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EVALUATION OF INFLAMMATORY BIOMARKERS FOR EARLY DIAGNOSIS AND PROGNOSIS OF SEPSIS IN CRITICALLY ILL PATIENTS: A REVIEW

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ABSTRACT

Sepsis remains one of the leading causes of mortality among critically ill patients worldwide, accounting for substantial healthcare burden and intensive care unit (ICU) admissions. Early diagnosis and timely therapeutic intervention are crucial for improving patient outcomes; however, clinical manifestations are often nonspecific during the initial stages of the disease. Inflammatory biomarkers have emerged as valuable tools for facilitating the early diagnosis, assessment of disease severity, and prediction of prognosis in septic patients. Biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), presepsin, lactate, and various cytokines have demonstrated varying degrees of diagnostic and prognostic utility. This review summarizes the current evidence regarding inflammatory biomarkers in sepsis, highlighting their biological roles, diagnostic performance, clinical applications, and limitations. Furthermore, recent advances in biomarker combinations and emerging molecular markers are discussed. Integrating multiple biomarkers with clinical scoring systems may enhance diagnostic accuracy and facilitate personalized management strategies in critically ill patients.

KEYWORDS: Sepsis, Inflammatory biomarkers, Procalcitonin, C-reactive protein, Interleukin-6, Presepsin, Prognosis, Intensive Care Unit.

1. INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection and represents one of the most significant challenges in critical care medicine. Despite advances in antimicrobial therapy and intensive care management, sepsis continues to be associated with high morbidity and mortality worldwide. According to the Global Burden of Disease Study, approximately 49 million cases of sepsis occur annually, resulting in nearly 11 million deaths.

The progression of sepsis is rapid, and delayed diagnosis significantly increases mortality. Conventional laboratory investigations and microbiological cultures often require several hours to days before definitive results become available. Blood cultures, considered the gold standard for identifying causative pathogens, frequently yield false-negative results due to prior antibiotic administration or low bacterial load. Consequently, inflammatory biomarkers have gained considerable attention as rapid diagnostic and prognostic tools.

Inflammatory biomarkers reflect activation of the innate immune system and systemic inflammatory response following infection. Their measurement assists clinicians in distinguishing bacterial infections from non-infectious inflammatory conditions, evaluating disease severity, monitoring therapeutic response, and predicting clinical outcomes.

2. Pathophysiology of Sepsis and Biomarker Release

Sepsis develops when invading microorganisms stimulate immune cells through pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Recognition of these molecules by pattern recognition receptors (PRRs), particularly Toll-like receptors (TLRs), activates intracellular signaling pathways that induce production of pro-inflammatory cytokines.

Early mediators including tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) initiate systemic inflammation. Excessive cytokine release contributes to endothelial dysfunction, increased vascular permeability, coagulation abnormalities, mitochondrial dysfunction, and multiple organ failure.

During this inflammatory cascade, several measurable biomarkers are released into circulation. Their concentrations correlate with disease progression and therefore provide valuable diagnostic and prognostic information.

3. Major Inflammatory Biomarkers in Sepsis

3.1 C-Reactive Protein (CRP)

CRP is an acute-phase protein synthesized by hepatocytes in response to IL-6 stimulation. Serum CRP levels begin to rise within 6–8 hours after infection and peak approximately 48 hours later.

Clinical Significance

- Widely available and inexpensive.
- Useful for monitoring treatment response.
- Elevated in bacterial infections and systemic inflammation.
- Limited specificity because levels also increase following trauma, surgery, burns, and autoimmune disorders.

Although CRP alone lacks sufficient specificity for early diagnosis, serial measurements provide valuable information regarding disease progression and antibiotic effectiveness.

3.2 Procalcitonin (PCT)

Procalcitonin is one of the most extensively studied biomarkers in sepsis. Under normal physiological conditions, it is synthesized by thyroid C-cells. During bacterial infections, however, multiple tissues produce PCT under cytokine stimulation.

Clinical Applications

- Early detection of bacterial sepsis.
- Differentiation of bacterial from viral infections.
- Monitoring antibiotic therapy.
- Prognostic assessment.

Compared with CRP, PCT demonstrates superior specificity for bacterial infections because viral infections suppress its production through interferon-γ.

Numerous studies have demonstrated that persistently elevated PCT concentrations are associated with increased mortality and poor clinical outcomes.

3.3 Interleukin-6 (IL-6)

IL-6 is among the earliest cytokines released following infection and plays a central role in initiating acute inflammatory responses.

