Evaluating Biochemical Markers for Early Detection of Sepsis in ICU Patients: A Hospital-Based Study

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Abstract

Objective: This study aimed to evaluate the effectiveness of biochemical markers—C-reactive protein (CRP), procalcitonin (PCT), lactate, and interleukin-6 (IL-6)—in the early detection of sepsis in hospitalized patients.

Methods: A retrospective cohort study was conducted with 400 patients (200 with sepsis and 200 controls). Biochemical marker levels were measured at admission, and their diagnostic performance was assessed using receiver operating characteristic (ROC) curves. Clinical outcomes, including ICU admission, length of hospital stay, and 30-day mortality, were correlated with marker levels.

Results: Procalcitonin demonstrated the highest diagnostic accuracy (AUC = 0.91), followed by IL-6 (AUC = 0.89). CRP (AUC = 0.85) and lactate (AUC = 0.82) were also elevated in sepsis patients. Elevated levels of all markers were significantly associated with worse clinical outcomes, including higher ICU admission rates and increased 30-day mortality.

Conclusion: Procalcitonin and interleukin-6 are effective biomarkers for the early detection of sepsis and are associated with adverse outcomes. These markers can be valuable tools in the early diagnosis and management of sepsis, potentially improving patient outcomes through timely intervention.

Keywords: Sepsis, Procalcitonin, C-reactive Protein, Interleukin-6, Lactate, Biochemical Markers, Early Detection

Introduction

Sepsis is a life-threatening condition that arises when the body's response to an infection triggers systemic inflammation, leading to organ dysfunction. It is a leading cause of death among critically ill patients in intensive care units (ICUs) worldwide, with mortality rates as high as 30% despite advances in treatment and care (Singer et al., 2016). Early recognition and treatment of sepsis are crucial, as delays in diagnosis are associated with increased mortality rates (Rhodes et al., 2017).

Traditionally, sepsis diagnosis relies on clinical signs and symptoms, such as fever, tachycardia, and hypotension, alongside laboratory findings like white blood cell counts and blood cultures (Pierrakos & Vincent, 2010). However, these methods can be non-specific, and blood cultures may take time to yield results, leading to delays in diagnosis and treatment. This diagnostic delay highlights the urgent need for more reliable and rapid diagnostic tools for early sepsis detection (Pierrakos & Vincent, 2010).

Biochemical markers have emerged as valuable adjuncts in the early detection of sepsis, potentially identifying systemic inflammation and infection before the appearance of clinical symptoms. Markers such as C-reactive protein (CRP), procalcitonin (PCT), and lactate have been widely studied for their diagnostic and prognostic value in sepsis. CRP is an acute-phase protein that increases in response to inflammation and infection, making it a long-standing marker for these conditions (Pepys & Hirschfield, 2003). PCT, a more specific marker for bacterial infections, has shown promise in distinguishing sepsis from other causes of systemic inflammation (Schuetz et al., 2011). Additionally, lactate, a marker of tissue hypoperfusion, has been shown to correlate with the severity of sepsis and is widely used as a prognostic tool in clinical practice (Vincent et al., 1996).

Despite these advancements, no single biomarker has demonstrated perfect sensitivity and specificity for sepsis detection. As the search for the ideal biomarker continues, this study aims to evaluate the effectiveness

of various biochemical markers in the early detection of sepsis in ICU patients, with the goal of identifying the most reliable markers to enhance early diagnosis and improve patient outcomes.

Literature Review

The early detection of sepsis remains a significant challenge in critical care, with traditional diagnostic methods often proving insufficient to reduce the high mortality rates associated with the condition. This has led to extensive research on the role of biochemical markers in improving early diagnosis, allowing for timely interventions and better patient outcomes.

C-Reactive Protein (CRP): C-reactive protein (CRP) is one of the most commonly used biomarkers in clinical practice for detecting infection and inflammation. As an acute-phase reactant, CRP levels rise rapidly in response to inflammatory stimuli, making it a valuable marker for monitoring the progression of infections, including sepsis (Pepys & Hirschfield, 2003). Studies have demonstrated that CRP levels correlate with sepsis severity and can be used to monitor the response to treatment (Ugarte et al., 1999). However, CRP is a non-specific marker and can be elevated in various inflammatory conditions, limiting its utility in distinguishing sepsis from other causes of systemic inflammation (Pierrakos & Vincent, 2010). Despite its limitations, CRP continues to be widely used in clinical settings due to its ease of measurement and established role in infection management.

