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A Review on the Use of Biomarkers for Early Diagnosis of Sepsis and Associated Hemostatic Abnormalities

Ayomide Babatunde Ishola[1], Abdulrahman Opeyemi Abdulbasit[2]

[1]Department of Biomedical Sciences, Oklahoma State University Centre for Health Sciences, Tulsa, USA
[2]Department of Medical Microbiology and Parasitology, University of Ilorin Teaching Hospital, Ilorin, Nigeria
Email: Isholaayomide1@gmail.com, aabdulbasit5@gmail.com

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Abstract

Sepsis-related haemostatic disorders, especially disseminated intravascular coagulation (DIC), substantially impact morbidity and mortality; nevertheless, early diagnosis is difficult due to the absence of precise biomarkers. This study assesses novel biomarkers that connect immunological dysregulation and coagulation pathways, presenting opportunities for prompt detection and enhanced therapy. Proinflammatory cytokines (IL-6, TNF-α) and D-dimer are fundamental indicators, however they lack specificity. Emerging biomarkers such as presepsin (sCD14-ST), indicative of bacterial phagocytosis and predictive of coagulopathy within 24 hours, and interleukin-27 (IL-27), possessing both pro- and anti-inflammatory characteristics, provide enhanced diagnostic precision compared to traditional markers. Angiopoietin-2 (Ang-2), a principal modulator of endothelial dysfunction, exhibits a robust correlation with the risk of disseminated intravascular coagulation (DIC) (OR >5) and death, whereas neutrophil extracellular traps (NETs) and their constituents (e.g., citrullinated histones) establish mechanistic connections between thromboinflammation and organ failure. Neutrophil CD64 (nCD64), which is swiftly increased during bacterial sepsis, provides great specificity (>90%) for the detection of infections. These biomarkers target essential deficiencies in sepsis management, encompassing early diagnosis, dynamic risk stratification, and therapeutic monitoring. Obstacles persist in standardisation and clinical use; nonetheless, including these indicators in multimodal panels or point-of-care systems has the potential to transform sepsis management. Future research should concentrate on substantiating their efficacy in directing specific therapy, such as immunomodulation or anticoagulation, to alleviate sepsis-induced coagulopathy and enhance outcomes.

Keywords

Sepsis, Coagulopathy, Biomarkers, DIC, Presepsin, Angiopoietin-2, NETs

1. Introduction

The term "sepsis" derives from the Greek word signifying the decay or decomposition of organic matter, traditionally defined by Hippocrates as a perilous, malodorous biological deterioration of the body [1]. The definitions of sepsis and septic shock have undergone significant evolution since the early 1990s, culminating in a consensus definition established by the European Society of Intensive Care Medicine (ESICM) and Society of Critical Care Medicine (SCCM) in 2016. Sepsis is currently characterised as life-threatening organ failure resulting from a dysregulated host response to a suspected or confirmed infection [2]. If not identified early and addressed swiftly, it may advance to septic shock, multiple organ failure, and mortality. Septic shock, a variant of sepsis, is defined by severe circulatory, cellular, and metabolic dysfunctions, markedly elevating the risk of mortality [3]. The prevalence of sepsis continues to be significant, rendering it one of the foremost causes of mortality worldwide. In acknowledgment of its public health significance, the World Health Assembly and WHO designated sepsis as a global health priority in 2017, advocating for enhancements in prevention, detection, and management.

The pathophysiology of sepsis entails a complicated disturbance of immunological responses, characterised by a significant dysregulation of the balance between inflammation and anti-inflammation [4]. In contrast to a localised infection, sepsis triggers both pro-inflammatory and anti-inflammatory pathways, resulting in systemic cytokine release, activation of the complement cascade, and coagulation irregularities. These anomalies may lead to disseminated intravascular coagulation (DIC), a disease characterised by extensive clotting and haemorrhage, resulting in organ dysfunction and heightened mortality [5]. DIC is marked by the activation of the coagulation cascade, resulting in thrombus formation in small vessels, including capillaries, which cause considerable organ damage. The interplay between inflammation and coagulation underscores the intricate character of sepsis and its effects on the immune and coagulation systems [6].

The International Society on Thrombosis and Haemostasis (ISTH) advocates a two-step diagnostic approach for sepsis-induced coagulopathy (SIC), integrating Prothrombin Time (PT), platelet count, and the Sequential Organ Failure Assessment (SOFA) score to detect early coagulopathy [7]. Nonetheless, obstacles persist in the implementation of these diagnostic instruments at the bedside, especially in promoting early diagnosis. Notwithstanding attempts to resolve this issue, a significant deficiency persists in the identification of dependable biomarkers for the early detection of sepsis and its related coagulopathies

[8].

A rising demand exists for innovative diagnostic techniques to address these constraints, especially biomarkers that can facilitate more precise and prompt diagnosis of sepsis-induced coagulopathy [9]. The existing literature does not reach an agreement on the most useful biomarkers, and their diagnostic relevance in clinical practice is inadequately comprehended. This review is to objectively assess the function of biomarkers in the early detection of sepsis and its related haemostatic problems, emphasizing novel biomarkers and examining their potential to enhance patient outcomes. The review seeks to address this knowledge gap by offering insights into the identification of novel biomarkers that may facilitate more effective early treatments in sepsis therapy. Hence, the review aims to critically evaluate the role of biomarkers in the early diagnosis of sepsis and its associated hemostatic abnormalities, with a particular focus on novel biomarkers such as presepsin, IL-27, Angiopoietin-2, NET components, and neutrophil CD64. Specifically, we seek to compare their diagnostic accuracy, prognostic value, and time-to-detection against established markers like CRP, procalcitonin, and D-dimer. Furthermore, we assess the clinical utility of incorporating these emerging biomarkers into multiparametric diagnostic panels or point-of-care testing platforms, addressing current gaps in early detection and risk stratification.

