JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Interleukin-6 as a biomarker of sepsis and its clinical utility in predicting mortality: a prospective observational study

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Abstract

Introduction: Majority of patients admitted to intensive care units (ICUs) succumb to sepsis and its complications. However, currently available predictors fail to reliably gauge the severity of organ damage. There is a pressing need to identify biomarkers that can accurately forecast outcomes. Interleukin-6 (IL-6) has emerged as a potential biomarker, with some studies suggesting its utility as an early predictor of multi-organ failure in sepsis. This study evaluated the role of IL-6 in predicting mortality in an Indian ICU setting.

Methodology: This prospective observational study included adult patients diagnosed with sepsis and a quick SOFA score ≥ 2. IL-6 levels, SOFA scores, and other clinical parameters were measured within 24 hours of admission. Univariate and multivariate analyses identified factors associated with mortality.

Results: The overall ICU mortality rate was 39%. Multivariate analyses indicated that IL-6 levels, total SOFA scores, and number of antibiotics used were independently associated with mortality. The IL-6 levels showed strong positive correlations with the total SOFA score ($r = 0.77$, $p < 0.001$) and individual organ dysfunction scores; particularly in cardiovascular ($r = 0.61$, $p < 0.001$), renal ($r = 0.64$, $p < 0.001$), and central nervous system ($r = 0.6$, $p < 0.001$).

Conclusions: IL-6 levels, in combination with SOFA scores, provide a robust predictor of mortality in sepsis patients. The strong correlation between IL-6 levels and organ dysfunction scores suggests its potential as a biomarker for sepsis severity and progression.

Key words: septic shock; septicemia; IL-6; SOFA.

J Infect Dev Ctries 2025; 19(10):1470-1478. doi:10.3855/jidc.20800

(Received 02 September 2024 – Accepted 13 February 2025)

Introduction

Sepsis is defined as "a clinical syndrome with physiologic, biologic, and biochemical abnormalities caused by a dysregulated inflammatory response to infection" [1]. Sepsis and the consequent inflammatory reaction that follows can lead to multi-organ dysfunction syndrome (MODS) and death. Many critically ill patients die of sepsis and its complications. Sepsis is one of the main causes of mortality in patients admitted in the intensive care units (ICUs) of hospitals. It is not possible to conclusively estimate the global burden of sepsis. According to recent estimates, sepsis is a significant global health issue, affecting approximately 49 million people annually and leading to around 11 million deaths worldwide. This accounts for about 20% of all global deaths, making sepsis a critical cause of mortality, particularly in low- and middle-income countries where healthcare resources are limited [2,3]. The introduction of antibiotics about five to six decades ago reduced the mortality to about 30–50%, and further treatment advancements reduced mortality to about 18%. Although, the overall mortality has reduced over time, mortality due to sepsis remains high [4,5].

Excessive generation of humoral mediators (like cytokines), especially interleukin-6 (IL-6), can result in organ dysfunction, increased severity of illness, and further deterioration of critically ill patients. Early identification of sepsis and prompt initiation of treatment would increase the survival rate in critically ill patients [1]. The biomarker IL-6 is the earliest to get elevated in sepsis. Hence, it may be useful in predicting the severity of organ dysfunction. The sequential organ failure assessment (SOFA) score is commonly used for determining the level of organ failure. However, IL-6 levels may be able to predict earlier than the SOFA score [6].

The World Health Organization (WHO) states that

the most common cause of sepsis is pneumonia. There is a 93.4% greater risk of lethal outcomes in patients with pneumonia who have elevated IL-6 levels. When used as a predictor of mortality, the IL-6 level has been shown to have a sensitivity of 84% and specificity of 87% [7,8]. Sepsis biomarkers have a strong potential for increasing the rapidity with which sepsis can be diagnosed and for stratifying the risk.

The need for this study arises from several crucial factors, including the limited data on sepsis outcomes and prognostic factors in the Indian healthcare setting, and the potential synergy between IL-6 levels and SOFA scores in predicting sepsis outcomes [7–12]. This study examined various clinical parameters, comorbidities, and treatment factors alongside IL-6 levels, and aimed to provide a comprehensive analysis of factors influencing sepsis outcomes in the ICU. It also examined the correlation between specific organ dysfunctions and serum IL-6, which could be used as a biomarker to predict the severity or progression of organ failure in patients.