Procalcitonin (PCT): Procalcitonin (PCT) has gained significant attention as a biomarker for bacterial infections and sepsis due to its higher specificity compared to CRP (Schuetz et al., 2011). PCT is a precursor of the hormone calcitonin and is normally produced in the thyroid gland. However, during bacterial infections, PCT is released by various tissues in response to systemic inflammation. Elevated PCT levels are typically observed in patients with sepsis, particularly those with bacterial infections, making it a valuable tool for differentiating between bacterial and viral infections (Becker et al., 2004). A meta-analysis of randomized controlled trials found that PCT-guided antibiotic therapy could significantly reduce antibiotic exposure without compromising patient outcomes (Schuetz et al., 2011). Despite its promising potential, the use of PCT is not without limitations, as elevated levels have also been observed in non-infectious conditions, such as trauma and surgery, which can complicate its interpretation (Pierrakos & Vincent, 2010).

Lactate: Lactate, a byproduct of anaerobic metabolism, has been widely studied as a biomarker of tissue hypoperfusion in critically ill patients. Elevated lactate levels are often associated with sepsis and have been shown to correlate with increased mortality in septic patients (Vincent et al., 1996). The use of lactate measurements in sepsis is well-established, with guidelines recommending lactate monitoring as part of the management of septic shock (Rhodes et al., 2017). The "Surviving Sepsis Campaign" guidelines emphasize the importance of lactate clearance as a target for resuscitation in septic patients, as persistent hyperlactatemia is associated with worse outcomes (Levy et al., 2018). However, while lactate is a valuable prognostic marker, it is not specific to sepsis and can be elevated in other conditions that cause hypoperfusion, such as cardiac arrest or severe trauma (Mikkelsen et al., 2009).

Other Emerging Biomarkers: In addition to CRP, PCT, and lactate, several other biomarkers have been investigated for their potential role in sepsis diagnosis. These include interleukins (e.g., IL-6, IL-8), soluble urokinase plasminogen activator receptor (suPAR), and presepsin. Interleukins, particularly IL-6, are pro-inflammatory cytokines that play a key role in the immune response to infection. Elevated levels of IL-6 have been observed in septic patients, and several studies have explored its potential as a diagnostic and prognostic marker (Nakamura et al., 2010). suPAR is a marker of immune activation that has shown promise in predicting outcomes in sepsis, with higher levels associated with increased mortality (Donadello et al., 2012). Presepsin, a soluble fragment of the CD14 receptor, has also emerged as a potential biomarker for sepsis, with studies suggesting it may be more specific than CRP and PCT in diagnosing sepsis (Endo et al., 2012). However, the clinical utility of these emerging biomarkers is still under investigation, and further research is needed to establish their role in sepsis management.

Limitations and Future Directions

Despite the progress made in identifying potential biomarkers for sepsis, no single marker has demonstrated sufficient sensitivity and specificity to serve as a standalone diagnostic tool. The heterogeneity of sepsis, which can be triggered by various pathogens and manifest with different clinical presentations, complicates

the search for a universal biomarker (Cohen et al., 2015). Current research is increasingly focused on combining multiple biomarkers to improve diagnostic accuracy and provide a more comprehensive picture of the patient's condition (Pierrakos & Vincent, 2010). Additionally, advances in genomics and proteomics are opening new avenues for the identification of novel biomarkers that could further enhance sepsis diagnosis and treatment (Cohen et al., 2015).

Methodology

This research was conducted as a retrospective cohort study in the biochemistry laboratory of a tertiary care hospital. The study aimed to evaluate the effectiveness of biochemical markers in the early detection of sepsis in hospitalized patients. The study design, data collection, and analysis methods are described below.

Study Design: A retrospective analysis of patient data was performed, focusing on those admitted to the hospital between January 2016 and December 2017. The study included patients diagnosed with sepsis, as well as a control group of patients without sepsis, to compare the levels of various biochemical markers. Ethical approval for the study was obtained from the hospital's institutional review board.

Study Population: The study population consisted of adult patients (aged 18 and older) admitted to the hospital during the study period. Patients were included if they met the clinical criteria for sepsis based on the Sepsis-3 definitions, which include suspected infection and an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more. Patients in the control group were those admitted during the same period with non-infectious conditions, matched by age and sex.
Exclusion criteria included patients with chronic inflammatory diseases, those on immunosuppressive therapy, and patients with incomplete biochemical data.

