ORIGINAL ARTICLE

Diagnostic Potential of Serum Interleukin-6 in Predicting Bacteremia in Adult Patients with Sepsis: A Prospective Observational Study

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Abstract

Background: This study aimed to assess the potential of serum interleukin-6 (IL-6) as a diagnostic marker in predicting bacteremia and to determine its association with severity and outcome among sepsis patients.

Materials and methods: A prospective observational study was conducted, comprising a cohort of 118 patients admitted to the ICU with suspected sepsis from January 2019 to April 2020.

Results: Among the 108 patients analyzed, 60 (55.6%) were bacteremic and 48 (44.4%) were nonbacteremic. Of 60 patients with bacteremia, 13 (21.6%) had sepsis and 47 (78.3%) had septic shock. In predicting bacteremia, the area under the curve (AUC) for IL-6 was 0.512 [95% CI, 0.400–0.623]. The AUC for IL-6 in differentiating sepsis from septic shock was 0.724 [95% CI, 0.625–0.823]. The sensitivity and specificity for predicting bacteremia for IL-6 were 66% and 67%, respectively ($p < 0.001$). Multivariate analysis revealed that C-reactive protein (CRP) ($p = 0.04$) and APACHE II score ($p = 0.025$) were significant predictors of bacteremia, whereas lactate ($p = 0.04$), and APACHE II score ($p < 0.001$) were significant predictors of sepsis severity. Patients with elevated levels of procalcitonin PCT ($p = 0.024$), APACHE II ($p = 0.003$), and SOFA ($p = 0.002$) scores had significantly higher mortality rates.

Conclusion: C-reactive protein and APACHE II score, lactate and APACHE II score, and PCT, SOFA, and APACHE II scores performed better in predicting bacteremia, sepsis severity, and clinical outcome, respectively compared with IL-6.

Keywords: Bacteremia, Interleukin-6, Mortality, Sepsis, Septic shock.

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Highlights

This study found no significant difference in interleukin-6 (IL-6) levels between bacteremic and nonbacteremic patients, but did measure sepsis severity and outcome. C-reactive protein (CRP) was a better marker for the prediction of bacteremia. APACHE II score, procalcitonin (PCT), and lactate performed better than IL-6 in predicting sepsis severity. Procalcitonin, SOFA, and APACHE II were better mortality predictors than IL-6. Serial monitoring of biomarkers is vital, and more multicenter studies are needed to assess the utility of IL-6 in this situation.

Introduction

Sepsis, which affects millions of individuals globally each year, is a leading cause of mortality. Despite advances in medical care, 5.3 million deaths occur annually among adults due to sepsis. In 2016, the definition of sepsis was revised to a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] The overall in-hospital mortality remains as high as 25–30%. In recent years, sepsis and septic shock have shown an increasing prevalence.[1–3] The most important factors influencing the clinical course of sepsis and lowering mortality are early diagnosis and timely initiation of appropriate therapy.[4]

At present, isolating pathogens from blood cultures is considered the most reliable diagnostic test for sepsis. Nevertheless, only about ~30% of sepsis patients exhibit detectable bacteremia, and positive blood culture results may not be available until 48–72 hours. While blood cultures can identify microorganisms and guide subsequent antibiotic treatment, they are not effective in the initial

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Conflict of interest: None

diagnostic stage upon a patient's arrival at the hospital. Biomarkers utilized for sepsis diagnosis offer the advantage of faster results compared with microbiological tests.[5]

Several biomarkers, including CRP and PCT have been tested among sepsis patients to confirm bacterial infection but with contradictory results.[6] Interleukin-6 (IL-6) has received attention recently as a potentially useful diagnostic tool for sepsis patients. Activated macrophages and monocytes release the pro-inflammatory cytokine IL-6. This cytokine plays a crucial role in triggering the acute-phase response during bacterial infections.[7] In the absence of infection, serum IL-6 levels remain consistently low (typically ranging from 0.2 to 7.8 pg/mL) in healthy individuals. However, IL-6 exhibits a rapid and significant rise during the early stages of bacterial infection. Compared with PCT and CRP, IL-6 shows an earlier increase following exposure to bacterial components. Additionally, IL-6 demonstrates superior sensitivity and specificity compared with other biomarkers for the early diagnosis of sepsis.[8,9]

The current study sought to ascertain the efficacy of serum IL-6 as a diagnostic marker in predicting bacteremia among patients with sepsis, compare the performance of IL-6 with other biomarkers such as PCT, CRP, and serum lactate; and determine the association of serum IL-6 with sepsis severity and associated clinical outcomes.

Materials and Methods

Study Design

A prospective observational study was conducted in the Department of Medicine at a 2030-bed teaching hospital in Karnataka, India from January 2019 to April 2020. Before enrolling patients, Institutional Ethics Committee (IEC) approval (Reference No. IEC 538/2018) was obtained and informed consent was taken from the patients' families.

Study Population

All patients aged ≥18 years, admitted to the hospital with a clinical suspicion of sepsis, determined through the application of the quick sequential organ failure assessment (q-SOFA) scoring system, were selected in the study. Patients with fungemia, primary heart failure, HIV infection, malignancies, and those receiving chemotherapy were excluded from the study.

The sample size requisite for the study was computed by ascertaining the area under the receiver operating characteristic (ROC) curve for the assessment of the diagnostic capability of IL-6. The sample size (n) was derived using the formula, $n= Z^2_{1-\alpha/2}$ *var (AUC)/d^2, where $Z_{1-\alpha/2}$ is 1.96 at 95% confidence level (CI), d is 0.075, absolute precision for AUC and var (AUC) represents the variance of the AUC. Assuming the AUC for IL-6 to be at least 86.8 with 10% precision and a 95% confidence interval, the sample size needed was 50 in each group.