2. Mechanisms of Sepsis and Hemostatic Abnormalities

Sepsis commences upon the recognition of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). These compounds, including endotoxins, exotoxins, lipids, or DNA sequences, attach to toll-like receptors (TLRs) on antigen-presenting cells (APCs) and monocytes, initiating gene transcription associated with inflammation, immune response, and cellular metabolism. This activation leads to the production of inflammatory mediators, such as pro-inflammatory cytokines including IL-1, IL-12, TNF-α, and interferons (IFNs) (refer to **Table 1**), along with the subsequent activation of complement and coagulation pathways [10].

The immune system's response to infection, intended to safeguard the body, frequently results in progressive tissue damage and multi-organ malfunction during sepsis. In the advanced phases, a condition of immunosuppression known as "immunoparalysis" emerges. This condition is characterised by diminished immune cell activation, heightened apoptosis of immune cells, and T cell exhaustion, rendering patients susceptible to secondary infections, including opportunistic pathogens and viral reactivation [11].

Neutrophils are essential in the innate immune response, providing defence against infections. Severe bacterial infections can induce the release of both mature and immature neutrophils from the bone marrow, resulting in diminished phagocytosis and oxidative burst capabilities in these cells [12]. Clinical worsening in sepsis is frequently correlated with increased neutrophil numbers and the release

of neutrophil extracellular traps (NETs). These NETs, consisting of chromatin and granular proteins, ensnare pathogens that are unable to be phagocytised, including bigger microbes. Although NETs assist in fighting infections, their overproduction or inadequate breakdown leads to hypercoagulation, endothelial injury, and deteriorated patient outcomes [13]. NETs will serve as a pro-coagulant surface, enhancing FXII activation and platelet adhesion, hence encouraging thrombin generation, which may result in immunothrombosis, sepsis-induced endothelial dysfunction, and coagulation activation that might potentially lead to microvascular injury [14].

In sepsis, platelet reactivity escalates, considerably impacting haemostatic irregularities. Platelets possess damage-associated molecular pattern (DAMP) receptors, including TLR4, which are stimulated by bacterial endotoxins [15]. Moreover, heightened concentrations of hormones such as adrenaline and 5-hydroxytryptamine during sepsis further augment platelet reactivity. Sepsis also stimulates heightened thrombin production through the coagulation cascade, activating platelets via protease-activated receptors (PAR) 1 and 4, underscoring the interaction between coagulation and platelet activation processes [16].

Upon activation, platelets engage in multiple pathways essential in sepsis. Dense granules secrete adenosine diphosphate (ADP), enhancing platelet activation via P2Y1 and P2Y12 receptors. Alpha granules secrete P-selectin, which stimulates leukocytes and facilitates coagulation by binding to chemokines and pro-coagulant factors [17]. Platelet aggregates, leading to micro-or macrothrombosis, are formed through the activation of GPIIb/IIIa, interconnected by fibrinogen or von Willebrand factor (vWF). In sepsis, both fibrinogen and von Willebrand factor levels are increased, promoting platelet adherence to the endothelium. The transformation of platelets from a discoid to a stellate morphology improves their engagement with other components of the coagulation system. Platelet activation also produces inflammo-modulatory eicosanoids, including thromboxane A2 and prostaglandin E2, which have a role in inflammation [18].

Cytokines such as IL-6 enhance platelet activation by activating the collagen receptor GPVI. Sepsis is linked to thrombocytosis as a result of elevated thrombopoietin and cytokine-driven platelet synthesis [19]. Bacterial toxins induce endothelial damage, leading to the overexpression of tissue factor, which activates factor VII and initiates the extrinsic coagulation cascade, while also interacting with the intrinsic route through factor IX. The resultant thrombin synthesis enhances platelet activation, establishing a feedback loop. Furthermore, hypofibrinolysis is intensified by a thrombin-activatable fibrinolysis inhibitor (TAFI), which diminishes clot degradation [20].

These mechanisms result in substantial alterations in fibrin clot dynamics, encompassing a decrease in fibrin fibre diameter, an augmentation in network density, and expanded lysis regions, all of which contribute to the pathological clotting observed in sepsis [21].

Table 1. Various cytokine roles in sepsis.

Cytokine	Type	Origin	Role in Sepsis
IL-1	Pro-inflammatory	Mainly produced by macrophages, monocytes, and dendritic cells [9] [10].	IL-1 plays a key role in the early inflammatory response by inducing fever, activating immune cells, and stimulating the production of other pro-inflammatory cytokines. In sepsis, it contributes to the systemic inflammatory response and tissue damage [11].
IL-12	Pro-inflammatory	Produced by antigen-presenting cells (APCs) like macrophages, dendritic cells, and B cells [12] [13].	IL-12 promotes the differentiation of T-helper (Th) cells into Th1 cells, enhancing the immune response against infections. In sepsis, it helps modulate the balance between pro-inflammatory and anti-inflammatory responses but can contribute to excessive inflammation [14].
TNF-α	Pro-inflammatory	Produced mainly by macrophages, monocytes, and T cells [15].	TNF-α is one of the central mediators of systemic inflammation in sepsis. It leads to endothelial cell activation, vascular permeability, and tissue damage. High levels of TNF-α are associated with septic shock and multi-organ dysfunction [15].
IL-6	Pro-inflammatory	Macrophages, T cells, endothelium, fibroblasts, and other cell types in response to infection or injury [16].	IL-6 plays a key role in the acute-phase response, inducing the production of acute-phase proteins like C-reactive protein (CRP). In sepsis, IL-6 contributes to systemic inflammation, endothelial dysfunction, and can mediate fever. It also plays a role in the later stages of sepsis by contributing to immune suppression, making patients more vulnerable to secondary infections [18] [19].

