccioni et al.,(2025) Evaluation of Presepsin for Early Diagnosis of Sepsis in the Emergency Department	To evaluate the role of presepsin in early diagnosis of sepsis in emergency settings	Presepsin demonstrated excellent diagnostic accuracy (AUC = 0.946) for early detection of sepsis. The biomarker showed rapid elevation in early stages and strong correlation with infection severity	Presepsin is highly effective for early diagnosis of sepsis
10	Karagoz et al., (2025) Prognostic Value of Presepsin , Proadrenomedullin and Interleukin-6 in Sepsis : A Prospective Study From the Emergency Department	To evaluate the prognostic value of presepsin and IL-6 in septic patients	IL-6 levels were significantly higher in septic shock patients and in non-survivors. Presepsin levels were also elevated and associated with disease severity. Both biomarkers contributed to mortality prediction and clinical stratification	IL-6 and presepsin are important biomarkers for predicting severity and mortality in sepsis

Source: Processed by the authors from selected articles, 2026

RESULTS AND DISCUSSION

A total of 10 studies were included in this scoping review, consisting of observational and clinical studies published between 2016 and 2026, involving patients with sepsis or septic shock. Overall, the findings consistently showed that presepsin is a reliable biomarker for the diagnosis and prognosis of sepsis. Presepsin levels were significantly higher in septic patients and non-survivors, indicating a strong association with disease severity and mortality (Akkoç

et al., 2020; Baik et al., 2022; Kim et al., 2023; Piccioni et al., 2025). Its diagnostic performance was high, with AUC values ranging from 0.76 to 0.94 (Baik et al., 2022; Piccioni et al., 2025).

Similarly, interleukin-6 (IL-6) was identified as an important inflammatory biomarker associated with sepsis severity and mortality. IL-6 levels were significantly elevated in septic shock patients and non-survivors, reflecting its role as an early-response cytokine and a predictor of poor outcomes (Gamarra-Morales et al., 2024; Liu et al., 2021). Several studies also highlighted that a combined biomarker approach, involving presepsin and IL-6 alongside other markers such as CRP and PCT, improved diagnostic accuracy and prognostic performance compared to single biomarkers (Karagoz, 2025; Ragán et al., 2023; Sater et al., 2025).

In addition, both presepsin and IL-6 were shown to be useful for risk stratification and monitoring disease progression, as elevated levels were consistently associated with increased severity and mortality (Baik et al., 2022; Karagoz, 2025). In summary, presepsin demonstrates strong diagnostic performance, while IL-6 reflects inflammatory response and disease severity. The combination of both biomarkers enhances clinical utility for early detection and management of sepsis (Ragán et al., 2023; Sater et al., 2025).

This scoping review provides a comprehensive synthesis of current evidence on the complementary roles of presepsin and interleukin-6 (IL-6) as early diagnostic and prognostic biomarkers in sepsis. Unlike previous studies that primarily evaluated these biomarkers independently, this review highlights their combined clinical value in improving diagnostic accuracy and risk stratification. By integrating findings from multiple recent studies, it offers a more consolidated understanding of how infection-specific and inflammatory pathways can be jointly assessed in sepsis management. The findings consistently demonstrate that both presepsin and IL-6 are significantly associated with disease severity, clinical outcomes, and mortality, reinforcing their important and complementary roles in early diagnosis and prognosis of sepsis.

Diagnostic Performance of Presepsin

The findings of this scoping review consistently demonstrate that presepsin is a reliable biomarker for the diagnosis and prognosis of sepsis. Across several included studies, presepsin levels were significantly elevated in septic patients compared to non-septic conditions, indicating its strong diagnostic potential (Akkoç et al., 2020; Kim et al., 2023). Furthermore, presepsin showed high diagnostic accuracy, with area under the curve (AUC) values ranging from 0.76 to 0.94, reflecting moderate to excellent performance in detecting sepsis (Baik et al., 2022; Piccioni et al., 2025). In addition to its diagnostic value, presepsin was also consistently associated with disease severity and mortality, as higher levels were observed in non-survivors (Baik et al., 2022; Piccioni et al., 2025).

Biologically, presepsin reflects activation of the innate immune response following bacterial infection, which explains its rapid increase during the early phase of sepsis (Zhang et al., 2015). This characteristic provides an advantage over conventional biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT), which may show delayed responses or lack specificity (Pierrakos & Vincent, 2010) . Therefore, presepsin has strong potential as an early diagnostic biomarker in clinical practice.

