Review

From Biomarkers to Bedside Decisions: Integrating suPAR, Presepsin, Organ Dysfunction Scores, and Artificial Intelligence for Precision Risk Stratification and Clinical Decision-Making in Sepsis

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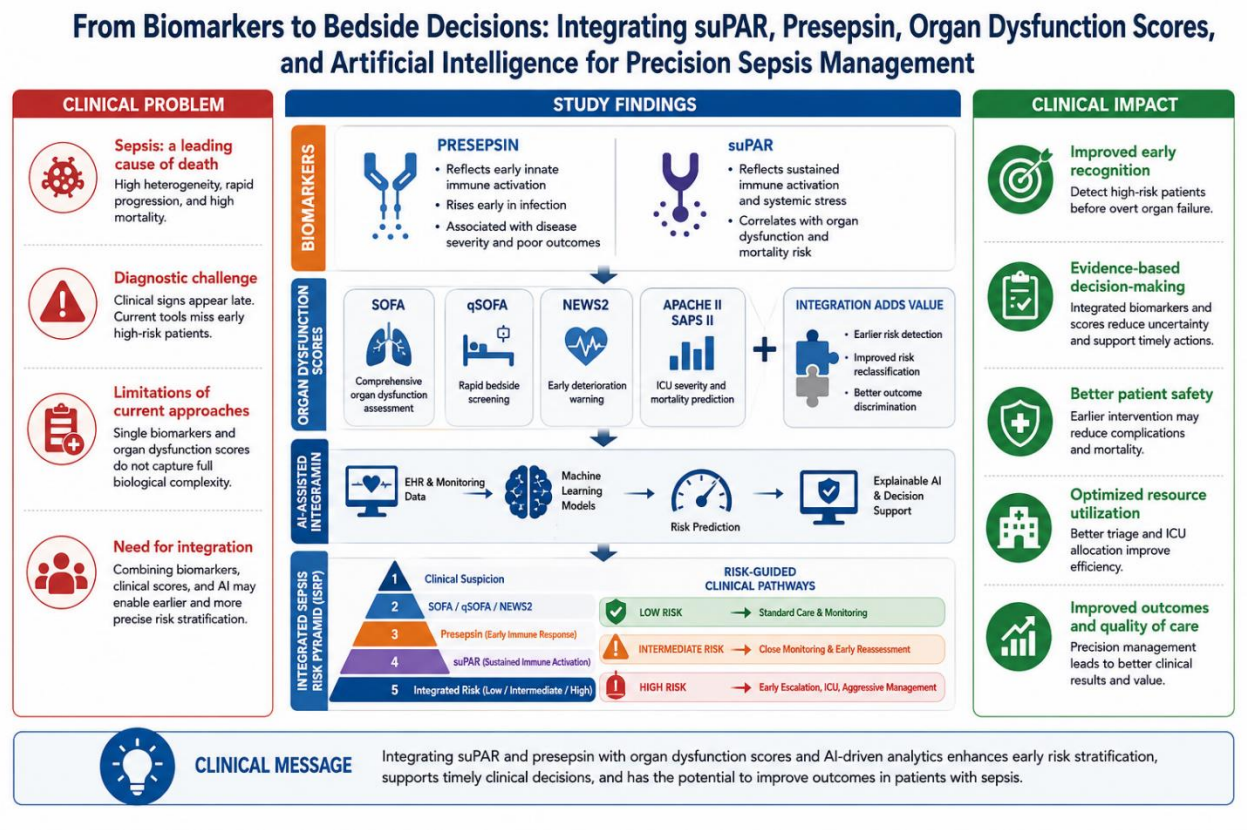
Abstract

Sepsis remains a major cause of morbidity and mortality worldwide despite substantial advances in antimicrobial therapy and critical care. Early recognition and accurate risk stratification are essential for improving patient outcomes, yet current diagnostic approaches based on clinical assessment and organ dysfunction scores often fail to capture the complex biological processes underlying disease progression. In recent years, increasing attention has focused on integrating circulating biomarkers with established clinical scoring systems to support more precise and individualized management. Among emerging biomarkers, soluble urokinase plasminogen activator receptor (suPAR) and presepsin have demonstrated considerable promise because they reflect complementary aspects of the host response. While suPAR primarily represents sustained immune activation and overall disease burden, presepsin is closely associated with early innate immune activation following pathogen recognition. This review summarizes the current evidence regarding the biological characteristics, diagnostic performance, and prognostic value of these biomarkers and discusses their integration with established organ dysfunction models, including SOFA, qSOFA, NEWS2, APACHE II, and SAPS II. Available evidence suggests that combining suPAR and presepsin with clinical severity scores improves risk stratification, particularly among patients with intermediate clinical risk, and may facilitate earlier recognition of disease progression, more accurate prognostic assessment, and better-informed therapeutic decisions. The review also explores emerging developments in precision medicine, including artificial intelligence–assisted predictive models, electronic health record–based clinical decision support systems, and dynamic multimodal risk assessment. Furthermore, we propose the Integrated Sepsis Risk Pyramid (ISRP) as a conceptual framework that combines clinical evaluation, organ dysfunction scoring, and biomarker assessment into a stepwise strategy for bedside decision-making. Collectively, these advances support a transition from isolated biomarker interpretation toward integrated, biologically informed, and data-driven approaches that have the potential to improve personalized sepsis management and optimize outcomes in critically ill patients.