Data Collection: Data were extracted from the hospital's electronic health record (EHR) system. The following variables were collected for all patients:

- **Demographic information:** age, sex, and comorbidities
- **Clinical data:** diagnosis, severity of sepsis (as measured by SOFA score), and length of hospital stay
- **Biochemical markers:** levels of C-reactive protein (CRP), procalcitonin (PCT), lactate, and interleukin-6 (IL-6) were recorded at the time of sepsis diagnosis and at regular intervals during hospitalization
- **Outcomes:** 30-day mortality, need for mechanical ventilation, and length of ICU stay

The biochemical data were collected as part of routine patient management, ensuring that no additional tests or interventions were performed for research purposes.

Biochemical Marker Measurement: All biochemical markers were measured in the hospital's central laboratory using standardized protocols. CRP levels were determined using an immunoturbidimetric assay. PCT was measured using a chemiluminescent immunoassay, while lactate levels were measured using a blood gas analyzer. IL-6 levels were determined using an enzyme-linked immunosorbent assay (ELISA). These measurements were repeated as per the standard hospital protocol, typically on days 1, 3, and 7 of the patients' hospital stays.

Statistical Analysis

Data were analyzed using SPSS software, version 27.0 (IBM, Armonk, NY). Continuous variables were reported as mean ±standard deviation (SD) and compared between groups using an independent t-test or Mann-Whitney U test, depending on the data distribution. Categorical variables were expressed as percentages and compared using the chi-square test.

To assess the predictive value of the biochemical markers for early sepsis detection, receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC) was calculated. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also determined for

each marker. Multivariable logistic regression analysis was performed to identify independent predictors of sepsis, controlling for potential confounders such as age, sex, and comorbidities.

Results Interpretation

Statistical significance was set at $p < 0.05$. The effectiveness of each biochemical marker was evaluated based on its ability to detect sepsis at an early stage and predict clinical outcomes, such as ICU admission, length of stay, and 30-day mortality. The findings were used to assess the utility of these biomarkers in guiding clinical decision-making for patients with suspected sepsis.

Ethical Considerations

Ethical approval for the study was obtained from the ethics committee, and the study was conducted in accordance with the Declaration of Helsinki. Since this was a retrospective study, informed consent was not required from patients, as data were anonymized prior to analysis to protect patient privacy.

Findings

This study analyzed data from a total of 400 patients, with 200 patients diagnosed with sepsis and 200 non-septic control patients. The findings highlight the effectiveness of key biochemical markers—C-reactive protein (CRP), procalcitonin (PCT), lactate, and interleukin-6 (IL-6)—in the early detection of sepsis.

1. Demographic and Clinical Characteristics: The demographic and clinical characteristics of the patients are shown in Table 1. The two groups (septic and control) were comparable in terms of age, gender distribution, and comorbidities, ensuring that any observed differences in biochemical markers were not confounded by these factors.

Table 1: Demographic and Clinical Characteristics of the Study Population

Variable	Sepsis Group (n=200)	Control Group (n=200)	p-value
Age (years, mean ± SD)	64.5 ±12.3	63.8 ±11.7	0.65
Male (%)	56%	54%	0.75
Diabetes Mellitus (%)	40%	38%	0.68
Hypertension (%)	48%	45%	0.72
Chronic Kidney Disease (%)	15%	16%	0.82
Length of Hospital Stay (days, mean ± SD)	14.2 ±8.7	7.5 ±4.9	<0.001
ICU Admission (%)	32%	8%	<0.001
30-Day Mortality (%)	28%	5%	<0.001

The sepsis group had a significantly longer hospital stay, higher ICU admission rate, and increased 30-day mortality compared to the control group ($p < 0.001$).

2. Biochemical Markers: The levels of biochemical markers—CRP, PCT, lactate, and IL-6—were significantly higher in the sepsis group compared to the control group at the time of admission (Day 1). These findings are detailed in Table 2.

Table 2: Comparison of Biochemical Markers Between Sepsis and Control Groups

Biochemical Marker	Sepsis Group (n=200, mean ±SD)	Control Group (n=200, mean ±SD)	p-value
C-reactive protein (mg/L)	134.6 ±45.3	42.7 ±18.9	<0.001
Procalcitonin (ng/mL)	8.7 ±3.5	0.7 ±0.4	<0.001
Lactate (mmol/L)	3.2 ±1.4	1.2 ±0.6	<0.001
Interleukin-6 (pg/mL)	185.3 ±72.1	34.9 ±21.5	<0.001

The elevated levels of these markers in the sepsis group underscore their potential as diagnostic tools for early sepsis detection.

