Int. J Med. Pharm. Res. (P-ISSN: 2958-3675 | E-ISSN: 2958-3683)
Available on: https://ijmpr.in/

International Journal
of Medical and Pharmaceutical Research

ORGINAL ARTICLE **OPEN ACCESS**

Evaluation of Biomarkers in Early Diagnosis and Prognosis of Sepsis in ICU Patients

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Received: 06-09-2024
Accepted: 03-11-2024
Available online: 09-11-2024

A B S T R A C T

Background*:** Sepsis is a life-threatening condition characterized by a dysregulated host response to infection. Early diagnosis and risk stratification are crucial for improving patient outcomes. This study aimed to evaluate the diagnostic and prognostic utility of biomarkers in critically ill patients with sepsis.Methods*:** In this prospective observational study, 160 patients (120 with sepsis, 40 with non-infectious SIRS) admitted to the ICU were included. Levels of procalcitonin (PCT), C-reactive protein (CRP), interleukin-6 (IL-6), soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), and lactate were measured within 24 hours of ICU admission. The diagnostic and prognostic performance of biomarkers was evaluated using receiver operating characteristic (ROC) curve analysis and logistic regression.***Results*:** PCT, IL-6, and lactate demonstrated good diagnostic performance in differentiating sepsis from non-infectious SIRS, with AUCs of 0.88, 0.82, and 0.75, respectively. The combination of PCT, CRP, and IL-6 yielded an AUC of 0.92. Lactate, IL-6, and PCT were strong predictors of 28-day mortality (AUCs: 0.80, 0.78, and 0.75, respectively), organ dysfunction, and ICU length of stay. The sepsis group had significantly higher SOFA scores at day 7 (median 6 vs. 3, $p<0.001$) and longer ICU stay (median 12 days vs. 7 days, $p<0.001$) compared to the non-infectious SIRS group.***Conclusions*:** Biomarkers, particularly PCT, IL-6, and lactate, have good diagnostic and prognostic utility in the management of sepsis in critically ill patients. The use of biomarker panels may further improve diagnostic accuracy and prognostic performance. These findings support the incorporation of biomarkers into clinical decision-making to facilitate early recognition and risk stratification of sepsis in the ICU setting.

Keywords: Sepsis, biomarkers, procalcitonin, interleukin-6, lactate, diagnosis, prognosis, intensive care unit.

INTRODUCTION

Sepsis is a life-threatening condition characterized by a dysregulated host response to infection, leading to organ dysfunction [1]. Despite advances in medical care, sepsis remains a major cause of morbidity and mortality in intensive care units (ICUs) worldwide [2]. Early diagnosis and timely initiation of appropriate treatment are crucial for improving patient outcomes. However, the clinical diagnosis of sepsis can be challenging, as the signs and symptoms are often nonspecific and overlap with other conditions [3].

Biomarkers have emerged as valuable tools to aid in the early recognition and risk stratification of sepsis in ICU patients. These biological molecules, measurable in blood or other body fluids, reflect the host's response to infection and the severity of the disease process [4]. Biomarkers can provide objective data to complement clinical assessment, guide therapeutic decisions, and predict patient outcomes.

Over the past decades, numerous biomarkers have been investigated for their potential utility in sepsis diagnosis and prognosis. These include markers of inflammation (e.g., C-reactive protein, procalcitonin), endothelial dysfunction (e.g., endocan, angiopoietins), coagulation (e.g., thrombomodulin, protein C), and organ dysfunction (e.g., lactate,

neutrophil gelatinase-associated lipocalin) [5, 6]. However, no single biomarker has demonstrated sufficient sensitivity and specificity to serve as a standalone diagnostic or prognostic tool for sepsis.

Recent research has focused on evaluating combinations of biomarkers, or biomarker panels, to improve the accuracy of sepsis diagnosis and risk stratification. For example, a study by Gibot*et al*., [7] showed that a panel of three biomarkers (procalcitonin, soluble triggering receptor expressed on myeloid cells-1, and the high-affinity interleukin-2 receptor α-chain) could accurately diagnose sepsis in ICU patients with suspected infection. Another study by Mikacenic*et al*., [8] identified a panel of 12 biomarkers associated with increased mortality risk in sepsis patients, highlighting the potential for biomarker-based prognostic models.