Data Collection

The patients who met the criteria for sepsis upon admission were included. Patient data were documented using a predefined form that included demographic characteristics, comorbidities, reason for hospitalization, vital signs, source of infection, duration of intensive care unit (ICU) stay, need for mechanical ventilation, SOFA score, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score. Vital signs, scoring system results, and laboratory parameters were recorded within the first 24 hours following admission to the ICU. Since this study was purely observational, the treating physician was responsible for making decisions regarding patient management and antimicrobial therapy, without any involvement from the study investigators. The outcome was assessed by observing the patient's clinical course during the hospital stay and noting their condition at the time of discharge (survivors/nonsurvivors).

Definitions

The q-SOFA score is a rapid bedside screening tool that identifies patients with suspected infections who are more likely to develop unfavorable outcomes outside of the ICU. The scoring system is designed with a range from 0 to 3, where three specific components are assigned one point each: altered mental status (Glasgow coma scale score <15), respiratory rate of ≥22 breaths per minute, or systolic blood pressure of ≤100 mm Hg.[2] Organ dysfunction was defined as a q-SOFA score of 2 or above.[2] Bacteremia was defined as the growth of bacteria on blood culture. Sepsis was defined as a life-threatening organ dysfunction resulting from a dysregulated host response to infection. Septic shock was defined clinically as sepsis with hypotension persisting despite adequate fluid resuscitation, and the requirement of vasopressors to maintain a mean arterial pressure (MAP) > 65 mm Hg accompanied by serum lactate level exceeding 2 mmol/L (18 mg/dL) indicating impaired tissue perfusion.[2] The SOFA and APACHE II scores were used to determine sepsis severity.[2,10]

Laboratory Analysis

Paired blood cultures were obtained and blood samples to measure levels of CRP, PCT, IL-6, and serum lactate were collected within 12 hours of ICU admission. The serum IL-6 level was measured by electrochemiluminescence Immunoassay (ECLIA). The measuring range of serum IL-6 is 1.5–5000 pg/mL. Values that fall below the lower limit of detection are reported as <1.5 pg/mL.

The serum procalcitonin concentration was quantified using TRACE (time-resolved amplified cryptate emission) technology using BRAHMS Kryptor. The measuring range of serum PCT is 0.02–100 ng/mL. The value <0.5 ng/mL indicates a reduced likelihood of sepsis and or/septic shock. C-reactive protein level was estimated via immunoturbidimetric assay using Roche/Hitachi Cobas c systems.

Routine laboratory and radiographic findings were obtained, such as complete blood counts, kidney function tests, liver function tests, serum electrolytes, coagulation parameters, arterial blood gas analysis, chest X-ray, and abdominal ultrasonography.

Statistical Analysis

Categorical variables were summarized using percentage and frequency, while continuous variables were represented as mean ± SD or median (IQR), as applicable. The Chi-square test was utilized to ascertain the relationship between two categorical variables. Furthermore, the Mann–Whitney *U* test was used to compare differences between numerical data sets. The ROC curve was used to determine the optimal cut-off value of IL-6 for predicting bacteremia, sepsis severity, and clinical outcomes, as well as sensitivity and specificity. The AUC determines the ability of a parameter to distinguish between two diagnostic groups. The AUC ranges were defined as failing (0.50–0.60), poor (0.60–0.70), fair (0.70–0.80), good (0.80–0.90), and excellent (0.90–1). *P*-value was considered to be statistically significant if <0.05. After identifying significant variables through the univariate analysis, they were incorporated into a multivariable logistic regression model to evaluate their combined effect in predicting bacteremia, sepsis severity, and clinical outcome. SPSS 20 software (IBM SPSS statistics, USA) was used to generate descriptive and inferential statistics.

Results

A total of 118 patients who were admitted to the medical ICU with the clinical suspicion of sepsis identified by q-SOFA score were evaluated throughout the study. Among these patients, 10 of them were excluded from the study due to leukemia, cardiac failure secondary to pulmonary edema, retroviral infection, and patients on chemotherapy. Of 108 patients, 60 (55.6%) had bacteremia, and the remaining 48 (44.4%) were nonbacteremic patients. Of 60 (55.6%) patients within the bacteremic group, 13 (21.6%) had sepsis and 47 (78.3%) had septic shock. Among 48 (44.4%) nonbacteremic patients, sepsis was noted in 20 (41.7%) and septic shock in 28 (58.3%) patients (Fig. 1).

Table 1 depicts the demographic and clinical characteristics of the patients included in the study. The mean age of the patients was 56.9 ± 16.7 years. However, age did not show statistical significance in determining bacteremia among septic patients. The gender distribution was 55% (60) male and 45% (48) female, with a male-to-female ratio of 1.25:1 with a statistically significant difference in determining bacteremia ($p = 0.044$). The most common underlying comorbidities were diabetes mellitus ($n = 64$, 60%) and chronic liver disease ($n = 20$, 18%).

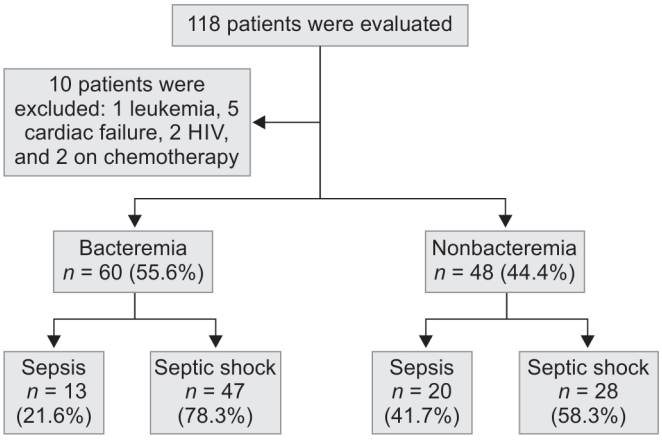

Fig. 1: Flowchart of enrolled patients

Site of Infections

The distribution of sites of infection was as follows: respiratory tract (54, 49.5%), hepatobiliary system (10, 9.3%), genitourinary system (10, 9.3%), central nervous system (9, 8.4%), skin and soft tissue infection (2, 1.8%), gastrointestinal tract (5, 4.6%), and bone and joint infection (1, 0.9%). The infection source was unknown in 17 (15.8%) patients.