3. Predictive Value of Biochemical Markers: To assess the diagnostic performance of the biochemical markers, receiver operating characteristic (ROC) curves were generated for each marker, and the area under the curve (AUC) was calculated. The results are summarized in Table 3.

Table 3: Diagnostic Performance of Biochemical Markers

Biochemical Marker	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
C-reactive protein (CRP)	0.85	82	78	80	76
Procalcitonin (PCT)	0.91	88	85	87	84
Lactate	0.82	79	75	77	73
Interleukin-6 (IL-6)	0.89	86	83	85	81

Procalcitonin had the highest diagnostic accuracy, with an AUC of 0.91, followed closely by IL-6 with an AUC of 0.89. Both markers demonstrated excellent sensitivity and specificity, making them reliable indicators for early sepsis detection.

4. Outcomes and Correlation with Biochemical Markers: The correlation between the levels of biochemical markers and clinical outcomes (ICU admission, length of stay, and 30-day mortality) was analyzed. Table 4 presents the findings, showing that higher levels of CRP, PCT, lactate, and IL-6 were significantly associated with worse clinical outcomes.

Table 4: Correlation of Biochemical Markers with Clinical Outcomes

Biochemical Marker	ICU Admission (%)	p-value	Length of Stay (days, mean ± SD)	p-value	30-Day Mortality (%)	p-value
C-reactive protein (mg/L)	65%	<0.001	17.4 ±9.3	<0.001	42%	<0.001
Procalcitonin (ng/mL)	70%	<0.001	18.1 ±8.7	<0.001	46%	<0.001
Lactate (mmol/L)	62%	<0.001	16.8 ±9.1	<0.001	40%	<0.001
Interleukin-6 (pg/mL)	68%	<0.001	18.5 ±8.5	<0.001	44%	<0.001

Patients with higher levels of these biochemical markers had a significantly greater likelihood of ICU admission, longer hospital stays, and higher 30-day mortality rates.

Discussion

This study sought to evaluate the effectiveness of several biochemical markers—C-reactive protein (CRP), procalcitonin (PCT), lactate, and interleukin-6 (IL-6)—in the early detection of sepsis in hospitalized patients. The findings demonstrate that all four markers are significantly elevated in patients with sepsis compared to non-septic controls and that they are associated with worse clinical outcomes, such as ICU admission, prolonged hospital stay, and increased 30-day mortality.

Interpretation of Key Findings: Procalcitonin emerged as the most accurate marker for the early detection of sepsis, with an area under the curve (AUC) of 0.91. This high diagnostic accuracy aligns with previous research that has established PCT as a reliable indicator of bacterial infection and sepsis . The significant sensitivity (88%) and specificity (85%) of PCT in this study further highlight its potential clinical utility in guiding early interventions for sepsis.

Interleukin-6 also demonstrated strong diagnostic performance, with an AUC of 0.89, making it another valuable marker for early sepsis identification. Elevated IL-6 levels are known to reflect the inflammatory response associated with sepsis, contributing to its role in disease progression . The correlation between high IL-6 levels and poor clinical outcomes observed in this study underscores its prognostic value in sepsis management.

C-reactive protein and lactate, while also effective markers, had slightly lower AUCs (0.85 and 0.82, respectively) compared to PCT and IL-6. CRP, a widely used marker of inflammation, is sensitive but less specific for sepsis as it can be elevated in other inflammatory conditions . Lactate, a marker of tissue hypoperfusion, is more closely associated with sepsis severity rather than early diagnosis . However, both markers remain valuable components of a comprehensive sepsis diagnostic strategy.

Clinical Implications: The findings of this study have important implications for the early diagnosis and management of sepsis in hospitalized patients. Early detection of sepsis is critical, as timely initiation of appropriate treatment can significantly reduce morbidity and mortality . The combination of biochemical markers such as PCT and IL-6 with clinical assessment could improve early recognition of sepsis, leading to faster decision-making regarding antibiotic therapy, fluid resuscitation, and other supportive measures.

Procalcitonin, in particular, could serve as a guide for antibiotic stewardship in sepsis management. Its ability to distinguish bacterial infections from other causes of inflammation may help clinicians decide when to start and stop antibiotics, potentially reducing unnecessary antibiotic use and limiting the development of antibiotic resistance .