Keywords: Sepsis; suPAR; Presepsin; Risk Stratification; Artificial Intelligence



Graphical Abstract. Integrated Precision Sepsis Management through the Combined Use of suPAR, Presepsin, Organ Dysfunction Scores, and Artificial Intelligence. Integrated use of suPAR, Presepsin, organ dysfunction scores, and artificial intelligence to enhance precision risk stratification and clinical decision-making in sepsis.

Introduction

Sepsis remains one of the leading causes of death among critically ill patients worldwide (1, 2). Despite advances in antimicrobial therapy, supportive care, and intensive care management, sepsis continues to impose a substantial clinical and economic burden on healthcare systems (2, 3). The condition is characterized by marked heterogeneity in presentation, progression, and outcomes, making timely recognition and risk assessment particularly challenging (4, 5). Early identification of patients at risk of deterioration is central to improving outcomes in sepsis (6, 7). However, current diagnostic approaches rely heavily on clinical assessment, routine laboratory findings, and organ dysfunction scores (2, 8). While these tools are widely used, they often provide limited insight into the underlying biological processes driving disease progression (9). In many cases, clinical signs emerge only after significant physiological disturbances have already developed (5, 8). Several biomarkers have been introduced to support the diagnosis and prognostic assessment of sepsis (9). Among the most commonly studied are C-reactive protein (CRP), procalcitonin (PCT), presepsin, and soluble urokinase plasminogen activator receptor (suPAR) (9, 10). Although these markers have shown clinical value in selected settings, no single biomarker has consistently demonstrated sufficient accuracy across the diverse spectrum of septic patients (10). Differences in patient characteristics, infection sources, immune responses, and comorbid conditions contribute to

considerable variability in biomarker performance. The limitations of single-biomarker strategies have become increasingly apparent (9, 10). Biomarkers often reflect only one aspect of the complex host response to infection and may fail to capture the dynamic interaction between inflammation, immune dysregulation, endothelial injury, and organ dysfunction (8). As a result, reliance on a single laboratory parameter may lead to incomplete risk assessment and suboptimal clinical decision-making (10).

Recent research has shifted toward integrated approaches that combine biological markers with established clinical scoring systems (11). Organ dysfunction models such as the Sequential Organ Failure Assessment (SOFA) score provide important prognostic information, yet they may benefit from the addition of biomarkers that reflect distinct pathophysiological pathways (10, 12). In this context, suPAR and presepsin have emerged as promising candidates because they offer complementary information regarding immune activation, disease severity, and clinical outcomes (9, 13). The growing availability of electronic health records, digital monitoring platforms, and predictive analytics has further strengthened the case for multimodal risk stratification (14). Rather than focusing on isolated biomarkers, contemporary sepsis management increasingly favors decision-support frameworks that integrate clinical, laboratory, and physiological data into a unified assessment strategy (15).

This review examines the current evidence on suPAR and presepsin in sepsis and critical illness, with particular emphasis on their integration with organ dysfunction models. We discuss their diagnostic and prognostic roles, explore their potential contribution to biomarker-guided clinical decision-making, and propose future directions for more precise and individualized risk stratification in critically ill patients.

Current Sepsis Definitions and Organ Dysfunction Models

The recognition and assessment of sepsis have evolved considerably over the past two decades (2, 8). Current clinical practice relies on a combination of diagnostic criteria and severity scoring systems to identify patients at risk of organ failure and poor outcomes (2). Although these tools have improved standardization, important limitations remain, particularly when early risk stratification is required (12). The introduction of the Sepsis-3 definition marked a major shift in the understanding of sepsis. Rather than focusing primarily on systemic inflammatory response criteria, Sepsis-3 emphasized life-threatening organ dysfunction resulting from a dysregulated host response to infection. This approach strengthened the link between sepsis diagnosis and clinically meaningful outcomes. However, the definition does not provide a complete solution for early identification, especially in patients who present before overt organ dysfunction develops (5, 8).

The Sequential Organ Failure Assessment (SOFA) score remains the cornerstone of organ dysfunction evaluation in sepsis. By incorporating respiratory, cardiovascular, neurological, hepatic, renal, and coagulation parameters, SOFA provides a structured assessment of disease severity (12). Higher scores are consistently associated with increased mortality risk (16). Despite its prognostic value, SOFA often requires laboratory measurements that may not be immediately available in all clinical settings (12). To facilitate rapid bedside assessment, the quick SOFA (qSOFA) score was introduced as a simplified screening tool. Its use of three easily obtainable clinical variables makes

it practical in emergency and resource-limited environments (8). Nevertheless, concerns regarding sensitivity have limited its role as a standalone screening method. A substantial proportion of patients with sepsis may not meet qSOFA criteria during the early stages of illness (17).