Distribution of Microorganisms

Out of the 60 subjects, blood cultures yielded positive results in 43 cases (71.7%) for gram-negative bacteria and in 17 cases (28.3%) for gram-positive bacteria. The isolated microorganisms from the blood cultures included *Escherichia coli* ($n = 24$, 40%), *Klebsiella* spp ($n = 10$, 16.7%), *Pseudomonas aeruginosa* ($n = 3$, 5%), *Acinetobacter baumannii* ($n = 5$, 8.3%) and *Burkholderia pseudomallei* ($n = 1$, 1.6%). Among the gram-positive organisms, the most common were *Enterococcus* spp ($n = 5$, 8.3%) and methicillin-resistant *Staphylococcus aureus* (MRSA) ($n = 5$, 8.3%), followed by methicillin-sensitive *S. aureus* (MSSA) ($n = 4$, 6.7%) and *Streptococcus pneumoniae* ($n = 3$, 5%).

Diagnostic and Prognostic Significance of Serum IL-6 Levels

The median (IQR) values of IL-6 between the groups with bacteremia and without bacteremia did not show a notable difference. However,

Table 1: Baseline characterization of the study population

Variables	*Bacteremic group n = 60 (55.6%)*	*Nonbacteremic group n = 48 (44.4%)*	*p-value*
Age			
>60 years	30 (27.7%)	15 (13.8%)	0.2
<60 years	30 (27.7%)	33 (30.5%)	
Sex			
Male	38 (35%)	22 (20%)	**0.044***
Female	22 (20%)	26 (25%)	
Severity of sepsis			
Sepsis	13 (21.6%)	20 (41.7%)	**0.025***
Septic shock	47 (78.3%)	28 (58.3%)	
Laboratory findings			
IL-6	205 (60.75–943.75)	204 (57.75–1062.25)	0.884
PCT	2.43 (0.53-14.93)	2.80 (0.40–11.0)	0.695
CRP	134.57 (64.63–263.96)	70.95 (15.25–168.75)	**0.008***
Lactate	23.05 (14.13–36.18)	21.40 (15.55–41.75)	0.783
SOFA score	8 (5.0–11.75)	7 (3.0–11.0)	0.145
APACHE II score	19 (13.0–24.0)	13.5 (9.0–21.75)	**0.024***
Mechanical ventilation	41 (68.3%)	27 (56.3%)	0.196
Length of ICU stay	6 (2–9.75)	2.5 (1.0–6.75)	**0.003***
Mortality	17 (28.3%)	14 (29.2%)	–

APACHE, acute physiology and chronic health evaluation; CRP, C-reactive protein; IL-6, interleukin 6; ICU, intensive care unit; PCT, procalcitonin; SOFA, sequential organ failure assessment; *The values in bold imply statistical significance ($p < 0.05$)

Table 2: Diagnostic and prognostic value of IL-16 and comparing IL-6 with other biomarkers and severity score

Variables	*Bacteremia n = 60*	*Nonbacteremia n = 48*	*Sepsis n = 33*	*Septic shock n = 75*	*Survivors n = 77*	*Nonsurvivors n = 31*
IL-6 (pg/mL) [median (IQR)]	205 (60.75–943.75)	204 (57.75–1062.25)	101 (28.50–204.00)	461 (77.00–1207.00)	112 (37.50–351.50)	294 (138.00–1079.00)
	$p = 0.884$		$p <$ **0.001***		$p =$ **0.002***	
PCT (ng/mL) [median (IQR)]	2.43 (0.53–14.93)	2.80 (0.40–11.0)	0.5 (0.20–2.70)	5.4 (1.32–35.53)	1.5 (0.30–9.30)	2.6 (0.90–18.0)
	$p = 0.695$		$p <$ **0.001***		$p =$ **0.045***	
CRP (mg/L) [median (IQR)]	134.57 (64.63–263.96)	70.95 (15.25–168.75)	77 (21.54–171.50)	103 (53.30–264.28)	77 (31.50–193.50)	100 (42.0–156.0)
	$p =$ **0.008***		$p = 0.071$		$p = 0.807$	
Lactate (mg/dL) [median (IQR)]	23.05 (14.13–36.18)	21.40 (15.55–41.75)	15.7 (12.95–24.15)	26.2 (18.00–47.00)	18.7 (13.85–27.80)	31 (18.60–56.0)
	$p = 0.783$		$p <$ **0.001***		$p =$ **0.003***	
SOFA score [median (IQR)]	8 (5.0–11.75)	7 (3.0–11.0)	3 (2.0–3.0)	10 (7.0–12.0)	4 (2.5–7)	10 (8–13)
	$p = 0.145$		$p <$ **0.001***		$p <$ **0.001***	
APACHE II [median (IQR)]	19 (13.0–24.0)	13.5 (9.0–21.75)	9 (5.5–13.0)	20 (14.0–25.0)	11 (6.5–15)	23 (13–20)
	$p =$ **0.024***		$p <$ **0.001***		$p <$ **0.001***	

*The values in bold imply statistical significance ($p < 0.05$); APACHE, acute physiology and chronic health evaluation; CRP, C-reactive protein, IQR, interquartile range; PCT, procalcitonin, SOFA, sequential organ failure assessment

Table 3: Comparing IL-6 with other biomarkers with respect to area under the curve

Variables	*AUC (95% CI)*	*Cut-off value*	*Sensitivity*	*Specificity*	*p-value*
IL-6 (pg/mL)					
Bacteremia	0.512 (0.400–0.623)	233	50%	54%	0.838
Sepsis severity	0.724 (0.625–0.823)	145	66%	67%	<**0.001***
Outcome	0.704 (0.592–0.817)	176	71%	68%	**0.002***
PCT (ng/mL)					
Bacteremia	0.522 (0.410–0.634)	2.33	51%	43%	0.695
Sepsis severity	0.771 (0.679–0.863)	1.8	70%	67%	<**0.001***
Outcome	0.632 (0.513–0.751)	1.8	58%	55%	**0.045***
CRP (mg/L)					
Bacteremia	0.632 (0.524–0.739)	99	60%	58%	**0.02***
Sepsis severity	0.614 (0.503–0.726)	99	55%	55%	0.059
Outcome	0.508 (0.381–0.634)	99	51%	55%	0.908
Lactate (mg/dL)					
Bacteremia	0.493 (0.382–0.605)	21.4	51%	52%	0.908
Sepsis severity	0.715 (0.615–0.815)	18.9	66%	67%	<**0.001***
Outcome	0.692 (0.517–0.812)	24.9	61.3%	66%	**0.004***