Despite these promising findings, the translation of biomarker research into clinical practice has been challenging. Factors such as the heterogeneity of sepsis populations, variability in biomarker assays, and the influence of comorbidities and treatment interventions can affect biomarker performance [9]. Moreover, the cost-effectiveness and practical feasibility of implementing biomarker testing in resource-limited settings need to be considered.

Aims and Objectives

The primary aim of this prospective observational study was to evaluate the utility of biomarkers in the early diagnosis and prognosis of sepsis in critically ill patients admitted to the intensive care unit (ICU) of a tertiary care center. The specific objectives were: (1) to assess the diagnostic performance of individual biomarkers and biomarker panels in differentiating sepsis from non-infectious systemic inflammatory response syndrome (SIRS); (2) to investigate the prognostic value of biomarkers in predicting mortality, organ dysfunction, and ICU length of stay in patients with sepsis; and (3) to compare the performance of biomarkers with conventional clinical and laboratory parameters in the diagnosis and risk stratification of sepsis.

Materials and Methods

Study Design and Setting

This was a single-center, prospective observational study conducted in the ICU of a tertiary care hospital. The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants or their legal representatives prior to enrollment.

Study Population

A total of 160 consecutive adult patients (age ≥18 years) admitted to the ICU with suspected or confirmed sepsis were included in the study. Sepsis was defined according to the Sepsis-3 criteria [1], which requires the presence of a suspected or documented infection and an acute increase of ≥2 points in the Sequential Organ Failure Assessment (SOFA) score. Patients with non-infectious SIRS, defined as meeting ≥2 SIRS criteria without evidence of infection, were included as controls. The exclusion criteria were: (1) age <18 years; (2) pregnancy; (3) immunosuppression (e.g., chemotherapy, chronic corticosteroid use); (4) terminal illness with an expected survival of <30 days; and (5) refusal to participate.

Data Collection

Demographic and clinical data, including age, sex, comorbidities, source of infection, and severity of illness scores (Acute Physiology and Chronic Health Evaluation II [APACHE II] and SOFA), were collected at the time of ICU admission. Blood samples for biomarker measurement were obtained within 24 hours of ICU admission and processed according to standardized protocols. The biomarkers evaluated in this study included procalcitonin (PCT), C-reactive protein (CRP), interleukin-6 (IL-6), soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), and lactate. Biomarker levels were measured using commercially available immunoassays, and the laboratory staff were blinded to the clinical data.

Outcome Measures

The primary outcome was the diagnostic performance of biomarkers in differentiating sepsis from non-infectious SIRS, assessed by the area under the receiver operating characteristic (ROC) curve (AUC). Secondary outcomes included 28-day mortality, organ dysfunction (assessed by the SOFA score), and ICU length of stay. Patients were followed up for 28 days or until death or hospital discharge, whichever occurred first.

Statistical Analysis

Continuous variables were expressed as median and interquartile range (IQR) and compared using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. The diagnostic performance of biomarkers was evaluated by ROC curve analysis, and the AUC, sensitivity, specificity, and predictive values were calculated at optimal cut-off points. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of mortality. Kaplan-

Meier survival curves were constructed to compare survival between groups, and differences were assessed using the log-rank test. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographic and Clinical Characteristics

A total of 160 patients were included in the study, with 120 patients in the sepsis group and 40 patients in the non-infectious SIRS group (Table 1). The median age was 65 years (IQR 55-75) in the sepsis group and 62 years (IQR 50-72) in the non-infectious SIRS group (p=0.15). There were no significant differences in sex distribution or comorbidities between the two groups. The most common sources of infection in the sepsis group were respiratory (45%), abdominal (30%), and urinary tract (20%). The sepsis group had significantly higher APACHE II scores (median 22, IQR 18-27) compared to the non-infectious SIRS group (median 18, IQR 14-23; p=0.001). Similarly, the SOFA scores were significantly higher in the sepsis group (median 8, IQR 6-10) compared to the non-infectious SIRS group (median 5, IQR 3-7; p<0.001).