The National Early Warning Score 2 (NEWS2) was developed to identify clinical deterioration across a broad range of acute conditions (18). Several studies have demonstrated its usefulness in detecting patients at risk of sepsis-related deterioration before the onset of advanced organ failure (18, 19). NEWS2 is widely used because of its simplicity and strong emphasis on physiological changes (18). However, it was not specifically designed for sepsis and may be influenced by noninfectious causes of acute illness (18, 20). Severity scoring systems such as Acute Physiology and Chronic Health Evaluation II (APACHE II) and Simplified Acute Physiology Score II (SAPS II) remain important tools in intensive care medicine (21, 22). Both scores provide estimates of disease severity and mortality risk using demographic, physiological, and laboratory variables (21). Their value is greatest after ICU admission, where they support prognostic assessment and benchmarking (21, 23). However, their complexity and dependence on multiple variables limit their usefulness for rapid decision-making in the early phases of sepsis (21, 23).

Although these models provide valuable clinical information, they largely reflect physiological consequences rather than underlying biological activity (24). Organ dysfunction scores indicate the extent of established injury but may not fully capture immune activation, inflammatory burden, or individual variations in host response (24). This limitation has driven growing interest in combining clinical scoring systems with biomarkers capable of identifying high-risk patients before significant organ failure becomes evident (25, 26). As sepsis management moves toward precision-based approaches, the integration of biomarker data with established organ dysfunction models may offer a more comprehensive strategy for risk stratification and clinical decision-making (14, 26) (Table 1).

Biological Basis of suPAR: From Pathophysiology to Clinical Utility

Soluble urokinase plasminogen activator receptor (suPAR) is the circulating form of the membrane-bound urokinase plasminogen activator receptor (uPAR). Under normal conditions, uPAR is expressed on several immune and endothelial cells (27). During infection, inflammation, or tissue injury, increased cellular activation leads to the release of suPAR into the circulation (27, 28). Unlike many inflammatory biomarkers that rise in response to a specific trigger, suPAR reflects the overall level of immune system activation. Elevated concentrations are observed across a wide range of acute and chronic conditions, including severe infections, systemic inflammation, cardiovascular disease, and critical illness (28, 29). This broad biological signal makes suPAR less suitable as a disease-specific diagnostic marker but potentially valuable as an indicator of disease severity (28, 30).

The relationship between suPAR and immune activation has attracted considerable attention in sepsis research (28, 30). Higher suPAR levels are often associated with a more pronounced host response and a greater risk of clinical deterioration (30, 31). Importantly, suPAR appears to reflect ongoing immune dysregulation rather than a transient inflammatory reaction (28). This characteristic may explain why elevated levels frequently correlate with adverse outcomes even when traditional inflammatory

markers show variable performance (28, 32). In addition to immune activation, increasing evidence links suPAR to endothelial injury and microvascular dysfunction (29, 33). Endothelial disruption is a key feature of sepsis and contributes to impaired tissue perfusion, organ failure, and mortality (33, 34). Because suPAR levels tend to rise in parallel with the severity of systemic injury, they may provide indirect information about processes that are not fully captured by routine laboratory tests or physiological measurements (30, 31). From a clinical perspective, the most consistent value of suPAR lies in prognostic assessment rather than diagnosis (28, 30). Numerous studies have reported associations between elevated suPAR concentrations and increased risks of intensive care admission, organ dysfunction, prolonged hospitalization, and mortality (30). These findings have been observed across emergency department populations, hospitalized patients, and critically ill cohorts (30, 35).

An important advantage of suPAR is its ability to identify patients at risk even before severe organ dysfunction becomes clinically apparent. While organ dysfunction scores such as SOFA reflect the consequences of disease progression, suPAR may provide additional information regarding the underlying biological stress driving that progression (28). This distinction is particularly relevant during the early stages of sepsis, when treatment decisions often need to be made under conditions of considerable uncertainty (36). However, suPAR should not be viewed as a standalone decision-making tool (13, 35). Elevated levels are not specific to sepsis and can be influenced by chronic inflammatory conditions, malignancy, renal dysfunction, and other comorbidities (28). For this reason, interpretation of suPAR is most meaningful when combined with clinical findings and established severity scores (13, 35).

Model	Main Purpose	Key Variables	Strengths	Limitations	Typical Clinical Use
Sepsis-3	Sepsis definition	Infection + organ dysfunction	Strong association with outcomes	Less useful for very early recognition	Diagnostic framework
SOFA	Organ dysfunction assessment	Six organ systems	Good prognostic performance	Requires laboratory data	ICU and hospital settings
qSOFA	Rapid bedside screening	Mental status, respiratory rate, blood pressure	Simple and fast	Lower sensitivity	Emergency and pre-ICU assessment
NEWS2	Early deterioration detection	Vital signs and consciousness level	Early warning capability	Not sepsis-specific	Emergency departments and wards
APACHE II	Severity and mortality prediction	Physiological and chronic health variables	Extensive validation	Complex calculation	ICU prognosis
SAPS II	Mortality prediction	Demographic and physiological data	Broad ICU applicability	Limited value for early diagnosis	ICU outcome assessment

Table 1. Comparison of Major Sepsis Definitions and Organ Dysfunction Models

Current evidence increasingly supports the use of suPAR as part of a multimodal risk stratification strategy (13, 35). Rather than answering whether a patient has sepsis, suPAR may help clinicians determine how sick a patient is likely to become. This shift from diagnosis toward prognosis represents one of the most important developments in the clinical application of the biomarker (30, 35). As precision-based approaches continue to evolve, suPAR is likely to play a growing role in integrated assessment models that combine biomarkers, organ dysfunction scores, and real-time clinical data. Such models may offer a more accurate framework for identifying high-risk patients and supporting individualized management decisions in sepsis and critical illness (14, 35) (Table 2).