*The values in bold imply statistical significance ($p < 0.05$); AUC, area under the curve; CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin

median values of IL-6 in the septic shock group [461 pg/mL (77.00–1207.00)] were higher than in the sepsis group [101 pg/mL (28.50–204.00)], this difference was statistically significant ($p < 0.001$). Likewise, as depicted in Table 2, the median IL-6 values between nonsurvivors 294 pg/mL (138.00–1079.00) and survivors 112 pg/mL (37.50–351.50) ($p = 0.002$) showed a significant difference.

Analyzing the predictive performance for bacteremia using interleukin -6 (IL-6), the AUC was determined to be 0.512 (95% CI, 0.400-0.623; $p = 0.838$) at a discriminative cut-off point of 223 pg/mL. Employing the ROC curve at the cut-off point of 233 pg/mL, IL-6 yielded 50% sensitivity and 54% specificity, which was not statistically significant in predicting bacteremia.

The AUC for IL-6 to differentiate between sepsis and septic shock was 0.724 (95% CI, 0.625–0.823; $p < 0.001$). At a threshold of 145 pg/mL for IL-6, the ROC curve exhibited a sensitivity and specificity of 66% and 67%, respectively, representing a notable, statistically significant finding. Additionally, a cut-off point of 176 pg/mL for IL-6 in forecasting mortality was identified, which demonstrated a sensitivity and specificity of 71% and 68%, respectively. Table 3 and Figure 2 depict these results were also statistically significant ($p = 0.002$).

Comparing IL-6 with Other Biomarkers and Scoring Systems in Predicting Bacteremia, Sepsis Severity, and Clinical Outcome

When IL-6 was compared with other biomarkers, there was a significant difference in the CRP levels in identifying bacteremia ($p = 0.008$). Similarly, a notable difference in the APACHE II score

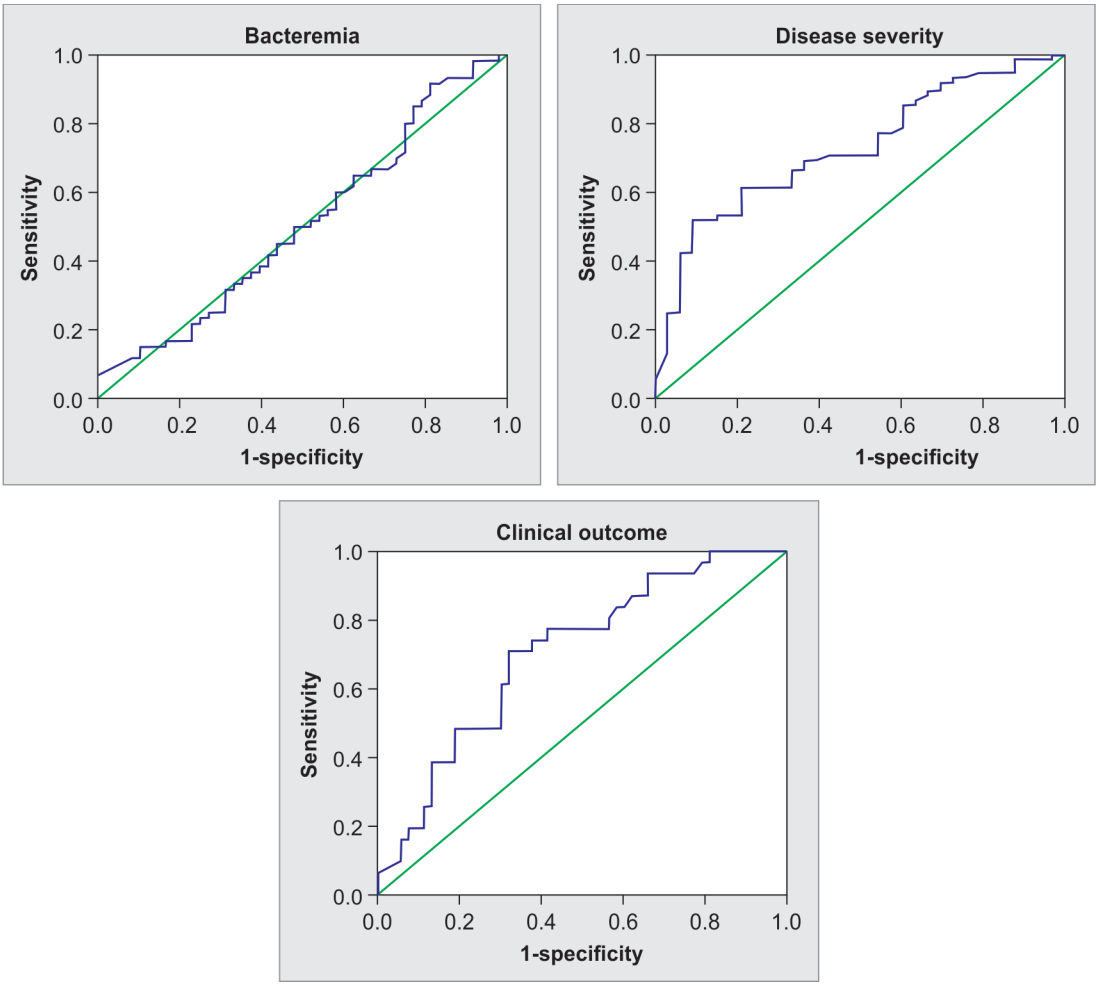

Fig. 2: Receiver operating characteristic curves analysis for cut-off levels of IL-6 in predicting bacteremia, severity of sepsis and clinical outcome

was observed between the cases with and without bacteremia ($p = 0.024$) as detailed in Table 2. In predicting bacteremia, the AUC value for CRP was reported as 0.632 (95% CI, 0.524-0.739) with a CRP cut-off value of 99 mg/dL. With a cut-off point of 99 mg/dL for CRP, the ROC curve indicated that the sensitivity was 60% and the specificity was 58%. These findings were statistically significant ($p = 0.02$), as presented in Table 3 and Figure 3.