3. Notable Biomarkers of Sepsis Diagnosis

A biomarker is a quantifiable indicator of a patient's clinical status that can be evaluated with precision and consistency. Biomarkers are highly valuable for diagnosing, prognosticating, and tracking treatment responses in patients with sepsis or suspected sepsis. They can facilitate early disease detection, risk assessment, targeted treatment (theranostics), and patient selection for clinical trials [22]. In sepsis, biomarkers are crucial for differentiating between infection and the host's inflammatory response, facilitating early detection and intervention. Biomarkers can ideally be utilized for risk assessment, diagnosis, monitoring therapy responses, and predicting patient outcomes.

Numerous biomarkers have been recognized as valuable for assessing sepsis (see Table 2), including C-reactive protein (CRP), procalcitonin (PCT), different cytokines, and cell surface markers [23].

3.1. Procalcitonin (PCT)

Since systemic inflammation prevents the release of procalcitonin (PCT) into the

bloodstream, serum levels of PCT are undetectable in healthy persons. In cases of sepsis resulting from bacterial infections, PCT production is stimulated in almost all organs, resulting in measurable concentrations in the bloodstream [24]. PCT levels are generally heightened during bacterial infections, while they stay down in viral infections. Increased PCT levels have been demonstrated to forecast bacteremia [25]. PCT can be identified in serum within 4 hours post-infection, with peak concentrations observed between 12 and 48 hours, and a half-life ranging from 22 to 26 hours. The fast response to infection and its proportional escalation with sepsis severity provide PCT a valuable biomarker for the early detection and risk assessment of septic patients [26]. It is especially beneficial for differentiating between culture-negative and culture-positive sepsis, as well as non-infectious diseases, presenting considerable potential for the diagnosis of bacterial sepsis [27].

3.2. C-Reactive Protein (CRP)

C-reactive protein (CRP) is an acute-phase reactant synthesized by the liver in response to acute inflammatory states, such as infections. CRP serves as a highly sensitive indicator for sepsis. The concentration in the blood increases swiftly within 2 hours of the initiating event and reaches its zenith at around 48 hours [28]. The swift elevation of CRP in reaction to infection, along with its equally swift reduction upon the resolution of the ailment, renders it a dependable indicator for tracking disease development and resolution [29]. C-reactive protein (CRP) is essential for the early identification of sepsis and serves as a dependable prognostic marker for unfavorable outcomes in septic individuals [29]. Recent investigations indicate that the C-reactive protein to platelet ratio (CPR) functions as a new marker representing both inflammation and coagulation states in septic patients [30].

3.3. Pro-Inflammatory Cytokines

Pro-inflammatory cytokines, including TNF-α, IL-1 β, and IL-6, are pivotal to the immune response during sepsis. They facilitate the primary immune response and play a role in systemic inflammation, fever, and endothelial activation [31]. Sepsis is generally linked to a dysregulated immune response, marked by an intensified pro-inflammatory condition. This amplified immune response is believed to facilitate disease development, resulting in tissue and organ damage [32]. Studies indicate that cytokine levels in sepsis are heightened relative to healthy individuals and may frequently mirror or fall below those observed in non-lethal acute or chronic inflammatory diseases. For example, TNF-α levels may rise nearly tenfold in comparison to healthy individuals [33]. The disparity between pro-inflammatory cytokines and anti-inflammatory mediators in sepsis exacerbates the condition's pathogenesis and aids in forecasting disease severity and prognosis. The sustained increase of these cytokines is associated with adverse clinical outcomes, including multi-organ failure [34].

Table 2. Some notable biomarkers for the detection of sepsis.