Diagnostic Value

- Detectable within hours of infection.
- Reflects severity of systemic inflammation.
- High IL-6 levels correlate with septic shock and multiple organ dysfunction syndrome (MODS).

Because IL-6 rises before CRP, it may facilitate earlier diagnosis. However, rapid fluctuations and laboratory complexity limit routine clinical application.

3.4 Presepsin

Presepsin is a soluble CD14 subtype released during monocyte activation after bacterial phagocytosis.

Recent studies suggest that presepsin possesses excellent sensitivity and specificity for early sepsis diagnosis.

Clinical benefits include:

- Rapid diagnosis
- Assessment of disease severity
- Mortality prediction
- Monitoring therapeutic response

Several investigations report that presepsin performs comparably or better than CRP and PCT, particularly during early disease stages.

3.5 Lactate

Although lactate is not a direct inflammatory biomarker, it reflects tissue hypoperfusion and cellular metabolic dysfunction.

Elevated serum lactate indicates:

- Severe sepsis
- Septic shock
- Poor tissue oxygenation
- Increased mortality risk

Serial lactate clearance has become an important target in sepsis resuscitation protocols.

4. Emerging Biomarkers

Recent advances in molecular diagnostics have identified several promising biomarkers.

Interleukin-8 (IL-8)

Associated with neutrophil activation and disease severity.

Tumor Necrosis Factor-α (TNF-α)

One of the earliest inflammatory cytokines released during infection.

Soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1)

Improves discrimination between infectious and non-infectious systemic inflammation.

Pentraxin-3 (PTX3)

Correlates strongly with endothelial dysfunction and organ failure.

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Useful for predicting acute kidney injury associated with sepsis.

Cell-Free DNA and MicroRNAs

Novel molecular biomarkers currently under investigation for personalized diagnosis and prognosis.

5. Biomarkers for Prognosis

Besides facilitating diagnosis, inflammatory biomarkers provide valuable prognostic information.

Poor prognosis is associated with:

- Persistently elevated PCT
- High IL-6 concentrations
- Increased lactate levels
- Elevated presepsin
- High Sequential Organ Failure Assessment (SOFA) score

Combining biomarkers with clinical scoring systems such as SOFA and APACHE II significantly improves mortality prediction.

Serial biomarker measurements are generally more informative than single measurements because they reflect disease evolution and response to therapy.

6. Combination Biomarker Strategies

No single biomarker possesses ideal sensitivity and specificity for diagnosing sepsis. Recent research emphasizes combining multiple biomarkers.

Examples include:

- CRP + PCT
- PCT + IL-6
- Lactate + SOFA score
- Presepsin + PCT

- IL-6 + CRP + Lactate

These multimarker approaches improve diagnostic accuracy while reducing false-positive and false-negative results.

Artificial intelligence and machine learning algorithms are increasingly being developed to integrate biomarker data with electronic health records for early sepsis detection.

7. Limitations of Current Biomarkers

Despite their clinical usefulness, inflammatory biomarkers have several limitations.

- Lack of complete specificity.
- Variability among patient populations.
- Influence of chronic inflammatory diseases.
- High laboratory costs for newer biomarkers.
- Limited availability in resource-constrained healthcare settings.
- Absence of universally accepted cutoff values.

Therefore, biomarkers should complement—not replace—clinical judgmentand microbiological investigations.

8. Future Perspectives

Advances in genomics, transcriptomics, proteomics, and metabolomics are expected to revolutionize sepsis diagnostics.

Future research should focus on:

- Identification of highly specific biomarkers.
- Point-of-care testing.
- Multi-omics approaches.
- Personalized biomarker-guided therapy.
- Artificial intelligence-assisted diagnostic models.
- Validation through large multicenter clinical trials.

Such innovations may substantially improve early diagnosis and individualized treatment strategies for critically ill patients.

9. CONCLUSION

Inflammatory biomarkers have transformed the clinical approach to sepsis by enabling earlier diagnosis, assessment of disease severity, monitoring of therapeutic response, and prediction of prognosis. Among currently available biomarkers, procalcitonin, CRP, IL-6, presepsin, and lactate have demonstrated significant clinical utility. However, no single biomarker provides

sufficient diagnostic accuracy when used alone. Integrating multiple biomarkers with established clinical scoring systems offers the most reliable strategy for early recognition and management of sepsis. Continued research into emerging molecular biomarkers and precision medicine approaches is expected to further improve patient outcomes in critically ill populations.

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