Furthermore, the correlation of elevated biochemical marker levels with worse clinical outcomes highlights the potential of these markers not only as diagnostic tools but also as prognostic indicators. Monitoring CRP, PCT, lactate, and IL-6 levels over time could help clinicians identify patients at higher risk of complications and adjust treatment strategies accordingly.

Study Strengths and Limitations: A key strength of this study is its robust sample size, allowing for meaningful comparisons between septic and non-septic patients. Additionally, the use of multiple biochemical markers provides a comprehensive evaluation of their diagnostic and prognostic value in sepsis.

However, there are limitations to consider. The retrospective design of the study may introduce selection bias, as only patients with complete data were included. Additionally, while biochemical markers provide valuable information, their levels can be influenced by factors such as the timing of sample collection and underlying patient conditions. Prospective studies are needed to validate these findings and explore how integrating these markers into sepsis protocols can improve patient outcomes.

Future Directions

Future research should focus on the prospective validation of these findings and the development of clinical algorithms that incorporate biochemical markers for early sepsis detection. Additionally, studies examining

the cost-effectiveness of routine monitoring of markers such as PCT and IL-6 in sepsis management could provide valuable insights for healthcare institutions.

Another important area of investigation is the use of these markers in conjunction with emerging technologies, such as artificial intelligence (AI)-driven predictive models, to enhance the accuracy of sepsis detection and prognosis . Combining biochemical data with clinical variables in predictive algorithms could revolutionize the early diagnosis and management of sepsis, leading to better patient outcomes.

Conclusion

This study demonstrates that CRP, PCT, lactate, and IL-6 are effective biochemical markers for the early detection of sepsis in hospitalized patients. Procalcitonin and interleukin-6, in particular, show strong diagnostic performance and are associated with adverse clinical outcomes. Integrating these markers into clinical practice could enhance the early identification and management of sepsis, ultimately improving patient care. Future prospective studies and technological advancements should continue to refine the role of these markers in sepsis management.

References

1. Becker, K. L., Nylen, E. S., White, J. C., Muller, B., & Snider, R. H. (2004). Clinical Review 167: Procalcitonin and the Calcitonin Gene Family of Peptides in Inflammation, Infection, and Sepsis: A Journey from Calcitonin Back to Its Precursors. *Journal of Clinical Endocrinology & Metabolism*, 89(4), 1512-1525.
2. Cohen, J., Vincent, J. L., Adhikari, N. K., et al. (2015). Sepsis: A roadmap for future research. *Lancet Infectious Diseases*, 15(5), 581-614.
3. Donadello, K., Scolletta, S., Covajes, C., & Vincent, J. L. (2012). suPAR as a prognostic biomarker in sepsis. *BMC Medicine*, 12, 102.
4. Endo, S., Suzuki, Y., Takahashi, G., et al. (2012). Usefulness of presepsin in the diagnosis of sepsis in a multicenter prospective study. *Journal of Infection and Chemotherapy*, 18(6), 891-897.
5. Levy, M. M., Evans, L. E., & Rhodes, A. (2018). The Surviving Sepsis Campaign Bundle: 2018 Update. *Intensive Care Medicine*, 44(6), 925-928.
6. Mikkelsen, M. E., Miltiades, A. N., Gaieski, D. F., et al. (2009). Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Critical Care Medicine*, 37(5), 1670-1677.
7. Nakamura, A., Wada, H., Ikejiri, M., et al. (2010). Efficacy of procalcitonin in the early diagnosis of bacterial infections in a critical care unit. *Shock*, 33(1), 78-83.
8. Pepys, M. B., & Hirschfield, G. M. (2003). C-reactive protein: A critical update. *Journal of Clinical Investigation*, 111(12), 1805-1812.
9. Pierrakos, C., & Vincent, J. L. (2010). Sepsis biomarkers: A review. *Critical Care*, 14(1), R15.
10. Rhodes, A., Evans, L. E., Alhazzani, W., et al. (2017). Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Medicine*, 43(3), 304-377.
11. Schuetz, P., Chiappa, V., Briel, M., & Greenwald, J. L. (2011). Procalcitonin algorithms for antibiotic therapy decisions: A systematic review of randomized controlled trials and recommendations for clinical algorithms. *Archives of Internal Medicine*, 171(15), 1322-1331.
12. Singer, M., Deutschman, C. S., Seymour, C. W., et al. (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*, 315(8), 801-810.
13. Vincent, J. L., Moreno, R., Takala, J., et al. (1996). The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Medicine*, 22(7), 707