RESEARCH PAPER

The Role of Inflammatory Markers in Sepsis

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Abstract
Background: Sepsis is a life-threatening condition caused by a dysregulated response to infection that can lead to multiple organ dysfunction and death. Early diagnosis remains difficult because the clinical presentation is often nonspecific. Inflammatory biomarkers have become important tools for supporting diagnosis, assessing disease severity, and monitoring treatment response.
Aim: To review the current evidence on inflammatory biomarkers used in sepsis, with emphasis on their pathophysiological basis and clinical applications.
Subjects and Methods: A narrative review of the published literature was conducted to summarize the mechanisms of inflammatory marker release in sepsis and to evaluate the clinical value of commonly used and emerging biomarkers for diagnosis, prognosis, and treatment monitoring.
Results: Conventional biomarkers, including C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), remain widely used in clinical practice. Emerging biomarkers such as presepsin, lactate, plasma renin, ICAM-1, VEGFR2, and urokinase-type plasminogen activator (uPA) provide additional information regarding disease severity, septic shock, and patient outcomes. Current evidence suggests that combining biomarkers with clinical evaluation and severity scoring systems provides better diagnostic and prognostic performance than relying on a single marker.
Conclusion: Inflammatory biomarkers support many aspects of sepsis management, including diagnosis, risk assessment, treatment monitoring, and antibiotic stewardship. Their interpretation should always be considered alongside clinical findings, microbiological results, and established scoring systems to improve patient assessment.
Keywords: Sepsis; Inflammatory biomarkers; Procalcitonin; C-reactive protein; Septic shock; Prognosis.
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I. Introduction

Sepsis as a systemic inflammatory response syndrome (SIRS) caused by an infection can cause damage to the body tissues and organs themselves and can even be life-threatening.It is difficult to recognize patients with sepsis because without a specific clinical signs. Despite the great improvement in detect this disease,septic patients are a heterogeneous group and their condition has been very difficult to recognize especially in the early stages **[1]**.

II. Definition of Inflammatory Markers

Inflammatory markers are measurable biological molecules that reflect the activation and magnitude of the body's immune and inflammatory responses. During infection, tissue injury, or systemic inflammation, immune cells release a variety of cytokines, acute-phase proteins, and cellular mediators that can be detected in blood or other body fluids. In sepsis, these biomarkers provide valuable information regarding the presence of infection, the intensity of systemic inflammation, disease severity, and response to treatment. Although no single inflammatory marker is sufficiently sensitive and specific to diagnose sepsis independently, combining biomarker measurements with clinical assessment and severity scoring systems significantly improves diagnostic accuracy and prognostic evaluation **[2]**.

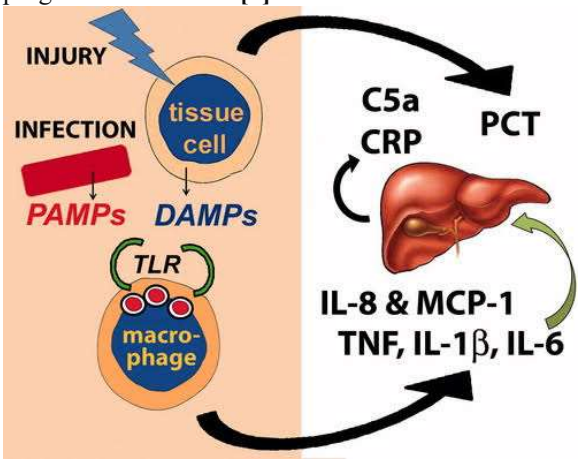

Figure 1: Biomarkers of sepsis **[3]**.

III. The pathophysiology of sepsis

The pathophysiology of sepsis involves a complex interaction between invading pathogens and the host immune system. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) activate innate immune

cells through pattern recognition receptors, particularly Toll-like receptors (TLRs), triggering a cascade of inflammatory signaling pathways. This activation results in the release of numerous pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-8, and interferon-gamma (IFN-γ). Simultaneously, anti-inflammatory cytokines such as IL-10 are produced to limit tissue damage. An imbalance between these pro-inflammatory and anti-inflammatory responses contributes to immune dysregulation, endothelial dysfunction, coagulation abnormalities, microvascular injury, and ultimately organ failure **[4]**.