Biomarker	Clinical Range	Significance in Early Detection	Clinical Indications
C-reactive protein (CRP)	Normal: < 10 mg/L; Sepsis: > 100 mg/L (may vary with severity)	CRP is an acute-phase reactant that rises rapidly in response to inflammation or infection. Elevated levels can help diagnose sepsis, but it lacks specificity [35].	Used to monitor infection, inflammation, and response to treatment. Elevated levels may indicate sepsis or other inflammatory conditions [35].
Procalcitonin (PCT)	Normal: < 0.1 ng/mL; Sepsis: > 0.5 ng/mL (threshold varies based on severity)	PCT is a biomarker that increases significantly during bacterial infections, making it useful for diagnosing sepsis, especially in differentiating bacterial from viral infections [36].	Used in diagnosing bacterial infections, guiding antibiotic therapy, and assessing sepsis severity and progression [36].
Interleukin-6 (IL-6)	Normal: < 5 pg/mL; Sepsis: > 100 pg/mL (varies based on severity)	IL-6 is a key pro-inflammatory cytokine that is elevated during sepsis, reflecting the systemic inflammatory response. It can be an early indicator of infection and sepsis [37].	Used for early detection of sepsis, monitoring inflammatory response, and predicting sepsis progression and outcomes [37].
Interleukin-1 (IL-1)	Normal: < 10 pg/mL; Sepsis: > 50 pg/mL (varies with severity)	IL-1 is a critical pro-inflammatory cytokine in the initiation of sepsis. Its elevated levels contribute to fever, endothelial dysfunction, and tissue damage in sepsis [24].	Used to assess inflammatory response and tissue injury in sepsis and to monitor the response to treatment [24].
Tumor Necrosis Factor-alpha (TNF-α)	Normal: < 10 pg/mL; Sepsis: > 50 pg/mL (varies with severity)	TNF-α is a potent cytokine involved in the systemic inflammatory response during sepsis. Elevated levels are associated with septic shock and organ dysfunction [38].	Used to assess the severity of sepsis, predict organ dysfunction, and monitor response to therapy [38].
Interferon-gamma (IFN-γ)	Normal: < 50 pg/mL; Sepsis: > 200 pg/mL	IFN-γ is a cytokine that activates immune cells and regulates the immune response. In sepsis, elevated IFN-γ can indicate an excessive inflammatory response [39].	Used to evaluate immune response to infection and monitor sepsis progression. Elevated IFN-γ can indicate severe infection [39]
Soluble CD14 (sCD14)	Normal: < 0.5 ng/mL; Sepsis: > 2 ng/mL	sCD14 is a marker of monocyte activation during bacterial infections. Elevated sCD14 levels are associated with the early stages of sepsis and can be used to assess bacterial infection [40].	Used for diagnosing sepsis and monitoring immune activation in response to infection [40].

4. Notable Biomarkers for Hemostatic Abnormalities in Sepsis

4.1. Proinflammatory Cytokines and Chemokines

Proinflammatory cytokines and chemokines are crucial biomarkers in sepsis, significantly contributing to the development of haemostatic disorders (see **Table 3**), such as disseminated intravascular coagulation (DIC). Critical cytokines, including tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), instigate endothelial activation and coagulation cascade dysregulation by enhancing tissue factor (TF) production and platelet aggregation [41]. This mechanism promotes microthrombosis, worsening sepsis-associated coagulopathy (SAC). In addition to their involvement in immunological dysregulation, these cytokines offer essential insights into the activation of the coagulation cascade, acting as dual indicators of both inflammatory and haemostatic responses [42]. Thus, monitoring cytokine profiles may facilitate clinical decision-making, especially in directing treatment interventions aimed at coagulation abnormalities.

4.2. D-Dimer

D-dimer levels are often increased in sepsis due to simultaneous activation of coagulation and fibrinolysis. In advanced stages, D-dimer levels may normalise or decrease due to the suppression of fibrinolysis. Increased D-dimer is indicative of DIC and acts as a significant marker for illness advancement. In the initial phase of sepsis, hyperfibrinolysis leads to elevated D-dimer levels, but in the latter phases, diminished fibrinolytic activity may inhibit D-dimer production despite ongoing fibrin synthesis [43]. Elevated D-dimer, a particular breakdown product of cross-linked fibrin, indicates both thrombin production and subsequent fibrinolysis [44]. Studies indicate a 23-fold elevation in D-dimer levels in sepsis patients relative to controls, highlighting its significance as a marker of endogenous fibrinogenesis and secondary fibrinolysis [45].

4.3. Coagulation Factors

Sepsis causes substantial dysregulation of coagulation factors, such as fibrinogen, activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombomodulin, activated protein C (aPC) and tissue factor (TF) [46]. This dysregulation leads to a complex interaction between hypercoagulability and the risk of haemorrhage. Fibrinogen levels generally increase in early sepsis but may decrease in later stages due to consumptive coagulopathy [47]. The pathogenesis of sepsis-induced coagulopathy (SIC) is defined by elevated tissue factor expression on monocytes, thrombin production mediated by neutrophil extracellular traps (NETs), endothelial damage, and compromised anticoagulant mechanisms. Laboratory results frequently indicate increased procoagulant indicators (e.g., tissue factor, thrombin-antithrombin complexes) in conjunction with mild decreases in anticoagulant factors such as antithrombin III. Thrombocytopenia frequently occurs in early sepsis,

but fibrinogen levels are typically normal or raised upon admission to the intensive care unit (ICU) [9].

Table 3. Notable biomarkers of hemostatic abnormalities in sepsis.

Biomarker	Laboratory Significance	Indication	Level in Sepsis	Role in Hemostatic Dysregulation
Proinflammatory Cytokines (TNF-α, IL-6)	Reflect immune activation and endothelial dysfunction	Immune dysregulation, DIC risk assessment	Elevated in early sepsis, may persist in severe cases	Promote TF expression, platelet activation, and microthrombosis, leading to coagulopathy [48].
D-Dimer	Fibrin degradation product (marker of fibrinolysis)	Diagnosis/ monitoring of DIC and hyperfibrinolysis	Early sepsis: ↑↑ (hyperfibrinolysis) Late sepsis: Normal/↓ (fibrinolysis shutdown) [49]	Indicates thrombin generation and fibrinolytic activity; high levels suggest DIC [49].
Fibrinogen	Acute-phase reactant, essential for clot formation	Hypercoagulability vs. consumption coagulopathy	Early sepsis: ↑ (acute phase) Late sepsis: ↓ (consumption) [50]	Initially elevated due to inflammation but declines in DIC due to excessive clotting and consumption.
PT/aPTT	Measures extrinsic & intrinsic coagulation pathways	Coagulation cascade dysfunction	Prolonged (indicating coagulopathy) [51]	Reflects factor deficiency due to consumption, liver dysfunction, or anticoagulant depletion.
Thrombomodulin (TM)	Endothelial glycoprotein, regulates coagulation	Endothelial injury & DIC	Elevated (due to endothelial damage) [52]	Binds thrombin, activating protein C; loss contributes to hypercoagulability.
Tissue Factor (TF)	Initiator of extrinsic coagulation pathway	Hypercoagulability & DIC	Elevated (monocyte/ endothelial expression) [53]	Triggers thrombin generation via factor VIIa, promoting microthrombosis.
Activated Protein C (aPC)	Natural anticoagulant, anti-inflammatory	Severe sepsis/DIC (deficiency worsens prognosis)	Reduced (due to consumption & inhibition) [54]	Deficiency leads to unchecked thrombin formation and impaired fibrinolysis.
Antithrombin III (ATIII)	Major inhibitor of thrombin & coagulation factors	Anticoagulant system failure	Reduced (consumption & degradation) [55]	Loss exacerbates hypercoagulability by unopposed thrombin activity.
Platelet Count	Thrombocytopenia indicates consumption/DIC	Thrombosis/ bleeding risk	Early sepsis: ↓ (consumption) Later: may recover [56]	Platelet activation contributes to microthrombi; low counts increase bleeding risk.