This prospective, observational study aimed to elucidate the role of IL-6 in conjunction with other clinical factors in predicting sepsis outcomes in an Indian ICU setting. The results of this study can be particularly valuable in critical care settings where early identification of organ dysfunction can guide treatment decisions.

Methodology

Study design

This was a prospective, observational, single-center study conducted at a multispecialty hospital in Karnataka, India, over a one-year period. The minimum sample size was calculated assuming a mortality rate of 35% (based on prior studies) and an expected effect size of 0.47, with a power of 80%, and a significance level of 0.05. A minimum sample size of 72 patients was required to detect a statistically significant association between IL-6 levels and mortality outcomes [4,5].

Population selection

The patients were enrolled sequentially upon admission to the ICU until the sample size of 72 was reached. Patients admitted more than once during the study period were included only for their first admission. Patients aged ≥ 18 years, of either gender, admitted to the ICU with a diagnosis of sepsis, and with a quick-SOFA score ≥ 2 [13,14] were included; if they were provided consent to participate. Patients with conditions that can modulate IL-6 levels and confound results were excluded from the study. Patients with immunodeficiency disorders or human immunodeficiency virus (HIV) infection, patients who received blood transfusion in the previous 3 months, patients with a history of immunomodulator or corticosteroid therapy in the previous 6 months, and patients with hematological malignancies were excluded.

Data collection

An initial screening was performed for the patients admitted to the ICU and they were recruited if they met the inclusion criteria. After enrolling the patients, the baseline demographic details, type of infection, comorbidities, duration of ICU stay, antibiotics used, and duration of antibiotics use were recorded. Plasma IL-6 concentrations were quantified using specific sandwich enzyme-linked immunosorbent assays. PaO_2/FiO_2, platelets levels, bilirubin levels, mean arterial pressure, Glasgow coma scale (GCS), and creatinine and urine volume levels were noted to calculate respiratory, coagulation, liver, cardiovascular, central nervous system, and renal dysfunction respectively. The total SOFA score was calculated based on these individual system scores within 24 hours of admission [15]. The patients were followed up till they obtained clinical improvement or death.

Ethical considerations

The study was approved by the institutional ethics committee (approval no: 111-27144-172-214022) prior to commencement. All procedures conformed to the principles of the Declaration of Helsinki. Informed consent was obtained from all subjects before enrolling in the study.

Statistical analyses

Descriptive statistics were used to summarize patient characteristics. Continuous variables were expressed as median with interquartile range (Q1–Q3), and categorical variables are expressed as percentages. The Shapiro-Wilk test was used for checking the normality of the data.

Univariate analysis was performed using Fisher's exact test or Chi-square test for categorical variables, and the Mann-Whitney U test for continuous variables, given the non-normal distribution of the data. Factors found to be clinically and statistically significant in the univariate analysis were included in a multivariate binomial logistic regression model. The model fit was assessed, and a receiver operating characteristic (ROC) curve was generated to evaluate the predictive performance of the model, including sensitivity,

specificity, and area under the curve (AUC).

Correlation analysis was performed using Spearman's correlation coefficient to assess the relationship between IL-6 levels and various clinical parameters, including SOFA scores, number of comorbidities, and the number of antibiotics used.

Statistical significance was set at $p < 0.05$, although some analyses were based on more stringent thresholds ($p < 0.01$, $p < 0.001$) as indicated in the results section.

Results

The study included 72 patients with sepsis admitted to the ICU. The median age of the patients was 70 years (Q1–Q3: 58–76), with 56% male and 44% female participants. The primary reasons for ICU admission were severe infections other than respiratory (47%), mixed infections (25%), pneumonia (22%), and other infections (6%).

Comorbidities were common among the patients, and cardiovascular disease (88%) and diabetes mellitus (79%) were the most prevalent. The median number of comorbidities was 2 (Q1–Q3: 2–2). The median duration of ICU stay was 8 days (Q1–Q3: 5–13), and the median number of antibiotics used was 2 (Q1–Q3: 1–2).

The median total SOFA score was 10 (Q1–Q3: 4.75–15), and the median IL-6 level was 395.20 pg/mL (Q1–Q3: 162.5–1152.5). The overall mortality rate in the ICU was 39% (Table 1).

A univariate analysis using Man Whitney U test and Fisher's exact test was performed since the data were not normally distributed, as evidenced by the Shapiro-wilk normality test. Figures 1 and 2 represent the results of the univariate analysis. Among all the factors that were analyzed, the total SOFA score, individual system score components, IL-6 levels, number of comorbidities, antibiotic use, and presence of chronic kidney disease (CKD) were significantly different between the patients who improved and those who died.