Biological Basis of Presepsin: Linking Innate Immune Response to Early Clinical Assessment

Presepsin is a soluble fragment derived from cluster of differentiation 14 (CD14), a receptor involved in the recognition of microbial components by the innate immune system (37, 38). CD14 plays an important role in the early host response to infection by facilitating interactions between immune cells and pathogen-associated molecular patterns (39, 40). During this process, cleavage of membrane-bound CD14 generates circulating presepsin, which can be measured in blood. The biological link between presepsin and innate immunity provides a rationale for its use in sepsis.

Biological Feature	Clinical Relevance
Immune activation	Reflects the overall intensity of the host response
Persistent inflammatory burden	Identifies patients with sustained biological stress
Endothelial dysfunction	Associated with microvascular injury and organ failure
Disease severity	Correlates with severity across different care settings
ICU admission risk	Higher levels are linked to increased need for intensive care
Mortality prediction	Consistently associated with short- and long-term mortality
Early risk stratification	May identify high-risk patients before overt organ dysfunction
Standalone diagnosis	Limited value due to low disease specificity
Integration with SOFA and other scores	Enhances prognostic assessment and clinical decision-making

Table 2. Clinical Significance of suPAR in Sepsis and Critical Illness

Unlike biomarkers that mainly reflect downstream inflammation, presepsin is released during the initial stages of pathogen recognition. As a result, increasing levels may indicate activation of the host defense response at a relatively early point in the disease course (38).

Several studies have demonstrated elevated presepsin concentrations in patients with bacterial infections and sepsis. The marker appears to be closely associated with the intensity of the host–pathogen interaction and may rise before significant organ dysfunction becomes clinically evident. This characteristic has generated interest in its potential role as an early warning biomarker in emergency and critical care settings. The kinetic profile of presepsin is another feature that has attracted attention. Concentrations often increase rapidly following infectious stimulation and may change in parallel with clinical evolution. This dynamic behavior may allow clinicians to monitor disease progression and treatment response more

effectively than biomarkers with slower biological responses. However, variations in renal function and patient characteristics should be considered when interpreting results (38). From a diagnostic perspective, presepsin has demonstrated promising performance in distinguishing infectious from noninfectious causes of systemic inflammation (41). Nevertheless, diagnostic accuracy varies across studies and patient populations (42). Differences in infection source, disease severity, comorbid conditions, and assay methods contribute to this variability. Consequently, presepsin should not be viewed as a standalone diagnostic test (38).

The greatest clinical value of presepsin may lie in its integration with established clinical assessment tools. When combined with organ dysfunction scores, physiological parameters, and other laboratory markers, presepsin can contribute to a more comprehensive evaluation of patient risk. This approach aligns with the growing shift from single-marker strategies toward multimodal models of sepsis assessment (38). Recent evidence also suggests that presepsin may provide prognostic information beyond diagnosis alone (38, 42). Higher concentrations have been associated with greater disease severity, increased risk of organ dysfunction, longer hospital stays, and higher mortality rates (43). These findings support its potential role within risk stratification frameworks designed to guide clinical decision-making in patients with suspected or confirmed sepsis. As sepsis management increasingly emphasizes early recognition and individualized care, presepsin represents a biologically relevant marker that connects pathogen detection with clinically actionable information. Its future value is likely to depend less on its isolated performance and more on its contribution to integrated diagnostic and prognostic models (38) (Table 3).

Characteristic	Presepsin	CRP	PCT	IL-6
Biological source	CD14 cleavage product	Acute-phase protein	Prohormone of calcitonin	Pro-inflammatory cytokine
Main pathway reflected	Pathogen recognition and innate immunity	Systemic inflammation	Infection-related inflammatory response	Early inflammatory signaling
Time to rise after infection	Early	Relatively delayed	Intermediate	Very early
Diagnostic utility in sepsis	Moderate to high	Moderate	High	Variable
Prognostic value	Good	Limited to moderate	Good	Moderate
Monitoring disease progression	Potentially useful	Limited	Useful	Variable
Specificity for infection	Moderate	Low	Higher than CRP	Limited
Influence of noninfectious inflammation	Present	Significant	Present	Significant
Integration with severity scores	Promising	Limited	Established	Emerging
Main clinical strength	Early host-response signal	Widely available	Strong infection support	Rapid inflammatory response
Main limitation	Renal function effects and assay variability	Low specificity	Cost and heterogeneity	Short half-life and variability