Notes: ↑ = Elevated, ↓ = Reduced, Normal/↓ = May normalize or decrease in advanced stages. DIC = Disseminated Intravascular Coagulation, SIC = Sepsis-Induced Coagulopathy.

5. Emerging Biomarkers for the Detection of Sepsis Associated Hemostatic Abnormalities

The absence of early, precise diagnostic indicators results in delayed identification in around 25% of sepsis cases, leading to inadequate treatment responses and deteriorated clinical outcomes. This diagnostic deficiency highlights the pressing want for dependable biomarkers that can enable early diagnosis of sepsis [57]. Moreover, there is an increasing necessity for dynamic biomarkers capable of monitoring real-time metabolic changes and objectively evaluating illness severity, especially in infection-induced coagulopathies [58]. This section examines developing biomarkers of clinical importance that could improve the diagnosis, risk classification, and management of haemostatic disorders associated with sepsis (as seen in **Table 4**).

Presepsin (sCD14-ST), a soluble variant of CD14, is gaining recognition as a valuable biomarker for the early diagnosis and monitoring of sepsis, especially in detecting sepsis-induced coagulopathy, a significant consequence of sepsis [59]. It derives from CD14, a receptor for bacterial lipopolysaccharide (LPS) complexes, which activates toll-like receptor 4 (TLR4)-mediated inflammation during infection. In contrast to traditional inflammatory indicators, presepsin levels are more closely associated with the severity of bacterial infections rather than with generalized inflammation, as it is generated during the phagocytosis of pathogens [60]. Clinical investigations indicate that presepsin levels are raised in patients with sepsis, showing no significant distinction between Gram-positive and Gram-negative infections, highlighting its extensive applicability. Presepsin's elevated specificity and strong validation in both experimental and clinical environments establish it as a superior early diagnostic and prognostic biomarker relative to procalcitonin (PCT) [61]. Presepsin levels are typically low in healthy adults, with median values around 200 pg/mL and 95th percentile upper limits ranging between 314 and 339 pg/mL [62]. However, standard reference intervals remain inconclusive due to limited sample sizes in existing studies. In neonates particularly among preterm and term infants presepsin concentrations are significantly higher, with reported median values ranging from 578 to 620 pg/mL and 95th percentile values reaching up to 1370 pg/mL [62]. These elevated levels are influenced by factors such as gestational age, mode of delivery, and postnatal adaptation, underscoring the need for age-specific reference ranges. While presepsin shows promise as a rapid biomarker for early sepsis detection, often within 2-3 hours, its clinical cut-off values must be interpreted with caution, taking into account population-specific characteristics and assay methodologies. Further large-scale studies are needed to establish globally accepted thresholds for its routine diagnostic use [63]. In response to bacterial infections, their concentration rises within 2 hours, contingent upon disease severity, with reported cut-off levels for sepsis ranging from 400 to 600 pg/ml. The initial rise in presepsin levels during the sepsis cascade and other bacterial illnesses has rendered it a compelling marker for laboratory analysis [64]. Presepsin offers several notable advantages

over traditional biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) in the context of sepsis and sepsis-associated coagulopathy. It demonstrates a significantly faster kinetic profile, with serum levels rising within 2 hours and peaking by 3 hours after infection onset substantially earlier than PCT, which typically increases between 8 to 24 hours post-infection [65]. Presepsin also exhibits superior sensitivity, particularly in intensive care settings; meta-analyses have reported a pooled sensitivity of 0.94 for neonatal sepsis, compared to 0.78 for PCT and 0.86 for CRP. Additionally, presepsin has clinical utility in guiding antibiotic therapy, enabling more precise escalation or de-escalation decisions and thereby minimizing unnecessary antibiotic exposure [66]. Importantly, it holds prognostic value by predicting the development of severe complications such as acute kidney injury (AKI), septic shock, disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), and overall clinical deterioration. Collectively, these attributes support the use of presepsin as a promising biomarker for early diagnosis, risk stratification, and therapeutic monitoring in sepsis management [67]. The initial stage in establishing Presepsin as a widely recognized biomarker is its incorporation into laboratory parameters at a reasonable cost, comparable to the integration of other markers historically. This integration would enable regular evaluation of Presepsin levels, promoting wider clinical application and additional study into its diagnostic and prognostic value in critical illness [68].