Significant differences were found in IL-6, PCT, lactate levels, APACHE II, and, SOFA scores when compared with other factors in determining the severity of sepsis (Table 2). The AUC values for IL-6, PCT, and lactate were 0.724 (95% CI, 0.625–0.823; $p < 0.001$), 0.771 (95% CI, 0.679–0.863; $p < 0.001$), and 0.715 (95% CI, 0.615–0.815; $p < 0.001$), respectively, to distinguish sepsis from septic shock. The study defined the optimal cut-off values for differentiating sepsis from septic shock as being 145 pg/mL for IL-6 (with a sensitivity of 66% and specificity of 67%), 1.8 ng/mL for PCT (with a sensitivity of 70% and specificity of 67%), and 18.9 mg/dL for lactate (with a sensitivity of 66% and specificity of 67%) (Table 3 and Fig. 3).

The mortality rate in this study was 28.7% ($n = 31$). Table 2 presents a significant difference in the levels of IL-6, PCT, and lactate, as well as APACHE II and SOFA scores between survivors and nonsurvivors. These biomarkers and clinical scores were compared with other factors to assess clinical outcomes, and they were found to be statistically relevant predictors of survival. The optimal cut-off values for predicting mortality were determined as 176 pg/mL for IL-6 (71% sensitivity and 68% specificity), 1.8 ng/mL for PCT (58% sensitivity and 55% specificity), and 24.9 mg/dL for lactate (61.3% sensitivity and 66% specificity). The AUC values for IL-6 were 0.704 (95% CI, 0.592-0.817; $p = 0.002$), 0.632 for PCT (95% CI, 0.513–0.751; $p = 0.045$), and 0.692 for lactate (95% CI, 0.517-0.812; $p = 0.004$) (see Table 3 and Fig. 3).

C-reactive protein levels and APACHE II scores were found to be significant predictors of bacteremia in the univariate analysis. The multivariate analysis reinforced that CRP (OR, 1.004; 95% CI, 1.000–1.009; $p = 0.04$) and APACHE-2 score (OR, 1.089; 95% CI, 1.011-1.173; $p = 0.025$) are significant predictive factors. In terms of sepsis severity, the univariate analysis identified lactate, PCT, IL-6, and APACHE II scores as significant factors. However, in the multivariate analysis, only lactate (OR, 1.048; 95% CI, 0.999–1.101; $p = 0.04$), and APACHE II score (OR, 1.261; 95% CI, 1.112–1.429; $p < 0.001$) remained significant. The univariate study revealed lactate, PCT, IL-6, APACHE-2 score, and SOFA score as significant outcome predictors. However, only PCT (OR, 0.973; 95% CI, 0.951-0.996; $p = 0.024$), SOFA score (OR, 1.59; 95% CI, 1.184–2.134; $p = 0.002$), and APACHE-II score (OR, 1.269; 95% CI, 1.082–1.488; $p = 0.003$) remained significant in the multivariate analysis (Table 4).