Table 3. Comparison of Presepsin with Commonly Used Sepsis Biomarkers

Evidence Synthesis: Prognostic Performance of Sepsis Biomarkers

When the available evidence is put together, a clear pattern appears. Most biomarkers in sepsis show some level of prognostic value, but their performance is not uniform across outcomes or patient settings (44, 45). The differences become more visible when endpoints such as mortality, ICU admission, organ failure, and diagnostic accuracy are compared side by side (44, 45). Procalcitonin (PCT) is one of the most studied biomarkers in this context (44). It shows relatively consistent performance in identifying bacterial infection and supporting clinical decision-making (46). Its association with ICU admission and disease severity is well documented, although its ability to independently predict mortality is moderate and varies across cohorts (44, 47).

C-reactive protein (CRP) remains widely used because of availability and cost, but its prognostic value is limited. It reflects systemic inflammation rather than infection-specific pathways. As a result, its performance in predicting organ failure or mortality is generally weaker compared to more specific biomarkers (44). Interleukin-6 (IL-6) is an early inflammatory mediator and tends to rise rapidly during the initial phase of infection. It shows stronger association with early disease activity and severity. However, its short half-life and high biological variability reduce its reliability for routine prognostic use in isolation (48, 49). suPAR has shown more consistent associations with long-term outcomes in critically ill patients. Elevated levels are frequently linked with increased mortality risk, higher likelihood of ICU admission, and progression to organ dysfunction. Its strength lies in reflecting sustained immune activation rather than transient inflammatory changes (28, 50).

Presepsin is more closely linked to innate immune activation and early host response to infection (49, 51). It performs well in early risk identification and has shown moderate to good prognostic value for ICU admission and organ failure. However, its diagnostic accuracy can vary depending on renal function and patient population (44, 49, 51). When these biomarkers are compared collectively, no single marker provides complete coverage across all clinically relevant outcomes (44, 49). This limitation supports the shift toward combined biomarker strategies, especially when integrated with organ dysfunction scores such as SOFA or early warning systems (49). The overall evidence suggests that biomarkers should not be interpreted in isolation (44, 49). Their value increases when they are used as part of structured clinical frameworks that integrate physiological data, organ dysfunction scoring, and real-time clinical assessment (49) (Table 4).

Biomarker	Mortality	ICU admission	Organ failure	Diagnostic accuracy
PCT	Moderate to good association	Good predictive value	Moderate	High for bacterial infection
CRP	Low to moderate	Low to moderate	Low	Moderate, non-specific
IL-6	Moderate	Moderate to good	Moderate	Variable, early phase useful
suPAR	Strong and consistent	Strong	Strong association	Moderate, non-specific
Presepsin	Moderate to good	Moderate to good	Moderate	Good, but variable across settings

Table 4. Prognostic Performance of Major Sepsis Biomarkers.

Integration with Organ Dysfunction Models

Organ dysfunction scores remain the backbone of sepsis severity assessment, but they are not designed to capture biological activity at the molecular level (8, 49). This gap has led to increasing interest in combining these models with circulating biomarkers to improve early risk detection and clinical decision-making (8, 10, 49). The Sequential Organ Failure Assessment (SOFA) score on its own provides a structured estimate of organ dysfunction (8). It is strongly linked with mortality and ICU outcomes, but it often reflects established injury rather than early physiological stress (8, 10, 52). This limits its sensitivity in the early phase of sepsis, when intervention may have the greatest impact (10, 49). When presepsin is added to SOFA, the model gains an additional layer of information related to innate immune activation (38, 53, 54). This combination improves early risk identification in several studies, particularly in patients who have not yet developed overt organ failure (53, 55). The main advantage of this approach is earlier signal detection, which may support faster clinical escalation (36, 53, 55). Adding suPAR to SOFA shifts the model toward a broader view of systemic stress and persistent immune activation. suPAR contributes prognostic stability, especially for longer-term outcomes such as mortality and prolonged ICU stay (28, 50, 56, 57). This combination tends to improve risk discrimination across heterogeneous patient populations (28, 57, 58).

The most comprehensive biomarker-based approaches combine SOFA with complementary biomarkers such as presepsin and suPAR. These approaches integrate organ dysfunction, early immune activation, and sustained inflammatory burden (10, 38, 57, 58). It provides a more complete representation of disease severity compared to any single marker or score alone (10, 38, 58). From a statistical perspective, improvements in model performance are often assessed using Net Reclassification Improvement (NRI) (59). Studies suggest that adding biomarkers to SOFA can correctly reclassify patients into more accurate risk categories, particularly in intermediate-risk groups where clinical uncertainty is highest (53, 59). This is the subgroup where decision-making is often most difficult (36, 49). Clinical utility is another key consideration. The combined models are most valuable when they change management decisions rather than simply improving statistical performance (10, 36). In practice, this includes earlier ICU admission, closer monitoring, or escalation of antimicrobial and hemodynamic support (36). The real benefit lies in shifting decisions before irreversible organ failure develops (36, 49).