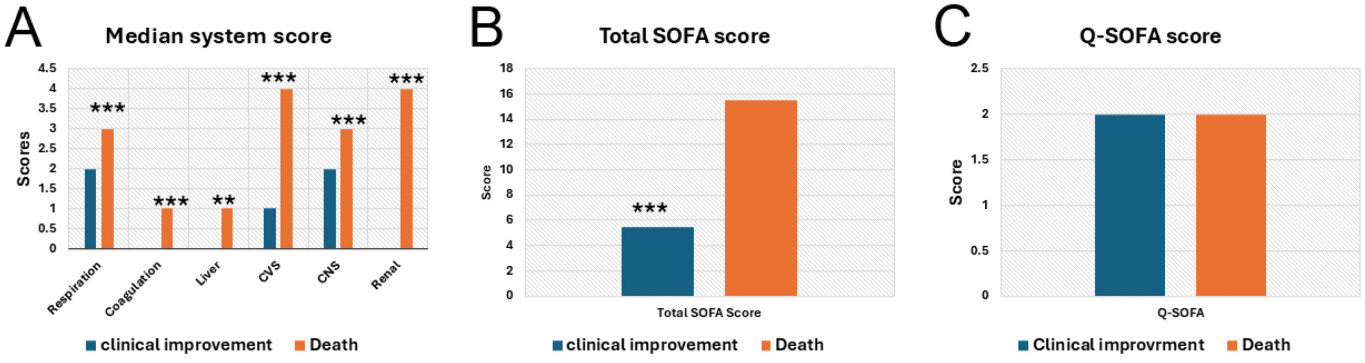
Table 1. Characteristics of patients admitted to the intensive care unit (ICU).

Characteristic	N (%), median (Q3, Q1)
Median age (Q3, Q1), years	70 (76, 58)
Gender (%)	
Male	56%
Female	44%
Reason for ICU admission (%)	
Severe infection other than respiratory infection	47%
Pneumonia	22%
Mixed infection	25%
Other infection	6%
Comorbidities (%)	
Diabetes mellitus	79%
Cardiovascular disease	88%
Chronic kidney disease	22%
Chronic liver disease	8%
Others	10%
Median number of comorbidities (Q3, Q1)	2 (2, 2)
Median duration of ICU stay (Q3, Q1)	8 (13, 5)
Median number of antibiotics (Q3, Q1)	2 (2, 1)
Antibiotics received before admission to ICU (%)	24%
Q-SOFA score (Q3, Q1)	2 (3, 2)
SOFA score; median (Q3, Q1)	
Respiratory system	3 (3, 1.75)
Coagulation	0 (1, 0)
Liver	0 (1, 0)
CVS	3 (4, 1)
CNS	2 (3, 1)
Renal	0 (4, 0)
Median total SOFA score (Q3, Q1)	10 (15, 4.75)
Outcome (%)	
Mortality	39%
Clinical outcome	61%
Median IL6 level (Q3, Q1)	395.20 (1152.5, 162.5)

SOFA: sequential organ failure assessment; CVS: cardiovascular system; CNS: central nervous system.