Biomarker Levels in Sepsis and Non-infectious SIRS Groups

The sepsis group had significantly higher levels of all evaluated biomarkers compared to the non-infectious SIRS group (Table 2). The median PCT levels were 8.2 ng/mL (IQR 2.5-22.1) in the sepsis group and 0.8 ng/mL (IQR 0.3-1.9) in the non-infectious SIRS group (p<0.001). CRP levels were also significantly higher in the sepsis group (median 156 mg/L, IQR 98-220) compared to the non-infectious SIRS group (median 68 mg/L, IQR 32-112; p<0.001). Similarly, IL-6, sTREM-1, and lactate levels were significantly elevated in the sepsis group compared to the non-infectious SIRS group (p<0.001 for all comparisons).

Diagnostic Performance of Biomarkers

The diagnostic performance of individual biomarkers and biomarker panels in differentiating sepsis from non-infectious SIRS is presented in Table 3. PCT had the highest area under the receiver operating characteristic curve (AUC) of 0.88 (95% CI 0.83-0.93), with a sensitivity of 80%, specificity of 85%, positive predictive value (PPV) of 94%, and negative predictive value (NPV) of 61% at a cut-off value of 2.0 ng/mL.sTREM-1 and IL-6 also demonstrated good diagnostic performance, with AUCs of 0.85 (95% CI 0.79-0.91) and 0.82 (95% CI 0.76-0.88), respectively. The combination of PCT, CRP, and IL-6 as a biomarker panel yielded the highest AUC of 0.92 (95% CI 0.88-0.96), with a sensitivity of 88%, specificity of 90%, PPV of 96%, and NPV of 75%.

Predictors of 28-day Mortality

Univariate logistic regression analysis identified age, APACHE II score, SOFA score, PCT, CRP, IL-6, sTREM-1, and lactate as significant predictors of 28-day mortality (Table 4). In the multivariate analysis, age (OR 1.03, 95% CI 1.00-1.06; p=0.04), APACHE II score (OR 1.10, 95% CI 1.03-1.18; p=0.007), SOFA score (OR 1.22, 95% CI 1.07-1.40; p=0.003), PCT (OR 1.05, 95% CI 1.01-1.09; p=0.02), IL-6 (OR 1.001, 95% CI 1.000-1.002; p=0.04), and lactate (OR 1.22, 95% CI 1.05-1.42; p=0.009) remained independent predictors of mortality.

Comparison of Outcomes

The sepsis group had a higher 28-day mortality rate (30%) compared to the non-infectious SIRS group (15%), although this difference did not reach statistical significance (p=0.06) (Table 5). The sepsis group had significantly higher SOFA scores at day 7 (median 6, IQR 4-9) compared to the non-infectious SIRS group (median 3, IQR 2-5; p<0.001). The ICU length of stay was also significantly longer in the sepsis group (median 12 days, IQR 8-18) compared to the non-infectious SIRS group (median 7 days, IQR 5-11; p<0.001).

Prognostic Performance of Biomarkers

The prognostic performance of biomarkers in predicting 28-day mortality, organ dysfunction, and ICU length of stay is shown in Table 6. Lactate had the highest AUC for predicting 28-day mortality (0.80, 95% CI 0.73-0.87; p<0.001), followed by IL-6 (AUC 0.78, 95% CI 0.71-0.85; p<0.001) and PCT (AUC 0.75, 95% CI 0.68-0.82; p<0.001). Similar trends were observed for the prediction of organ dysfunction and ICU length of stay, with lactate, IL-6, and PCT demonstrating the best prognostic performance among the evaluated biomarkers.

Table 1: Demographic and Clinical Characteristics of the Study Population

Characteristic	Sepsis (n=120)	Non-infectious SIRS (n=40)	P-value
Age, years	65 (55-75)	62 (50-72)	0.15
Male sex, n (%)	72 (60%)	22 (55%)	0.57
Comorbidities, n (%)			
- Diabetes	48 (40%)	14 (35%)	0.57
- Hypertension	66 (55%)	20 (50%)	0.58

- Chronic lung disease	30 (25%)	12 (30%)	0.53
Source of infection, n (%)			
- Respiratory	54 (45%)	-	-
- Abdominal	36 (30%)	-	-
- Urinary tract	24 (20%)	-	-
- Other	6 (5%)	-	-
APACHE II score	22 (18-27)	18 (14-23)	0.001
SOFA score	8 (6-10)	5 (3-7)	<0.001

Data are presented as median (IQR) or n (%).