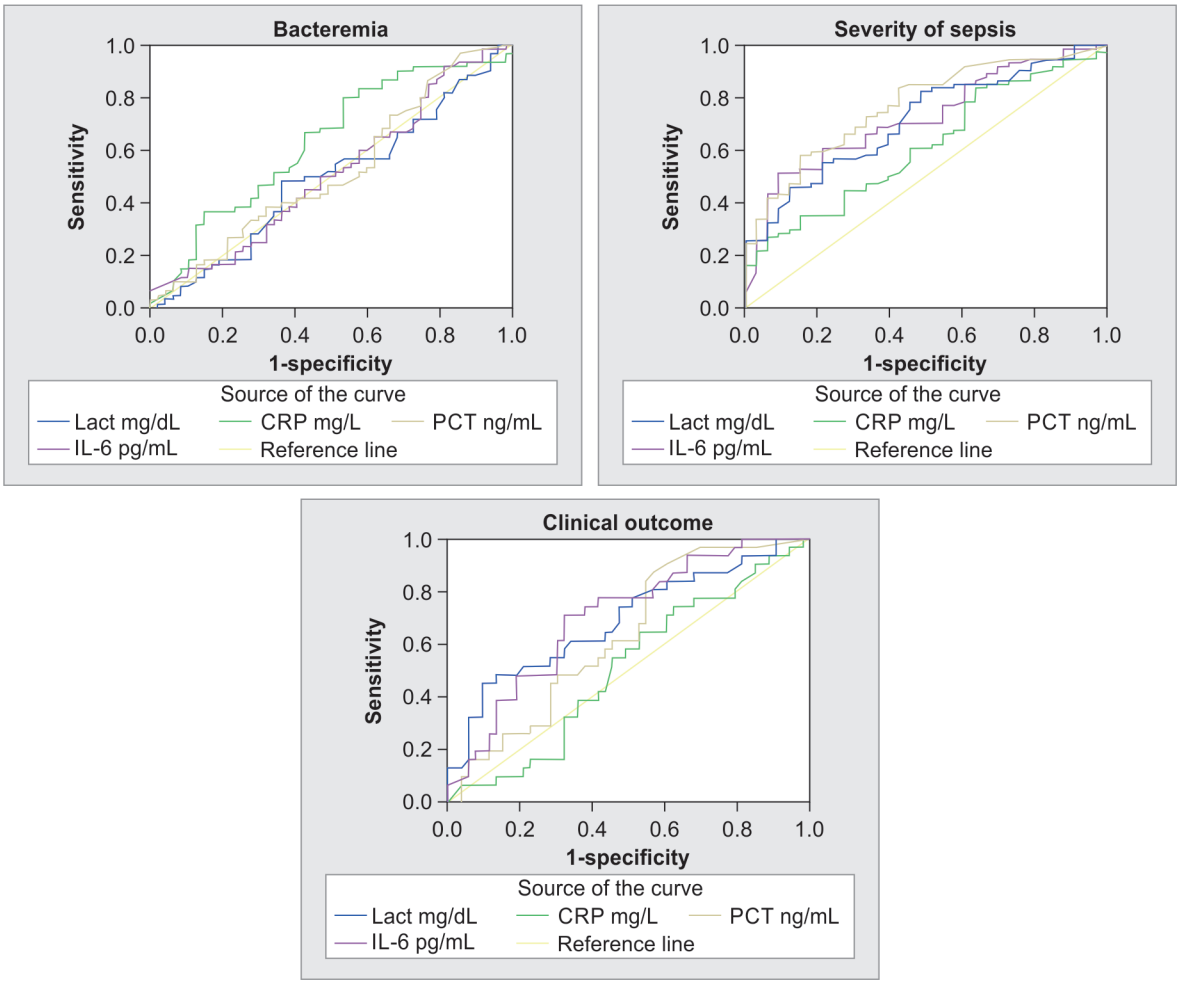

Fig. 3: Receiver operating characteristic curve of biomarkers in predicting bacteremia, severity of sepsis and clinical outcome

Table 4: Univariate and multivariate analysis of factors in predicting bacteremia, sepsis severity and clinical outcome

Variables	*Bacteremia*		*Sepsis severity*		*Outcome*	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Lactate	0.996 (0.983–1.010)	0.992 (0.974–1.011)	1.061 (1.02–1.103)	1.048 (0.999–1.101)	1.034 (1.009–1.059)	1.002 (0.959–1.047)
	$p = 0.783$	$p = 0.493$	$p <$ **0.001***	$p =$ **0.04***	$p =$ **0.003***	$p = 0.931$
CRP	1.004 (1.000–1.007)	1.004 (1.000–1.009)	1.004 (1.000–1.008)	1.004 (0.997–1.011)	0.999 (0.995–1.003)	1.005 (0.997–1.014)
	$p =$ **0.008***	$p =$ **0.04***	$p = 0.07$	$p = 0.234$	$p = 0.807$	$p = 0.240$
PCT	1.003 (0.995–1.012)	0.995 (0.985–1.006)	1.085 (1.013–1.162)	1.059 (0.986–1.137)	1.001 (0.992–1.010)	0.973 (0.951–0.996)
	$p = 0.695$	$p = 0.366$	$p <$ **0.001***	$p = 0.114$	$p =$ **0.045***	$p =$ **0.024***
IL–6	1.000 (1.000–1.000)	1.000 (1.000–1.000)	1.001 (1.000–1.002)	1.000 (0.999–1.001)	1.000 (1.000–1.001)	1.000 (1.000–1.001)
	$p = 0.884$	$p = 0.851$	$p <$ **0.001***	$p = 0.669$	$p =$ **0.002***	$p = 0.612$
SOFA	1.07 (0.979–1.168)	0.956 (0.83–1.06)	–	–	1.473 (1.249–1.738)	1.59 (1.184–2.134)
	$p = 0.145$	$p = 0.521$	–	–	$p <$ **0.001***	$p = 0.002$*
APACHE II	1.053 (1.006–1.103)	1.089 (1.011–1.173)	1.214 (1.119–1.317)	1.261 (1.112–1.429)	1.27 (1.149–1.403)	1.269 (1.082–1.488)
	$p =$ **0.024***	$p =$ **0.025***	$p <$ **0.001***	$p <$ **0.001***	$p <$ **0.001***	$p =$ **0.003***

*The values in bold imply statistical significance ($p < 0.05$); CI, confidence interval; OR, odds ratio

Discussion

Multiorgan dysfunction is the hallmark of sepsis, and it is known that a number of inflammatory markers rise during this process. However, our study focused exclusively on serum IL-6 and compared its performance with that of PCT, CRP, lactate, SOFA, and APACHE II scores in predicting bacteremia, sepsis severity, and patient outcomes.

In a previous study, von Lilienfeld-Toal et al. highlighted the effectiveness of IL-6 as a marker in distinguishing episodes of bacteremia from nonbacteremia. They identified a cut-off level of 297 pg/mL, which demonstrated a sensitivity of 72% and specificity of 62% ($p = 0.016$). It is worth noting that their study involved hematological malignancy patients with febrile neutropenia.[11] In contrast, our findings revealed no significant difference in serum levels of IL-6 in nonbacteremic episodes compared with bacteremic episodes, with a cut-off level of 233 pg/mL yielding 50% sensitivity and 54% specificity ($p = 0.838$). However, it is imperative to note that our study excluded the patients with malignancy as the literature suggests that IL-6 is produced and secreted by inflammatory cells and tumor cells.[12] Previous studies on IL-6 for predicting bacteremia were conducted among children with febrile neutropenia with cancer.[13,14] As a result, we believe additional prospective studies are needed to investigate the diagnostic potential of IL-6 in predicting bacteremia in immunocompetent adults.

Our study observed a significant difference in CRP levels between the bacteremic and nonbacteremic groups in our study, implying that CRP could be a better biomarker in differentiating bacterial from non-bacterial episodes compared with PCT levels, which did not differ significantly between the two groups. Demirdal T et al. study revealed that neither CRP nor PCT proved effective in predicting bacteremia and it also demonstrated that PCT performed better than CRP as biomarker in predicting mortality.[15] In contrast, Diepold et al. observed that IL-6 exhibited the highest sensitivity and specificity (90% and 85% respectively) in predicting bacteremia and severe bacterial infection.[16] Nonetheless, our study demonstrated slightly better sensitivity and specificity for CRP (60% sensitivity and 58% specificity) compared with IL-6. With respect to disease severity scores, it was observed that only APACHE II score showed a significant association with bacteremia in the current study. However, a previous study has found that the SOFA score is a very useful tool in predicting the outcome among septic patients, whereas APACHE II score was not reliable in predicting the mortality rate.[17] However, studies regarding the severity scores and their association with bacteremia are not available till date.