Interleukin-27 (IL-27) has demonstrated initial potential in a recent preliminary investigation by [69], revealing good specificity and positive predictive values for bacterial infections in critically ill patients. Interleukin-27 (IL-27), a heterodimeric cytokine consisting of EBI3 and p28 subunits, is synthesised by antigen-presenting cells during inflammatory responses. Its distinctive capacity to regulate both proinflammatory (e.g., Th1 activation) and anti-inflammatory (e.g., IL-10 induction) pathways render it especially pertinent in sepsis, when immunological dysregulation precipitates coagulopathy. IL-27 facilitates thromboinflammation by enhancing endothelial activation, tissue factor expression, and neutrophil extracellular trap (NET) release, which are all critical mechanisms in sepsis-associated disseminated intravascular coagulation (DIC) [70]. An IL-27 cut-off value of ≥ 5 ng/mL has demonstrated strong diagnostic performance as a "rule-in" test for sepsis, with a reported specificity of 95%. However, the observed reduction in positive predictive value may be attributed to the lower prevalence of sepsis in the current cohort compared to the original study, which reported a prevalence nearly five times higher (56% vs. current rates) [71]. Meta-analytic data further support IL-27's diagnostic potential, showing a pooled sensitivity of 0.84, specificity of 0.71, and an area under the curve (AUC) of 0.88, indicating substantial overall accuracy. These findings highlight IL-27's promise as a clinically relevant biomarker, particularly in pediatric and intensive care settings, though standardized diagnostic thresholds are still needed to facilitate routine clinical adoption [72]. Clinically, IL-27 concentrations correlate with the degree of sepsis and organ dysfunction,

providing superior specificity compared to conventional indicators such as C-reactive protein or procalcitonin. The dynamic expression pattern, characterised by early elevation during hyperinflammation and subsequent decrease in immunoparalysis, may assist in identifying discrete phases of coagulopathy [73]. Research indicates that IL-27 serves as a predictor for the course of DIC and associated mortality, underscoring its prognostic significance. In contrast to generic inflammatory markers, IL-27 explicitly associates immunological and coagulation pathways, establishing it as a mechanistically relevant biomarker. Additional validation may establish IL-27 as a mechanism for early identification and tailored therapy of sepsis-induced coagulopathy [74].

In patients with sepsis-induced coagulopathy, elevated IL-27 levels may reflect a more severe or complex infection, whereas lower levels may suggest a milder disease course or an alternative diagnosis [75]. In neonates, IL-27 has shown diagnostic accuracy comparable to PCT in terms of sensitivity and negative predictive value (NPV), although it exhibits slightly lower specificity than C-reactive protein (CRP). Importantly, IL-27 testing presents several advantages over traditional diagnostics, including lower contamination risk, faster turnaround times, and reduced blood volume requirements, which are critical factors in neonatal care. As an ELISA-based assay, IL-27 is also cost-effective compared to PCT and blood cultures, making it a viable candidate for integration into standard diagnostic workflows, particularly for early detection of sepsis and sepsis-induced coagulopathy [76].

Angiopoietin-2 (Ang-2) demonstrates potential as a biomarker for sepsis-induced coagulopathy, with increased levels associated with endothelial dysfunction, inflammation, and worse outcomes, including mortality [77].

Angiopoietins, specifically Angiopoietin-1 (Ang-1) and Angiopoietin-2 (Ang-2), have been identified as potential biomarkers for sepsis owing to their pivotal roles in vascular control and endothelial dysfunction. These vascular growth factors interact with the TIE-2 receptor on endothelial cells, with Ang-1 serving as a stabilising agonist that preserves vascular integrity, whereas Ang-2 operates as a context-dependent antagonist that enhances vascular permeability. In sepsis, the equilibrium between these two angiopoietins is disturbed, as Ang-2 levels significantly increase in reaction to inflammatory cytokines such as TNF-α, resulting in endothelial barrier compromise, capillary leakage, and organ hypoperfusion. The Ang-2/Ang-1 ratio is clinically significant, since it correlates substantially with illness severity, organ dysfunction, and mortality in septic patients. Angiopoietin dysregulation significantly contributes to critical sepsis sequelae, such as acute lung damage and disseminated intravascular coagulation, by influencing endothelial activation and interacting with other mediators like VEGF [78]. Angiopoietins, particularly Ang-2, possess the capacity to indicate real-time endothelial damage, rendering them more specific for sepsis-induced vascular dysfunction than general inflammatory markers. Angiopoietins serve as clinically significant biomarkers that connect sepsis pathophysiology with patient management, owing

to their predictive value for outcomes such as septic shock and multiple organ dysfunction syndrome, along with their potential as therapeutic targets for vascular stabilization [79]. Several studies have proposed clinically relevant cut-off values for Angiopoietin-2 (Ang-2) in the context of sepsis and critical illness [80]. A diagnostic threshold of 5.61 ng/mL has been identified using Youden's index for the detection of sepsis, while a lower cut-off of 767.3 pg/mL effectively distinguishes patients with septic shock from those with severe sepsis [81]. Additionally, Ang-2 concentrations exceeding 5000 pg/mL have been suggested as a criterion for ICU admission in patients with COVID-19, and a cut-off of 5.1 ng/mL has been associated with increased in-hospital mortality among sepsis patients [82]-[84].