Risk stratification improves as more dimensions of the disease are captured (10, 58). SOFA provides structural assessment of organ failure, presepsin reflects early immune response, and suPAR captures sustained biological stress (8, 28, 38, 57). Together, they allow a stepwise classification of patients into low, intermediate, and high-risk categories with greater precision (10, 38, 57, 58). Overall, integration of biomarkers with organ dysfunction models represents a move from static scoring toward dynamic, biologically informed decision-making. This approach aligns with the broader shift toward precision-based critical care, where risk is continuously refined rather than assessed at a single time point (10, 58).

Biomarker-Guided Therapeutic Decision-Making in Sepsis

Treatment decisions in sepsis are often made under time pressure and with incomplete clinical information (36). Organ dysfunction scores and vital signs provide important signals, but they do not always capture the biological stage of disease. This has increased interest in using biomarkers to support more structured and timely clinical decisions (10, 58). One of the most relevant areas is antibiotic stewardship (10, 36). Early and

appropriate antibiotic therapy remains central to sepsis management (36). However, overtreatment is common in patients with non-bacterial inflammation. Biomarkers such as presepsin and suPAR may help distinguish patients with active infectious processes from those with alternative causes of systemic response (38, 57, 58). This may support more informed antimicrobial decision-making and treatment monitoring, although evidence for biomarker-guided antibiotic de-escalation based specifically on presepsin or suPAR remains limited (36, 38, 58). ICU triage is another critical decision point. Emergency and ward-based clinicians often face uncertainty when deciding which patients require intensive care (36). Biomarker-guided assessment can complement clinical scores by identifying patients with hidden severity (10, 58). Elevated suPAR or rising presepsin levels may indicate a higher risk of adverse outcomes even before overt organ dysfunction becomes clinically apparent (38, 57, 58). This may support ICU triage by helping identify patients most likely to deteriorate (10, 38, 57, 58).

Vasopressor initiation is closely linked to the progression of circulatory failure in sepsis (36). Traditional indicators such as blood pressure and lactate levels may not fully reflect underlying vascular dysfunction. Biomarkers associated with immune activation and endothelial injury can provide additional context (10, 58). In patients with elevated suPAR, early hemodynamic instability may signal a higher probability of progression to shock, supporting earlier vasopressor consideration in selected cases (10, 36, 57). Renal replacement therapy decisions often depend on a combination of biochemical thresholds and clinical status (36). However, organ dysfunction scores alone may not predict which patients will progress to severe renal injury (10, 58). Biomarkers reflecting systemic inflammation and immune dysregulation may help identify patients at higher risk of multi-organ failure, supporting earlier planning for renal support in high-risk groups (10, 58). Escalation and de-escalation of therapy remain some of the most complex decisions in critical care (36). Over-escalation can expose patients to unnecessary interventions, while delayed escalation can worsen outcomes (36). Biomarker trends may assist in this balance (10, 38, 58). Rising levels of presepsin or persistently elevated suPAR may support treatment escalation, while declining values in stable clinical conditions may contribute to decisions regarding controlled de-escalation when interpreted alongside clinical findings (10, 38, 57, 58). Overall, biomarker-guided decision-making does not replace clinical judgment (10, 36, 38, 57, 58). Instead, it adds a biological layer to existing clinical frameworks (10, 58). The main value lies in reducing uncertainty, especially in early or intermediate phases of sepsis where treatment decisions have the greatest impact on outcomes (10, 38, 57, 58).

Precision Medicine and AI-Assisted Sepsis Models

Sepsis care is moving toward a more dynamic and data-driven model. Traditional scoring systems and single biomarkers provide useful snapshots, but they do not fully capture the complexity of patient trajectories (10, 58, 60). This has led to growing interest in combining clinical scores, biomarkers, and electronic health record data into integrated predictive systems (58, 60, 61). A key development in this area is the combination of suPAR, presepsin, and SOFA with real-world EHR data. Each component contributes a different layer of information. SOFA reflects organ dysfunction, suPAR reflects sustained immune activation, and presepsin captures early innate immune response (10, 38, 57, 58). When these are combined with longitudinal clinical data, the overall picture becomes more stable and clinically meaningful. Machine learning models have been increasingly used to process this high-dimensional data (60). These models can identify patterns that are not easily visible through

traditional statistical approaches. In sepsis, this may include early signs of deterioration, subtle changes in physiological trends, or risk patterns across heterogeneous patient groups (60). However, the clinical value of these models depends on transparency and interpretability, not just predictive accuracy (61).

Explainable AI has therefore become an important requirement in clinical decision support systems. Clinicians need to understand why a model assigns high risk to a specific patient. Without interpretability, even highly accurate models may have limited adoption in real clinical settings. Methods such as feature importance analysis and local explanation tools are being used to improve transparency (61). Clinical decision support systems represent the practical interface between AI models and bedside care. These systems integrate predictions into workflows and present risk estimates in a clinically usable format. In sepsis, this may include early warning alerts, deterioration risk scores, or suggestions for escalation of care. The goal is not to replace clinicians but to support earlier and more consistent decision-making (38, 61). Real-time risk prediction is one of the emerging applications of this approach. Continuous updating of risk estimates using sequential clinical data may allow earlier detection of deterioration compared to static assessments. This is particularly relevant in sepsis, where patient status can change rapidly over short periods (60, 61). The integration of biomarkers such as suPAR and presepsin into predictive models has been explored mainly in prognostic and risk stratification contexts. These biomarkers may add complementary biological information that improves risk assessment when combined with clinical variables (10, 58).