Inflammatory markers are measurable biological molecules that reflect the intensity of the systemic inflammatory response. These biomarkers have become indispensable tools in the diagnosis, risk stratification, monitoring, and prognosis of patients with sepsis. Conventional inflammatory markers, including C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), and white blood cell count (WBC), are routinely used in clinical practice because they are widely available and relatively inexpensive. However, their diagnostic accuracy varies, particularly in distinguishing bacterial infections from non-infectious inflammatory conditions **[5]**.

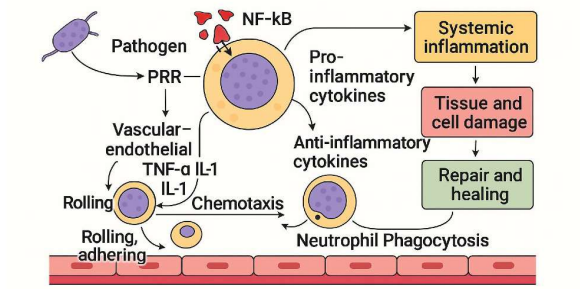

Figure 2: Mechanism of Sepsis **[6]**

IV. Pathophysiological Basis of Inflammatory Marker Release in Sepsis

Sepsis develops when the host immune response to infection becomes dysregulated, resulting in widespread inflammation and organ dysfunction. The recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) by pattern recognition receptors, particularly Toll-like receptors (TLRs), activates intracellular signaling pathways such as nuclear factor-kappa B (NF-κB). This activation stimulates the release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, and IL-8. Simultaneously, anti-inflammatory mediators such as IL-10 are produced to regulate the inflammatory response. The imbalance between these opposing mechanisms contributes to endothelial dysfunction, coagulation abnormalities, microvascular thrombosis, tissue hypoperfusion, and ultimately multiple organ dysfunction syndrome. The circulating levels of inflammatory biomarkers reflect these pathological processes and therefore have important diagnostic and prognostic implications **[7]**.

- **C-Reactive Protein (CRP)**

C-reactive protein is one of the most widely used inflammatory biomarkers in clinical medicine. It is synthesized by hepatocytes in response to IL-6 stimulation and begins to rise approximately six hours after the onset of inflammation, reaching peak concentrations within 24 to 48 hours. CRP participates in host defense by activating the complement system and promoting phagocytosis of microorganisms. In patients with sepsis, elevated CRP levels indicate systemic inflammation but are not specific for bacterial infection, as CRP may also increase in trauma, surgery, autoimmune diseases, and malignancy. Despite this limitation, serial CRP measurements are useful for monitoring disease progression and evaluating response to antimicrobial therapy **[8]**.

- **Procalcitonin (PCT)**

Procalcitonin has emerged as one of the most reliable biomarkers for bacterial sepsis. Under normal physiological conditions, PCT is produced by thyroid C cells as the precursor of calcitonin. During systemic bacterial infection, however, multiple tissues release large amounts of procalcitonin in response to bacterial endotoxins and inflammatory cytokines. Serum PCT levels increase within two to four hours of infection and reach peak concentrations within 12 to 24 hours. Compared with CRP, procalcitonin demonstrates greater specificity for bacterial infections and correlates more closely with disease severity, septic shock, and mortality. Furthermore, serial PCT measurements are widely used to guide antibiotic therapy, helping reduce unnecessary antibiotic exposure without compromising patient safety **[9]**.

- **Interleukin-6 (IL-6)**

Interleukin-6 is a multifunctional cytokine produced by macrophages, monocytes, endothelial cells, and fibroblasts following microbial invasion. It is one of the earliest cytokines released during sepsis and plays a pivotal role in stimulating acute-phase protein synthesis, activating immune cells, and regulating inflammatory responses. Elevated IL-6 concentrations have been consistently associated with increased disease severity, organ dysfunction, prolonged intensive care unit stay, and mortality. Due to its rapid elevation after infection, IL-6 is considered

a valuable early biomarker for sepsis, although its routine clinical use is limited by cost and laboratory availability **[10].**

- **Tumor Necrosis Factor-Alpha (TNF-α)**

Tumor necrosis factor-alpha is a major pro-inflammatory cytokine released primarily by activated macrophages during the early stages of infection. TNF-α promotes leukocyte recruitment, endothelial activation, increased vascular permeability, and production of other inflammatory mediators. Excessive TNF-α production contributes to hypotension, disseminated intravascular coagulation, tissue injury, and multiple organ failure. Although serum TNF-α rises rapidly during sepsis, its short half-life limits its usefulness as a routine diagnostic biomarker. Nevertheless, TNF-α remains essential for understanding the immunopathogenesis of sepsis **[11]**.