Compared to traditional biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT), Ang-2 offers specific advantages, particularly in the assessment of sepsis and septic shock. While CRP and PCT primarily reflect systemic inflammation and bacterial infection, Ang-2 is more directly associated with endothelial dysfunction and increased vascular permeability hallmarks of sepsis pathophysiology [85]. Elevated Ang-2 levels serve as an indicator of endothelial injury, providing valuable insights into disease severity and progression that may not be fully captured by CRP or PCT. Moreover, Ang-2 has demonstrated prognostic value, with elevated levels correlating with a higher risk of mortality in sepsis and other severe conditions. Its expression has also been linked to clinical severity scores such as SOFA and APACHE II, and in some cases, Ang-2 mRNA levels have shown greater predictive accuracy than these traditional scoring systems [84].

Although CRP remains a widely used marker for systemic inflammation and is valuable for monitoring infections and cardiovascular risk, its diagnostic specificity particularly in the early stages of sepsis is limited. PCT offers improved specificity for bacterial infections and is useful in guiding antibiotic therapy, but it lacks the endothelial specificity that characterizes Ang-2 [86]. Therefore, while CRP and PCT are indispensable tools in clinical settings, Ang-2 provides a unique and complementary perspective, enhancing clinicians' ability to assess vascular damage, gauge disease severity, and predict patient outcomes in sepsis.

Neutrophil extracellular traps (NETs) are emerging as a promising novel biomarker for sepsis-induced coagulopathy, since their elevated creation in sepsis is associated with a procoagulant milieu, thrombin production, and the onset of disseminated intravascular coagulation (DIC) [87]. NETs provide a dual function in sepsis: they are crucial for pathogen entrapment and elimination, yet they also promote thromboinflammation. In sepsis-induced disseminated intravascular coagulation (DIC), neutrophil extracellular traps (NETs) release DNA, histones, and granular proteins that establish a procoagulant surface, promoting platelet adhesion, thrombin production, and fibrin deposition. Research by [88] and [89] demonstrates that NETs are increased in individuals with septic DIC, establishing a direct correlation with the advancement of coagulopathy. Histones and extracellular DNA in NETs notably stimulate platelets, enhance thrombin generation, and disrupt

anticoagulant pathways (e.g., protein C system), worsening microthrombosis and organ damage. Clinically, measuring NETs using surrogate markers such as NEUT-SFL (neutrophil side scatter fluorescence) or citrullinated histones (H3Cit) may facilitate early diagnosis of DIC and inform targeted therapy (e.g., DNase to dismantle NETs). Consequently, NETs serve as both a molecular catalyst and a prospective biomarker for sepsis-related coagulopathy [90].

Neutrophil CD64 (nCD64), an Fc-gamma receptor present in neutrophils, is emerging as a possible biomarker for sepsis and sepsis-induced coagulopathy, demonstrating promise for early diagnosis and prognosis due to its fast elevation upon activation. CD64 (FcγRI), the high-affinity IgG receptor, has been identified as a unique biomarker for sepsis owing to its dynamic expression and pathophysiological significance. In resting neutrophils, CD64 is expressed at low levels (~1000 molecules/cell), but experiences a fast upregulation (10-fold within 4-6 hours) when exposed to proinflammatory cytokines (e.g., IFN-γ, G-CSF) or bacterial components [91]. The swift onset combined with a brief half-life (returning to baseline within days following infection) renders it optimal for identifying acute infection and differentiating active sepsis from non-infectious inflammation. The therapeutic value of CD64 is augmented by its functional role in phagocytosis, serving as the principal mediator of IgG-opsonized pathogen clearance and directly associating biomarker increase with the host's innate immune response [92]. Practical benefits encompass assay stability following blood collection, minimal sample volume requirements, and standardised flow cytometry methods. Studies indicate that advanced diagnostic methods exhibit greater accuracy than traditional markers (e.g., CRP, WBC) for bacterial sepsis, achieving high sensitivity and specificity (>90%) in both adults and neonates [93]. These characteristics establish CD64 as a real-time infection biomarker and a means for assessing therapy efficacy.

In the context of sepsis-induced coagulopathy, the neutrophil CD64 (nCD64) threshold value, commonly utilized for sepsis diagnosis, is typically regarded as 1311 molecules per cell. This number has exhibited commendable sensitivity and specificity in sepsis diagnosis, as seen by studies employing this cut-off point [94]. A cut-off value of 1311 molecules per cell demonstrates great diagnostic accuracy, with a sensitivity of 89.9% and specificity of 85.7%. Comparative analyses have shown that nCD64 surpasses traditional markers like procalcitonin (PCT), which exhibits a sensitivity of 65.2% and specificity of 93.9%, as well as white blood cell (WBC) count, which has a sensitivity of 73.9% and specificity of 54.3%, especially in patients admitted to the ICU [95]. In the context of sepsis-induced coagulopathy, characterized by inflammation-driven thrombosis and consumptive coagulopathy akin to non-overt disseminated intravascular coagulation (DIC), nCD64 provides additional clinical significance by indicating immunological activation. The nCD64 index may function as a significant biomarker for forecasting the progression of sepsis. Observing alterations in nCD64 within the first 48 hours of admission may assist in forecasting the prognosis of septic patients. Integrating the changes

of the nCD64 index within the initial 48 hours with the APACHE II score would significantly improve prediction accuracy [95].