Table 2: Biomarker Levels in Sepsis and Non-infectious SIRS Groups

Biomarker	Sepsis (n=120)	Non-infectious SIRS (n=40)	P-value
PCT, ng/mL	8.2 (2.5-22.1)	0.8 (0.3-1.9)	<0.001
CRP, mg/L	156 (98-220)	68 (32-112)	<0.001
IL-6, pg/mL	280 (120-650)	95 (40-180)	<0.001
sTREM-1, pg/mL	420 (280-700)	180 (100-300)	<0.001
Lactate, mmol/L	2.8 (1.9-4.2)	1.6 (1.2-2.2)	<0.001

Data are presented as median (IQR).

Table 3: Diagnostic Performance of Biomarkers in Differentiating Sepsis from Non-infectious SIRS

Biomarker	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Cut-off
PCT	0.88 (0.83-0.93)	80%	85%	94%	61%	2.0 ng/mL
CRP	0.80 (0.74-0.86)	75%	70%	88%	50%	100 mg/L
IL-6	0.82 (0.76-0.88)	78%	75%	90%	55%	150 pg/mL
sTREM-1	0.85 (0.79-0.91)	82%	80%	92%	62%	250 pg/mL
Lactate	0.75 (0.68-0.82)	70%	65%	85%	45%	2.0 mmol/L
PCT + CRP + IL-6	0.92 (0.88-0.96)	88%	90%	96%	75%	-

PPV: Positive Predictive Value, NPV: Negative Predictive Value.

Table 4: Univariate and Multivariate Logistic Regression Analyses for Predictors of 28-day Mortality

Predictor	Univariate OR (95% CI)	P-value	Multivariate OR (95% CI)	P-value
Age, years	1.04 (1.01-1.07)	0.005	1.03 (1.00-1.06)	0.04
APACHE II score	1.15 (1.08-1.22)	<0.001	1.10 (1.03-1.18)	0.007
SOFA score	1.35 (1.20-1.52)	<0.001	1.22 (1.07-1.40)	0.003
PCT, ng/mL	1.08 (1.04-1.12)	<0.001	1.05 (1.01-1.09)	0.02
CRP, mg/L	1.01 (1.00-1.02)	0.001	-	-
IL-6, pg/mL	1.002 (1.001-1.003)	<0.001	1.001 (1.000-1.002)	0.04
sTREM-1, pg/mL	1.002 (1.001-1.003)	<0.001	-	-
Lactate, mmol/L	1.35 (1.18-1.54)	<0.001	1.22 (1.05-1.42)	0.009

OR: Odds Ratio, CI: Confidence Interval.

Table 5: Comparison of Outcomes between Sepsis and Non-infectious SIRS Groups

Outcome	Sepsis (n=120)	Non-infectious SIRS (n=40)	P-value
28-day mortality, n (%)	36 (30%)	6 (15%)	0.06
SOFA score at day 7	6 (4-9)	3 (2-5)	<0.001
ICU length of stay, days	12 (8-18)	7 (5-11)	<0.001

Data are presented as median (IQR) or n (%).

Table 6: Prognostic Performance of Biomarkers in Predicting 28-day Mortality, Organ Dysfunction, and ICU Length of Stay

Biomarker	28-day Mortality AUC (95% CI)	P-value	Organ Dysfunction AUC (95% CI)	P-value	ICU Length of Stay AUC (95% CI)	P-value
PCT	0.75 (0.68-0.82)	<0.001	0.72 (0.65-0.79)	<0.001	0.70 (0.63-0.77)	<0.001
CRP	0.68 (0.60-0.76)	0.001	0.65 (0.57-0.73)	0.002	0.63 (0.55-0.71)	0.006
IL-6	0.78 (0.71-0.85)	<0.001	0.75 (0.68-0.82)	<0.001	0.72 (0.65-0.79)	<0.001
sTREM-1	0.72 (0.64-0.80)	<0.001	0.70 (0.62-0.78)	<0.001	0.68 (0.60-0.76)	0.001
Lactate	0.80 (0.73-0.87)	<0.001	0.78 (0.71-0.85)	<0.001	0.75 (0.68-0.82)	<0.001

AUC: Area Under the Curve, CI: Confidence Interval.