Despite these advances, several challenges remain. Data quality, missing values in EHR systems, and variability in laboratory measurements can affect model performance. In addition, external validation across different hospitals and patient populations is essential before widespread clinical adoption (60, 61). Overall, precision medicine in sepsis is shifting from isolated measurements to integrated, continuously updated models (10, 58, 60). The combination of biomarkers, clinical scores, and AI-based analysis has the potential to support more individualized and timely clinical decision-making in critically ill patients (60, 61).

Proposed Clinical Framework: Integrated Sepsis Risk Pyramid (ISRP)

Current sepsis management commonly combines clinical assessment, organ dysfunction scores, and laboratory biomarkers to support diagnosis and risk stratification. Although these tools are widely used in clinical practice, no single approach fully integrates clinical findings, scoring systems, and biomarkers into a unified framework for routine decision-making (10, 58). To address this gap, the ISRP is proposed as a structured model that supports stepwise clinical reasoning by integrating these complementary sources of information. The ISRP is designed as a hierarchical framework in which each level contributes an additional layer of diagnostic and prognostic information. The model progresses from bedside clinical assessment to biomarker-guided evaluation and finally to integrated risk stratification. Its purpose is not to replace existing diagnostic tools but to organize them into a logical and clinically applicable decision pathway. Level 1 begins with clinical suspicion of sepsis. Initial assessment is based on the presence of suspected or confirmed infection together with clinical findings such as fever, hypotension, altered mental status, tachypnea, or other signs of systemic illness. At this stage, clinical judgment guides the initial evaluation before additional laboratory and biomarker data become available (8).

Level 2 incorporates the SOFA and qSOFA scores to objectively assess organ dysfunction and identify patients at increased risk of poor

outcomes (8, 62). The SOFA score provides a comprehensive evaluation of organ failure, whereas qSOFA offers a rapid bedside screening tool for early risk identification outside the intensive care setting. Together, these scoring systems provide the initial clinical assessment of disease severity (8, 62). Level 3 introduces presepsin as a biomarker of early host immune activation and bacterial infection (10, 38, 58). At this stage, the assessment expands beyond clinical manifestations and organ dysfunction to include the underlying biological response. Elevated presepsin concentrations may support the early diagnosis of sepsis and provide additional information in patients with uncertain clinical findings (38).

Level 4 incorporates suPAR as a biomarker reflecting persistent immune activation and systemic inflammation (10, 57). Elevated suPAR concentrations have consistently been associated with increased disease severity, organ dysfunction, and poor clinical outcomes in patients with systemic inflammation and sepsis. Therefore, suPAR provides additional prognostic information beyond conventional clinical assessment and may improve identification of patients at higher risk of deterioration (57).

Level 5 represents the final stage of integrated risk assessment. At this level, clinical findings, SOFA/qSOFA scores, presepsin, and suPAR are interpreted together to classify patients into low-, intermediate-, or high-risk categories. This integrated approach is intended to improve risk stratification by combining complementary clinical and biological information and may help reduce diagnostic uncertainty, particularly in patients with equivocal clinical presentations (10, 38, 57, 58).

The final stage translates risk categories into treatment pathways. Low-risk patients may be managed with standard monitoring and targeted therapy. Intermediate-risk patients require closer observation and early reassessment. High-risk patients may need aggressive intervention, including ICU admission, early hemodynamic support, and broader antimicrobial strategies (8, 10, 62). The ISRP model emphasizes a stepwise integration of clinical and biological data rather than isolated interpretation. It reflects a shift from single-point assessment to layered decision-making (10, 58). This structure may improve consistency in clinical judgment and reduce variability in early sepsis management, although prospective validation is still required (10, 58). Overall, the Integrated Sepsis Risk Pyramid provides a practical framework that links bedside evaluation with biomarker-driven risk stratification. Its value lies in organizing existing tools into a unified pathway that supports earlier and more precise clinical decisions (10, 38, 57, 58).