Ideal markers in sepsis should be able to significantly alter the clinical decision-making at the bedside. In individuals with septic shock, IL-6 levels were found to be significantly increased ($p < 0.001$). When applying a cut-off value of 145 pg/mL on the ROC curve, IL-6 demonstrated 66% sensitivity and 67% specificity. However, in the current study, IL-6 was not identified as an independent marker for predicting sepsis severity. Previous studies have indicated that among various markers such as CRP, PCT, and IL-6, IL-6 exhibited enhanced diagnostic efficacy in identifying infections among patients with organ dysfunction and septic shock.[18–20] In contrast, the present study revealed that serum lactate, reflecting hypoperfusion, especially in critically ill patients, served as an independent and effective marker for determining sepsis severity ($p = 0.04$). A study by Kibe et al. demonstrated that PCT outperformed IL-6, CRP, lactate, and other conventional markers like white blood cell (WBC) counts in determining sepsis severity; however, based on existing data, it lacks the accuracy to be used without clinical judgment.[21] Another study reported that while CRP and IL-6 seemed more effective than PCT as markers for the diagnosis of infection and sepsis, PCT demonstrated greater superiority in determining the severity of sepsis.[22] These discrepancies among studies could be attributed to variations in study settings, varying levels of severity, or divergent definitions of sepsis within the study population.

IL-6 has been identified as the foremost inflammatory biomarker for predicting clinical outcomes, according to several studies, and have independently demonstrated its predictive ability for in-hospital mortality.[23,24] In our study, we found that nonsurvivors had higher levels of IL-6, PCT, and lactate, which had a significant association with clinical outcomes. However, when multivariate analysis was performed, only PCT levels were identified as an independent predictor for sepsis-related mortality. In contrast to our study, another study revealed that IL-6 and lactate levels were independent predictors of mortality compared with PCT and CRP.[20] Some studies have indicated that PCT has a higher diagnostic efficacy than IL-6, CRP, and lactate in diagnosing sepsis severity as well as septic shock. The argument is that levels of PCT of survivors do not differ substantially from nonsurvivors, thus questioning the prognostic value of PCT.[25–28] Therefore, PCT should be considered as a supplementary tool in treating sepsis rather than in confirming the presence of infection or prognostication.

It has been emphasized that serial measurement of biomarkers will help to predict the outcome better than a single value, as there will be a likely change in the clinical course of patients during hospital stay due to nosocomial infections and other comorbidities.[29] In addition, SOFA and APACHE II showed a significant association with clinical outcomes in our study. The SOFA and APACHE II scores showed comparable results with another study in the determination of clinical outcomes, and there was no substantial difference between the two in terms of predicting mortality. However, both the scoring systems are did not show any utility in predicting bacteremia.[23]

Limitations

One limitation of the study was that it was carried out in a single center. Secondly, the patients included were in different stages of sepsis, including a few being referred from other hospitals as ours is a tertiary referral hospital. Further, some patients referred to our center might have received prior antibiotics, fluids, or vasopressors. Hence, the results of our study might be different in comparison with other studies. Heterogeneity in the characteristics and comorbidities among the study population as well as measurement of IL-6 only once within 12 hours of admission constitute the other limitations of the study.

Conclusion

Although IL-6 did not predict bacteremia in our study, IL-6 was shown to be effective in evaluating sepsis severity and clinical outcome. In the multivariate analysis, however, CRP was a better marker for predicting bacteremia rather than for assessing the magnitude of sepsis and outcome. Although IL-6 levels showed a significant increase as sepsis became more severe, lactate levels and APACHE II score emerged as independent predictors for sepsis severity. PCT, SOFA, and APACHE II scores were better predictors of mortality when compared with IL-6. The efficacy of IL-6 as a diagnostic marker in predicting bacterial sepsis would need to be assessed by future systematic multicenter studies with large sample sizes. A single biomarker cannot be used as the sole diagnostic parameter. Clinical judgment, combined with the use of biomarkers, will be more effective in treating sepsis and limiting mortality.

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Authors' Contributions

PR and CK: Contributions to the conception of the work. PR and CK: Involved in the design of the work. PR, CK, and VE: Carried out the acquisition of data. PR, CK, and MC: Contributed to the analysis of data. PR, CK, VE, and KP: Involved in the interpretation of data. PR, CK, MC, and KP: Prepared the draft manuscript. PR, CK, MC ,VE, and KP: Contributed to the revision of the manuscript.