- **Presepsin**

Presepsin is a soluble subtype of CD14 released from activated monocytes and macrophages during bacterial phagocytosis. It has recently gained attention as a highly promising biomarker for early diagnosis of bacterial sepsis. Serum presepsin levels rise rapidly after infection and have shown superior diagnostic performance compared with some conventional biomarkers in several clinical studies. Elevated presepsin concentrations have also been associated with septic shock, organ dysfunction, and increased mortality, suggesting its role as both a diagnostic and prognostic marker **[12]**.

V. Classification of Inflammatory Markers in Sepsis

Inflammatory biomarkers used in sepsis can be broadly classified into acute-phase proteins, cytokines, cell-derived biomarkers, endothelial activation markers, coagulation-related markers, and novel molecular biomarkers. Acute-phase reactants include C-reactive protein (CRP) and serum amyloid A, whereas cytokines comprise IL-6, IL-8, TNF-α, and IL-10. Cell-derived biomarkers include white blood cell count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR). Recently developed biomarkers such as presepsin, soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), pentraxin-3, pro-adrenomedullin, and heparin-binding protein have demonstrated promising diagnostic and prognostic value. Each biomarker reflects different aspects of the inflammatory cascade, making multimarker approaches increasingly valuable in clinical practice **[13].**

VI. Septic Shock Assessment and Septic Phenotype Biomarkers

Septic shock is a leading cause of illness and death in critically ill patients. It is characterized by severe dysfunction in circulation, cellular processes, and metabolism. Identifying reliable biomarkers for septic shock is essential for early diagnosis, risk assessment, and treatment monitoring. These biomarkers are connected to the pathophysiology of shock, kidney dysfunction, immunomodulation, and the various phenotypes of sepsis. In the context of septic shock, the most widely accepted and clinically utilized biomarker of shock severity is blood lactate **[14]**.

Elevated lactate levels reflect impaired tissue perfusion, mitochondrial dysfunction, and a shift toward anaerobic metabolism, all of which are hallmark features of circulatory failure in sepsis . Lactate has consistently been associated with poor prognosis and is included in sepsis guidelines as a key marker for early recognition and risk stratification. Lactate is a non-specific indicator that can be elevated due to various conditions not related to infection, such as seizures, liver dysfunction, or the use of beta-agonists **[15]**.

Recently, research has focused on the renin–angiotensin–aldosterone system (RAAS) as a potential factor in the pathophysiology of shock states. In this context, plasma renin has emerged as a promising biomarker for circulatory shock, especially in vasodilatory forms like septic shock. Elevated renin concentrations are thought to reflect the physiological compensation for these conditions: hypotension and peripheral vasodilation and may correlate with persistent hemodynamic instability. Crucially, renin levels appear to rise in response to shock-related hypoperfusion rather than infection per se, thereby distinguishing renin as a marker of shock, not of sepsis **[16]**.

VII. Biomarker for Earlier Discontinuation of Antibiotics

Biomarkers play a crucial role in distinguishing between infections and non-infections, aiding in the decision to discontinue antibiotics early. This dual function is especially important in emergency and critical care settings, where it can be difficult to determine the underlying causes of systemic inflammation. Procalcitonin (PCT) levels could safely support the decision not to initiate antibiotics in patients presenting to the emergency department with suspected lower respiratory tract infections, thereby reducing unnecessary antibiotic use without compromising patient outcomes. This “rule-out” capacity of PCT has since been replicated in multiple clinical settings, reinforcing its role in helping clinicians identify patients in whom a bacterial infection is unlikely **[17]**.

VIII. Biomarkers for Post-Acute Sepsis and Recurrence Prevention

During the post-acute phase of sepsis, the biomarkers are the same; often, their clinical trends

have more significance than a single value itself. The most widely studied biomarker in post-acute sepsis is procalcitonin: the serial PCT measurements can help differentiate between true sepsis recurrence and other non-infectious inflammation causes, such as post-septic immune reconstitution syndrome. However, PCT should always be interpreted alongside clinical findings, as it may remain elevated due to non-infectious inflammatory conditions **[18]**.