Future Directions in Sepsis Biomarkers and Clinical Decision-Making

Sepsis research is increasingly moving beyond the use of single biomarkers toward integrated biological and computational approaches for diagnosis, patient stratification, and risk prediction (63-67). Current research emphasizes not only improving diagnostic accuracy but also enabling earlier and more reliable prediction of clinical deterioration in real-world settings (63, 65-67). Multi-marker strategies are increasingly recognized as complementary to single biomarker approaches because different biomarkers reflect distinct components of the host response. Combining biomarkers such as suPAR, presepsin, CRP, and PCT may improve the assessment of disease severity and provide a more comprehensive evaluation of the inflammatory response than individual biomarkers alone (65, 68). This multimarker approach may better capture both immune activation and subsequent organ dysfunction while reducing dependence on a single biological signal (65). Continuous physiological monitoring combined with machine learning has emerged as another promising direction in sepsis research

(63, 64, 69). Physiological data obtained from bedside monitoring systems, including heart rate dynamics, respiratory rate, oxygen saturation, and blood pressure measurements, can serve as dynamic indicators of patient status (63, 64, 69). When integrated with laboratory biomarkers and other clinical information, these physiological data may provide a more comprehensive and continuous assessment of disease progression and improve early prediction of clinical deterioration (63, 64). Machine learning–based clinical decision support systems are increasingly being developed to integrate electronic health records, laboratory findings, and real-time physiological monitoring into predictive models for risk stratification and early detection of sepsis (63, 64). However, successful implementation of these systems in routine clinical practice requires transparency, interpretability, and clinician trust to ensure safe and reliable decision support (61).

Dynamic monitoring is increasingly recognized as an important component of sepsis management because it provides information beyond that obtained from single time-point measurements (63-65). Repeated assessment of biomarkers together with clinical scoring systems may improve understanding of disease trajectory and treatment response (65). Serial changes in biomarker concentrations and physiological parameters often provide greater clinical value than isolated measurements, particularly in rapidly evolving conditions such as sepsis (63, 65, 69).

Personalized sepsis management represents an important long-term objective of current research (66, 67). Patients with similar clinical presentations may exhibit markedly different molecular and immunological responses, reflecting the biological heterogeneity of sepsis (66, 67). Integrating biomarkers, clinical scores, physiological monitoring data, and machine learning approaches may facilitate earlier recognition of these differences and improve patient stratification (63, 64, 66, 67). Such approaches have the potential to support more individualized treatment strategies and optimize the management of critically ill patients (66, 67).

Conclusion

Sepsis remains a complex clinical syndrome where early recognition and accurate risk assessment continue to be major challenges. Current clinical definitions and organ dysfunction scores provide a useful foundation, but they are often insufficient for capturing the full biological and temporal dynamics of the disease. Biomarkers such as suPAR and presepsin have added new dimensions to sepsis evaluation. suPAR reflects sustained immune activation and overall disease burden, while presepsin is more closely linked to early innate immune response. Although neither marker is fully specific on its own, both contribute meaningful information when interpreted alongside clinical findings. Organ dysfunction models such as SOFA, qSOFA, NEWS2, APACHE II, and SAPS II remain central to clinical practice. However, their main limitation is that they primarily reflect established physiological impairment rather than early biological activity. This creates a gap between disease onset and clinical detection that biomarkers may help to reduce. The integration of biomarkers with organ dysfunction scores offers a more complete approach to risk stratification. Evidence suggests that combining suPAR and presepsin with SOFA improves patient classification, particularly in intermediate-risk groups where clinical uncertainty is highest. This integrated approach may support earlier intervention and more consistent clinical decision-making. Beyond traditional models, emerging approaches involving multi-marker panels, dynamic monitoring, and AI-based decision support systems are reshaping the field. These developments point toward a shift from static assessment to continuous, personalized risk evaluation in sepsis and critical illness. The

proposed Integrated Sepsis Risk Pyramid (ISRP) reflects this direction by organizing clinical suspicion, scoring systems, and biomarkers into a structured decision pathway. While further validation is required, such frameworks may help bridge the gap between biological signals and practical bedside decisions. Overall, future sepsis management is likely to depend on integrated models that combine clinical judgment, organ dysfunction scoring, biomarkers, and digital health data. This combined strategy offers a more precise and adaptive approach to managing a highly heterogeneous and rapidly evolving condition.

Implications for Patient Care

The evidence synthesized in this review supports a clinically integrated approach to sepsis assessment that combines biomarkers, organ dysfunction scores, and emerging artificial intelligence (AI)–based decision-support systems rather than relying on any single diagnostic or prognostic tool. While established scoring systems such as SOFA, qSOFA, and NEWS2 remain essential for evaluating disease severity, the addition of biomarkers including suPAR and presepsin may enhance risk stratification by providing complementary information on immune activation and biological stress. This integrated strategy has the potential to improve early recognition of patients at increased risk of clinical deterioration, facilitate more informed decisions regarding monitoring intensity, ICU triage, antimicrobial stewardship, and escalation of supportive care, and reduce uncertainty in intermediate-risk cases. Nevertheless, current evidence supports the use of these biomarkers as adjuncts to comprehensive clinical assessment rather than as standalone determinants of management, and further prospective validation is required before widespread implementation in routine practice. The incorporation of explainable AI models that integrate clinical, laboratory, and physiological data may further strengthen individualized risk prediction while preserving clinical transparency and supporting evidence-based decision-making. Collectively, these advances have the potential to improve healthcare quality, optimize resource utilization, enhance patient safety, and ultimately contribute to better clinical outcomes through more precise and personalized sepsis management.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

All authors contributed to the conception and design of the study, literature search, data interpretation, drafting of the manuscript, and critical revision of the article. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Ethics Statement

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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