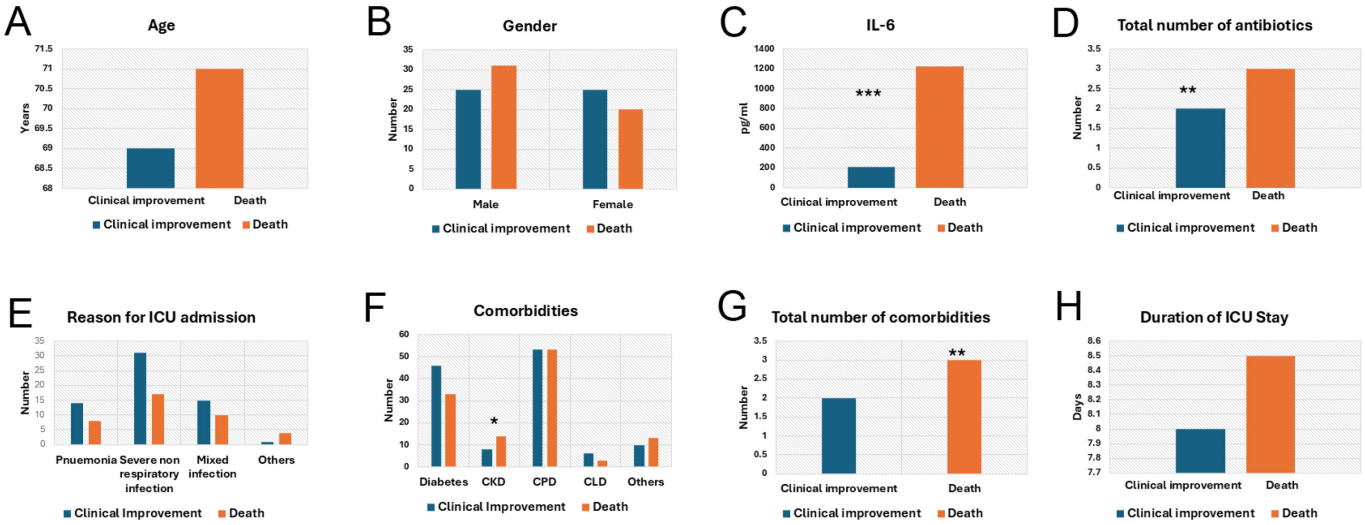
A multivariate analysis using binomial logistic regression was performed based on the results of univariate analysis. Clinically and statistically significant factors, including total SOFA score, IL-6 levels, total number of comorbidities, and total number

Figure 1. Relationship between different SOFA scores and mortality in the ICU.



A: Median difference in system sub score of SOFA; **B:** Median difference in total SOFA score; **C:** Median changes in Q-SOFA score. *$p = 0.05$; **$p = 0.01$; ***$p = 0.001$. SOFA: sequential organ failure assessment; ICU: intensive care unit; CVS: cardiovascular system; CNS: central nervous system.

Figure 2. Univariate analysis of factors affecting mortality in ICU.



A: Difference in age; **B:** Gender; **C:** IL6; **D:** Total number of antibiotics; **E:** Reason for ICU admission; **F:** Comorbidities; **G:** Total number of comorbidities; **H:** Duration of ICU stay; among patients with clinical improvement and mortality. *p = 0.05; **p = 0.01; ***p = 0.001. ICU: intensive care unit; CKD: chronic kidney disease; CPD: continuous peritoneal dialysis; CLD: chronic liver disease.

of antibiotics received, were included in the multivariate analysis.

The multivariate analysis indicated that the total SOFA score, total number of antibiotics, and IL-6 levels were independently associated with mortality when adjusted for other factors (Figure 3, Table 2). The IL-6 levels had the strongest association with the outcome; a unit increase in IL-6 levels was associated with a 28.02-fold increase in the odds of mortality (CI: 21.45–36.59). This was followed by the number of antibiotics (odds ratio: 4.08, CI: 2.53–6.58) and the SOFA score, with a statistically significant odds ratio of 1.42 and CI of 1.02–1.97; indicating that each unit increase in the SOFA score corresponded to a 42% increase in the odds of mortality. The total number of comorbidities, although included in the model, did not show a significant independent association in this multivariate analysis (odds ratio: 0.95, CI: 0.83–1.02). The high AUC value, along with good sensitivity and specificity, suggested that this combination of factors was highly effective in predicting the outcome.

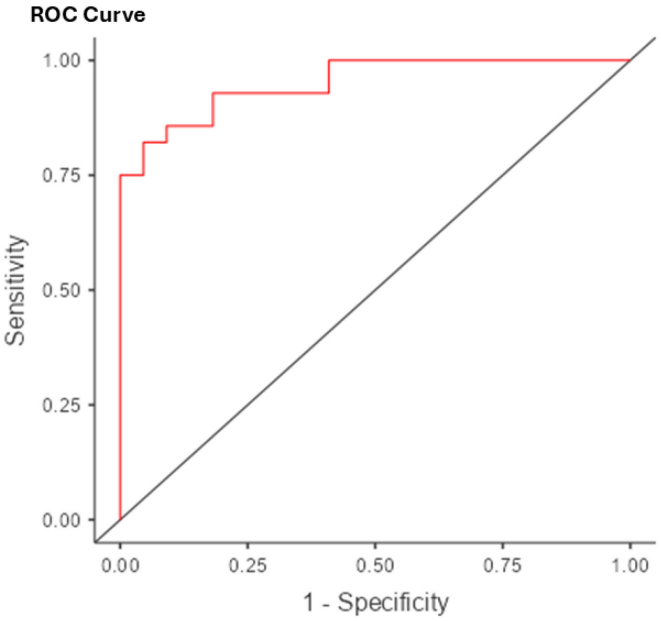
Figure 4 illustrates the correlations between IL-6 levels and various organ system dysfunction scores in sepsis patients. The figure comprises 6 scatter plots (A–F), each representing a different organ system. Spearman's correlation coefficients (r) are provided, indicating the strength and direction of the relationship between IL-6 levels and organ dysfunction scores. The respiratory dysfunction score (Figure 4A) showed a moderate positive correlation (r = 0.42, $p < 0.001$) with IL-6 levels. Liver dysfunction (Figure 4B) demonstrated a stronger positive correlation (r = 0.5, $p < 0.001$). The central nervous system (CNS)