IX. Clinical Applications of Inflammatory Markers in Sepsis

Inflammatory biomarkers have multiple clinical applications throughout the management of sepsis. They facilitate early diagnosis, differentiate bacterial from viral or non-infectious inflammatory conditions, estimate disease severity, predict organ dysfunction and mortality, monitor therapeutic response, and support antimicrobial stewardship. The integration of inflammatory biomarkers with clinical examination, microbiological findings, imaging studies, and severity scoring systems such as SOFA and APACHE II provides a more comprehensive assessment of septic patients than reliance on any single parameter alone **[19]**.

It is increasingly recognized that sepsis therapy should not be limited to antimicrobial treatment. Instead, great health benefits may be realized by correcting the dysregulated immune response which underlies septic shock pathobiology. Endothelial inflammation is a hallmark of sepsis and leads to shock and MODS. Several cytokines produced by activated endothelial have effects on the endothelia themselves and immune cells that interact with them: IL-6 has a role in angiogenesis. Endothelial activation induces expression of ICAM-1, which is involved in sepsis pathogenesis and is markers of end-organ failure, morbidity, and mortality in severe sepsis **[2]**.

It is well known that endothelial activation is crucial in sepsis. During inflammatory states, ICAM-1 was a vascular endothelial surface receptor that allows for leukocytes and other inflammatory cells to bind and translocate into local tissue. Up-to-date, many studies showed that its level is increased in patients with sepsis. the level of ICAM-1 and u-Plasminogen Activator was significantly increased in sepsis patients.Bavunoglu et al found that ICAM-1 had a high sensitivity (99%) and specificity (99%) for detecting sepsis **[7]**.

Furthermore, multiple mouse models have shown that ICAM-1 knockout mice with severe forms of sepsis have lower mortality rates. ICAM-1 level in the sepsis and the SIRS groups was significantly higher than that in the control group, and it is also higher in the sepsis group than in the SIRS group. high levels of serum ICAM-1 was associated with the development of MOF provides an interesting insight that ICAM-1 seem to crucial in the pathogenesis and may potentially work as a complementary tool for the physician in the diagnosis of sepsis **[17]**.

The levels of VEGF-C and VEGFR2 were decreased in sepsis patients compared with SIRS patients, and VEGFR2 has diagnostic value in sepsis patients. Vascular endothelial growth factor (VEGF) is crucial for vascular development and stimulate the formation of blood vessels. The over-production of VEGF is associated with acute inflammation. Two receptor tyrosine kinase (RTK) receptors have been identified for VEGF (VEGFR1 and VEGFR2). VEGFR2 is regarded as the main signalling receptor for angiogenesis, proliferation, and permeability **[7]**.

VEGFR2 knockout mice fail to develop blood islands or organised blood vessels resulting in early death. VEGFR2 also has a prosurvival function with anti-apoptotic effects on human umbilical venous endothelial cells (HUVECs).The VEGF family is involved in vascular permeability regulation in sepsis, via yet incompletely understood mechanisms. after LPS injection in mouse, VEGFR2 expression declined sharply in the lung. the plasma level of VEGFR2 decreases associated with severity of infection **[17]**.

The plasminogen activator (PA) system, an essential system in cell differentiation, migration and reconstruction, mainly contains urokinase-type plasminogen activator (uPA), uPA receptor (uPAR), tissue type plasminogen activator (tPA), plasminogen activator inhibitor-1 (PAI-1), and PAI-2 uPA commonly is expressed in neutrophils, monocytes, macrophages, and activated T cells, and is reported to be capable of regulating inflammation, immune responses, and human endothelial cell functions in cancers and several inflammatory diseases. uPA is beneficial in inflammation by activating T cells and may act as an antibiotic agent in mice model infected with *staphylococcus aureus*. Nonetheless, the impact of uPA in sepsis. Plasma levels of u-Plasminogen Activator (uPA) were significantly increased in sepsis patients compared with SIRS patients, and uPA has diagnostic value in sepsis **[2]**.

Conclusion

Inflammatory biomarkers provide useful information throughout the course of sepsis, from the initial diagnosis to monitoring treatment response and estimating prognosis. CRP and procalcitonin remain the most commonly used markers in routine practice, while biomarkers such as presepsin, lactate, plasma renin, ICAM-1, VEGFR2, and uPA offer additional insight into disease severity and the underlying inflammatory process. Because each biomarker reflects a different aspect of the host response, none is sufficiently accurate when used alone. A combination

of laboratory biomarkers, clinical examination, microbiological investigations, imaging findings, and validated scoring systems offers the most reliable approach for evaluating patients with sepsis. Further clinical studies are needed to define the optimal use of emerging biomarkers and their contribution to individualized patient management.

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