Neutrophil CD64 (nCD64) has demonstrated superior performance compared to conventional biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT), particularly in the early detection of sepsis. Upon activation, neutrophils markedly increase CD64 expression, and the nCD64 index which quantifies the proportion of activated neutrophils rises swiftly in response to systemic infection and inflammation, making it a highly sensitive indicator of early sepsis [96]. Although CRP and PCT are well-established acute-phase markers, their rise occurs on different timelines; PCT generally increases earlier than CRP yet may still trail behind nCD64 in acute infectious scenarios. Comparative studies have shown that nCD64 not only provides greater sensitivity and specificity in identifying sepsis at an early stage but also improves diagnostic differentiation between localized infections and systemic involvement, as nCD64 levels are significantly elevated in septic patients [97]. Furthermore, nCD64 has shown prognostic value, with some evidence suggesting it may better predict mortality risk than CRP or PCT. When used in combination with clinical scoring systems such as the SOFA score or alongside PCT, nCD64 can enhance diagnostic accuracy and patient stratification. Overall, these findings underscore the potential of nCD64 as a robust and clinically useful biomarker for the early diagnosis and prognosis of sepsis, though further large-scale studies are needed to validate its routine application [98].

6. Future Direction

Specific biomarkers include presepsin, IL-27, Angiopoietin-2 (Ang-2), and neutrophil CD64 (nCD64) exhibit diagnostic and prognostic significance; integrating these markers into multimodal panels may substantially enhance early identification and risk stratification in sepsis [99]. These combinations utilize the advantages of many biomarkers that reflect immunological activation (nCD64), endothelial dysfunction (Ang-2), and systemic inflammation (CRP, PCT) to offer a comprehensive perspective on the septic process [99]. Research indicates that the integration of presepsin with clinical assessments such as SOFA, or nCD64 with PCT, improves the sensitivity and specificity for diagnosing sepsis and predicting mortality. Such panels are especially advantageous during the first stage of infection, when clinical symptoms may be modest or non-specific [100].

Nonetheless, numerous problems are associated with the use of multimarker methodologies. This encompasses the absence of assay uniformity across platforms, elevated costs, analytical intricacy, and the necessity for expedited, point-of-care testing solutions. Furthermore, the interpretation of many indicators necessitates sophisticated clinical decision support to prevent overdiagnosis or uneven application among diverse patient populations [101]. Notwithstanding these constraints, the implementation of multimodal panels signifies a promising advancement in sepsis diagnoses, providing enhanced clinical precision, earlier intervention possibilities, and superior patient stratification [102].

Table 4. Comparative clinical utility of novel biomarkers in sepsis-associated hemostatic abnormalities.

Biomarker	Time to Rise	DIC Prediction	Mortality Correlation	Point-of-Care Use
Presepsin	2 - 3 hrs	High	Moderate	Emerging
IL-27	4 - 6 hrs	Moderate	High	Limited
Ang-2	6 - 12 hrs	Very High	Very High	Yes
NET markers	1 - 2 hrs	Very High	High	Limited
nCD64	4 - 6 hrs	Moderate	Low	Yes

Clinical utility ratings were based on published evidence concerning sensitivity, specificity, and relevance in sepsis-induced coagulopathy and mortality prediction. "Very High" = validated in multiple large-scale studies or guidelines; "High" = strong evidence with good predictive value; "Moderate" = promising results but limited data or sample sizes; "Low" = some potential but not yet clinically validated.

7. Conclusion

Sepsis-induced haemostatic abnormalities pose a significant treatment challenge, significantly contributing to multi-organ failure and mortality. Conventional biomarkers such as D-dimer and proinflammatory cytokines offer essential diagnostic utility; nevertheless, their lack of specificity and limits in dynamic monitoring highlights the necessity for innovative alternatives. Emerging biomarkers such as presepsin, IL-27, Angiopoietin-2, neutrophil CD64, and NET-associated markers offer promising avenues for the early diagnosis and risk stratification of sepsis and its associated hemostatic abnormalities. These biomarkers demonstrate proficiency in early detection (e.g., presepsin's rise within 2-3 hours), measurement of endothelial injury (Ang-2's prediction capacity for disseminated intravascular coagulation), and elucidation of mechanisms (the function of NETs in thromboinflammation). Their incorporation into clinical practice may facilitate precision strategies, such as biomarker-directed anticoagulation or immunomodulation. These biomarkers address limitations of conventional markers like CRP and PCT by providing faster detection, better specificity, and mechanistic insight into endothelial dysfunction and immune activation. However, to fully integrate these markers into routine clinical practice, several key areas warrant further investigation. These include the validation of biomarker cut-off values across diverse demographic and clinical populations, the development and standardization of rapid, point-of-care diagnostic platforms, and the exploration of biomarker-guided therapeutic strategies to tailor interventions and improve outcomes. Future multicenter studies with harmonized methodologies are essential to confirm diagnostic thresholds, enhance accessibility, and establish the prognostic and therapeutic value of these biomarkers in sepsis management.

Conflicts of Interest

The authors have declared that no conflicting interest exists.

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List of Abbreviations

SCCM	Society of Critical Care Medicine
ESICM	European Society of Intensive Care Medicine
DIC	Disseminated Intravascular Coagulation
ISTH	International Society on Thrombosis and Haemostasis
SIC	Sepsis-Induced Coagulopathy
SOFA	Sequential Organ Failure Assessment
PT	Prothrombin Time
PAMPs	Pathogen-Associated Molecular Patterns
DAMPS	Damage-Associated Molecular Patterns
TLRs	Toll-Like Receptors
APC	Antigen-Presenting Cells
NETs	Neutrophil Extracellular Traps
ADPs	Adenosine Diphosphate
TAFI	thrombin-activatable fibrinolysis inhibitor
CRP	C-reactive protein
PCT	procalcitonin
aPTT	Activated Partial Thromboplastin Time
TF	Tissue Factor