Role of IL-6 in Inflammation and Prognosis

In contrast to presepsin, interleukin-6 (IL-6) primarily reflects the host inflammatory response rather than infection specificity. The included studies consistently demonstrated that IL-6 levels were significantly elevated in patients with septic shock and in non-survivors, indicating its strong association with disease severity and mortality (Gamarra-Morales et al., 2024; Karagoz, 2025; Liu et al., 2021). As a pro-inflammatory cytokine, IL-6 plays a central role in the inflammatory cascade of sepsis and increases rapidly during infection, making it a valuable biomarker for early prognosis and monitoring disease progression (Tanaka et al., 2014).

However, IL-6 has limitations in diagnostic specificity, as it can also be elevated in non-infectious inflammatory conditions such as trauma or autoimmune diseases (Schuetz et al., 2017) . Therefore, while IL-6 is highly useful as a prognostic marker, its role as a standalone diagnostic biomarker remains limited.

Superiority of Combined Biomarker Approach

An important finding of this review is the advantage of combining presepsin and interleukin-6 (IL-6) within a multi-biomarker approach. Several studies have demonstrated that the combined use of these biomarkers improves diagnostic accuracy and prognostic performance compared to single biomarker assessment (Karagoz, 2025; Ragán et al., 2023; Sater et al., 2025). This combination enables clinicians to simultaneously capture infection-specific responses through presepsin and the magnitude of the inflammatory response through IL-6.

Furthermore, this review emphasizes the synergistic role of presepsin and IL-6, which has not been sufficiently explored within a unified framework in previous literature. While most studies have focused on individual biomarkers, integrating markers that reflect different biological pathways can significantly enhance diagnostic precision and support clinical decision-making.

This integrated approach allows for better discrimination of sepsis severity and more accurate prediction of clinical outcomes. Previous studies also support the use of multi-biomarker strategies, demonstrating improved early detection and reduced diagnostic uncertainty in sepsis management (Pierrakos & Vincent, 2010; Schuetz et al., 2017). Therefore, the combined use of presepsin and IL-6 represents a more comprehensive and clinically relevant strategy for sepsis evaluation.

The clinical implications of these findings are significant. Both presepsin and IL-6 can be utilized for early diagnosis, risk stratification, monitoring disease progression, and predicting mortality in septic patients. Presepsin appears to provide higher specificity for bacterial infection, while IL-6 reflects the intensity of systemic inflammation.

Their complementary roles make them particularly useful in critical care settings, where rapid and accurate clinical decisions are essential. The integration of these biomarkers into clinical practice may improve diagnostic accuracy, optimize treatment strategies, and ultimately enhance patient outcomes.

In summary, presepsin and IL-6 are complementary biomarkers with distinct but synergistic roles in sepsis. Presepsin demonstrates strong diagnostic accuracy and infection specificity, while IL-6 reflects inflammatory response and disease severity. The combination

of these biomarkers provides a more comprehensive and clinically useful approach for early diagnosis and prognosis of sepsis.

These findings suggest that a multi-biomarker approach represents a more clinically relevant strategy compared to conventional single-marker assessment. This study contributes to the growing body of evidence by reinforcing the importance of integrating both infection-specific and inflammatory biomarkers in early sepsis detection and prognosis. This study has several limitations. First, the number of included studies was relatively limited, which may affect the generalizability of the findings. Second, variations in study design, population characteristics, and biomarker cut-off values may introduce heterogeneity. Third, formal quality appraisal was not conducted, which may affect the strength of the conclusions. Future studies with standardized methodologies are needed to validate these findings.

CONCLUSION

This scoping review demonstrates that presepsin and interleukin-6 (IL-6) are valuable and complementary biomarkers for the early diagnosis and prognosis of sepsis. Presepsin shows strong diagnostic accuracy and higher specificity for bacterial infection, making it a reliable marker for early detection. In contrast, IL-6 reflects the intensity of the inflammatory response and is closely associated with disease severity and mortality. The evidence from the included studies indicates that both biomarkers are significantly elevated in septic patients, particularly in those with severe conditions and poor outcomes. Importantly, the combination of presepsin and IL-6 provides better diagnostic and prognostic performance compared to single biomarker use, as it integrates both infection-specific and inflammatory responses. Despite these promising findings, variability in cut-off values and study populations remains a limitation, highlighting the need for standardized thresholds and further large-scale studies. Future research should focus on validating these biomarkers in diverse clinical settings and integrating them with clinical scoring systems to improve early detection and patient management. In conclusion, the combined use of presepsin and IL-6 has strong potential to enhance early diagnosis, risk stratification, and clinical decision-making in sepsis, supporting their role in improving patient outcomes and advancing sepsis management strategies.

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