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References

1. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, et al. International Forum of Acute Care Trialists. Assessment of global incidence and mortality of hospital-treated sepsis. current estimates and limitations. Am J Respir Crit Care Med 2016;193(3):259–272. DOI: 10.1164/rccm.201504-0781OC.
2. Singer M, Deutschman CS, Seymour CW, Shnkar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8):801–810. DOI: 10.1001/jama.2016.0287.
3. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017;43(3):304–377. DOI: 10.1007/s00134-017-4683-6.
4. Vazquez-Grande G, Kumar A. Optimizing antimicrobial therapy of sepsis and septic shock: Focus on antibiotic combination therapy. Semin Respir Crit Care Med 2015;36:154–166. DOI: 10.1055/s-0034-1398742.
5. Molano Franco D, Arevalo-Rodriguez I, Roqué I Figuls M, Zamora J. Interleukin-6 for diagnosis of sepsis in critically ill adult patients. Cochrane Database of Syst Rev 2015;7:CD011811. DOI: 10.1002/14651858.
6. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis; A systematic review and meta-analysis. Lancet Infect Dis 2013;13(5):426–435. DOI: 10.1016/S1473-3099(12)70323-7.
7. Dahaba AA, Metzler H. Procalcitonin's role in the sepsis cascade. Is procalcitonin a sepsis marker or mediator? Minerva Anestesiol 2009;75:447–452. Corpus ID: 39501458.
8. Wu Y, Wang M, Zhu Y, Lin S. Serum interleukin-6 in the diagnosis of bacterial infection in cirrhotic patients: A meta-analysis. Medicine (Baltimore) 2016;95(41):e5127. DOI: 10.1097/MD.0000000000005127.
9. Lin S, Huang Z, Wang M, Weng Z, Zeng D, Zhang Y, et al. Interleukin-6 as an early diagnostic marker for bacterial sepsis in patients with liver cirrhosis. J Crit Care 2015;30:732–738. DOI: 10.1016/j.jcrc.2015.03.031.
10. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease Classification system. Crit Care Med 1985;13(10):818–829. DOI: 10.1097/00003465-198603000-00013.
11. von Lilienfeld-Toal M, Dietrich MP, Glasmacher A, Lehmann L, Breig P, Hahn C, et al. Markers of bacteremia in febrile neutropenic patients with hematological malignancies: Procalcitonin and IL-6 are more reliable than C-reactive protein. Eur J Clin Microbiol Infect Dis 2004;23(7):539–544. DOI: 10.1590/S1807-59322011001000006.
12. Kumari N, Dwarakanath BS, Das A, Bhatt AN. Role of interleukin-6 in cancer progression and therapeutic resistance. Tumour Biol 2016;37(9):11553-11572. DOI: 10.1007/s13277-016-5098-7.
13. Sahbudak Bal Z, Karadaş Özdemir N, Şen S, Yılmaz Karapınar D, Azarsız E, Aydemir Ş, et al. Diagnostic accuracy of interleukin-6, interleukin-8, and interleukin-10 for predicting bacteremia in children with febrile neutropenia. Turk J Haematol 2017;34(3):254–257. DOI: 10.4274/tjh.2016.0434.
14. Urbonas V, Eidukaitė A, Tamulienė I. The diagnostic value of interleukin-6 and interleukin-8 for early prediction of bacteremia and sepsis in children with febrile neutropenia and cancer. J Pediatr Hematol Oncol 2012;34(2):122–127. DOI: 10.1097/MPH.0b013e3182446a60.
15. Demirdal T, Sen P, Nemli SA. Diagnostic value of procalcitonin in predicting bacteremia in intensive care unit. Indian J Crit Care Med 2018;22(2):78–84. DOI: 10.4103/ijccm.IJCCM_437_17.
16. Diepold M, Noellke P, Duffner U, Kontny U, Berner R. Performance of Interleukin-6 and Interleukin-8 serum levels in pediatric oncology patients with neutropenia and fever for the assessment of low-risk. BMC Infect Dis 2008;8:28. DOI: 10.1186/1471-2334-8-28.
17. Desai S, Lakhani JD. Utility of SOFA and APACHE II score in sepsis in rural set up MICU. J Assoc Physicians India 2013;61(9):608–611.
18. Takahasi W, Nakada TA, Yazaki M, Oda S. Interleukin-6 levels act as a diagnostic marker in patients with organ dysfunction in intensive care units. Shock 2016;46(3):254–260. DOI: 10.1097/SHK.0000000000000616.
19. Behnes M, Bertsch T, Lepiorz D, Lang S, Trinkmann F, Brueckmann M, et al. Diagnostic and prognostic utility of soluble CD 14 subtype (presepsin) for severe sepsis and septic shock during the first week of intensive care treatment. Crit Care 2014;18(5):507. DOI: 10.1186/s13054-014-0507-z.
20. Song J, Park DW, Moon S, Cho HJ, Park JH, Seok H, et al. Diagnostic and prognostic value of interleukin-6, pentraxin 3, and procalcitonin levels among sepsis and septic shock patients: A prospective controlled study according to the Sepsis-3 definitions. BMC Infect Dis 2019;19(1):968. DOI: 10.1186/s12879-019-4618-7.
21. Kibe S, Adams K, Barlow G. Diagnostic and prognostic biomarkers of sepsis in critical care. J Antimicrob Chemother 2011;66(Suppl 2):ii33–40. DOI: 10.1093/jac/dkq523.
22. Gaïni S, Koldkjaer OG, Pedersen C, Pedersen SS. Procalcitonin, lipopolysaccharide-binding protein, interleukin-6 and C-reactive protein in community-acquired infections and sepsis: A prospective study. Crit Care 2006;10(2):R53. DOI: 10.1186/cc4866.
23. Jekarl DW, Lee SY, Lee J, Park YJ, Kim Y, Park JH, et al. Procalcitonin as a diagnostic marker and IL-6 as a prognostic marker for sepsis. Diagn Microbiol Infect Dis 2013;75(4):342–347. DOI: 10.1016/j.diagmicrobio.2012.12.011.
24. Miguel-Bayarri V, Casanoves-Laparra EB, Pallás-Beneyto L, Sancho-Chinesta S, Martín-Osorio LF, Tormo-Calandín C, et al. Prognostic value of the biomarkers procalcitonin, interleukin-6 and C-reactive protein in severe sepsis. Med Intensiva 2012;36(8):556–562. DOI: 10.1016/j.medin.2012.01.014.
25. Mustafić S, Brkić S, Prnjavorac B, Sinanović A, Porobić Jahić H, Salkić S. Diagnostic and prognostic value of procalcitonin in patients with sepsis. Med Glas (Zenica) 2018;15(2):93–100. DOI: 10.17392/963-18.
26. Gao L, Yang B, Zhang H, Ou Q, Lin Y, Zhang M, et al. DcR3, a new biomarker for sepsis, correlates with infection severity and procalcitonin. Oncotarget 2017;9(13):10934–10944. DOI: 10.18632/oncotarget.23736.
27. Yu H, Qi Z, Hang C, Fang Y, Shao R, Li C. Evaluating the value of dynamic procalcitonin and presepsin measurements for patients with severe sepsis. Am J Emerg Med 2017;35(6):835–841. DOI: 10.1016/j.ajem.2017.01.037.
28. Charles PE, Noel R, Massin F, Guy J, Bollaert PE, Quenot JP, et al. Significance of soluble triggering receptor expressed on myeloid cells-1 elevation in patients admitted to the intensive care unit with sepsis. BMC Infect Dis 2016;16(1):559. DOI: 10.1186/s12879-016-1893-4.
29. Gotts JE, Matthay MA. Sepsis: Pathophysiology and clinical management. BMJ 2016;343:1585. DOI: 10.1136/bmj.i1585.