DISCUSSION

This prospective observational study evaluated the utility of biomarkers in the early diagnosis and prognosis of sepsis in critically ill patients. The results demonstrate that biomarkers, particularly PCT, IL-6, and lactate, have good diagnostic and prognostic performance in differentiating sepsis from non-infectious SIRS and predicting mortality, organ dysfunction, and ICU length of stay.

The diagnostic performance of PCT in this study (AUC 0.88, sensitivity 80%, specificity 85%) is consistent with previous findings. In a meta-analysis by Wacker*et al*., [11], PCT had a pooled sensitivity of 77% and specificity of 79% for the diagnosis of sepsis. Similarly, a study by Kibe*et al*., [12] reported an AUC of 0.85 (95% CI 0.81-0.88) for PCT in differentiating sepsis from non-infectious SIRS. The slightly higher diagnostic performance observed in the current study may be attributed to the use of the Sepsis-3 criteria, which have improved specificity compared to previous definitions [13].

The combination of PCT, CRP, and IL-6 as a biomarker panel yielded the highest diagnostic performance (AUC 0.92) in this study. This finding is in line with the growing evidence supporting the use of biomarker panels to improve the accuracy of sepsis diagnosis. In a study by Kofoed*et al*., [14], a combination of six biomarkers (PCT, CRP, IL-6, soluble urokinase plasminogen activator receptor, soluble triggering receptor expressed on myeloid cells-1, and neutrophil count) had an AUC of 0.88 (95% CI 0.82-0.92) for the diagnosis of sepsis. The slightly higher AUC observed in the current study may be due to differences in the selected biomarkers and study population.

Lactate emerged as a strong predictor of mortality and organ dysfunction in this study, with an AUC of 0.80 for 28-day mortality and 0.78 for organ dysfunction. This is consistent with the well-established role of lactate as a marker of tissue hypoperfusion and severity of illness in sepsis [15]. In a study by Mikkelsen*et al*., [16], lactate levels ≥4 mmol/L were associated with a 28-day mortality rate of 36.7% compared to 12.0% in patients with lactate <2 mmol/L ($p<0.001$). The slightly lower mortality rate observed in the current study (30% in the sepsis group) may be due to differences in the study population and treatment strategies.

IL-6 also demonstrated good prognostic performance in this study, with an AUC of 0.78 for 28-day mortality. This finding is supported by a meta-analysis by Jamil*et al*., [17], which reported a pooled AUC of 0.79 (95% CI 0.74-0.83) for IL-6 in predicting mortality in sepsis. The study also highlighted the potential of IL-6 as an early marker of sepsis, with elevated levels observed up to 48 hours before clinical diagnosis.

The prognostic performance of PCT in this study (AUC 0.75 for 28-day mortality) is comparable to previous findings. In a meta-analysis by Liu *et al*., [18], PCT had a pooled AUC of 0.77 (95% CI 0.73-0.80) for predicting mortality in sepsis. However, the optimal cut-off value for PCT in predicting mortality remains unclear, with values ranging from 1.1 to 10.0 ng/mL reported in the literature [19].

The lack of statistical significance in the difference in 28-day mortality between the sepsis and non-infectious SIRS groups (30% vs. 15%, $p=0.06$) may be due to the relatively small sample size of the non-infectious SIRS group ($n=40$). This limitation is common in studies comparing sepsis with non-infectious SIRS, as the prevalence of non-infectious SIRS is lower in the ICU setting [20]. Larger studies with adequate power are needed to confirm the prognostic value of biomarkers in this context.

CONCLUSION

In conclusion, this study demonstrates the diagnostic and prognostic utility of biomarkers, particularly PCT, IL-6, and lactate, in the management of sepsis in critically ill patients. The combination of biomarkers as a panel may further improve diagnostic accuracy. These findings support the incorporation of biomarkers into clinical decision-making to facilitate early recognition and risk stratification of sepsis in the ICU setting. However, biomarkers should be interpreted in conjunction with clinical assessment and not used as a standalone tool. Future research should focus on validating these findings in larger, multicenter studies and evaluating the cost-effectiveness of biomarker-guided strategies in sepsis management.

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