Table 2. Multivariate binomial regression analyses of factors which were significant clinically and statistically in univariate analysis.

Factors	*p* value	Odds ratio
Total number of comorbidities	0.925	0.95
Total SOFA score	0.037	1.42
Total number of antibiotics	0.024	4.08
IL6 levels	0.028	28.02

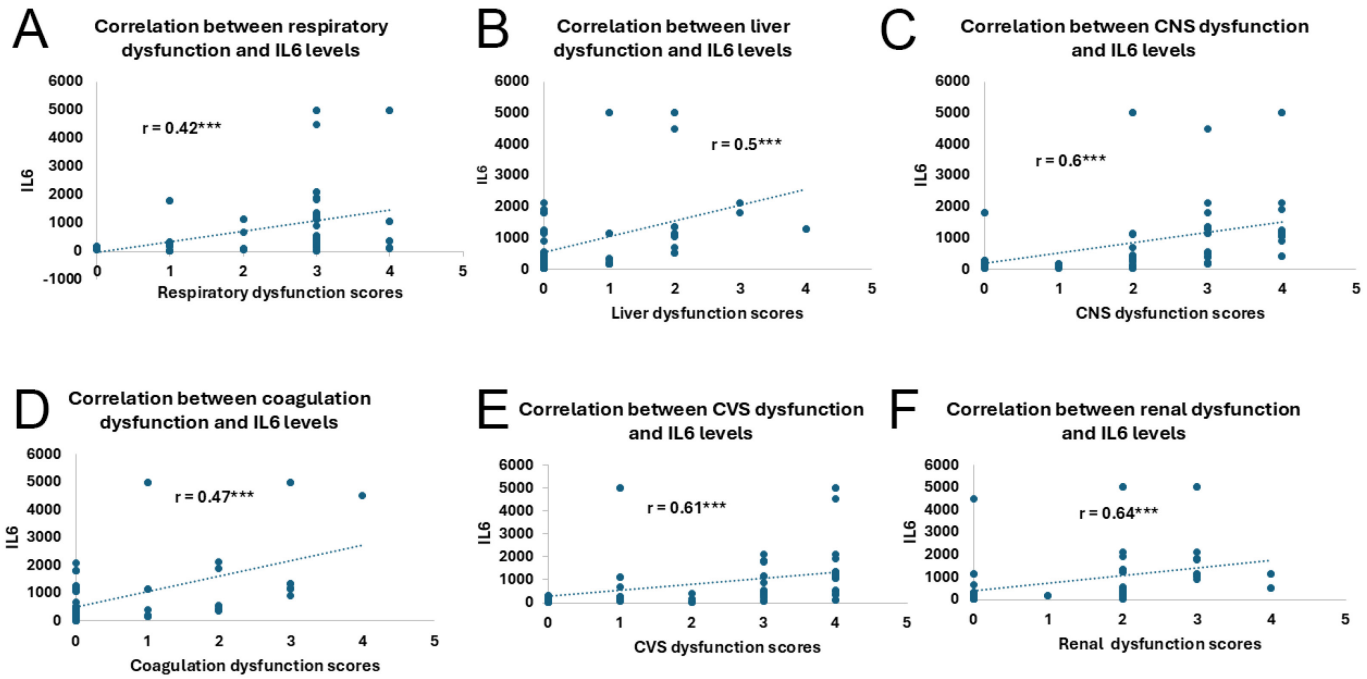
SOFA: sequential organ failure assessment.

Figure 3. Receiver operating characteristic (ROC) curve for the binomial regression analysis model.



Sensitivity- 0.86, Specificity- 0.91, AUC- 0.95

Figure 4. Correlation between different organ system scores and IL6 levels.



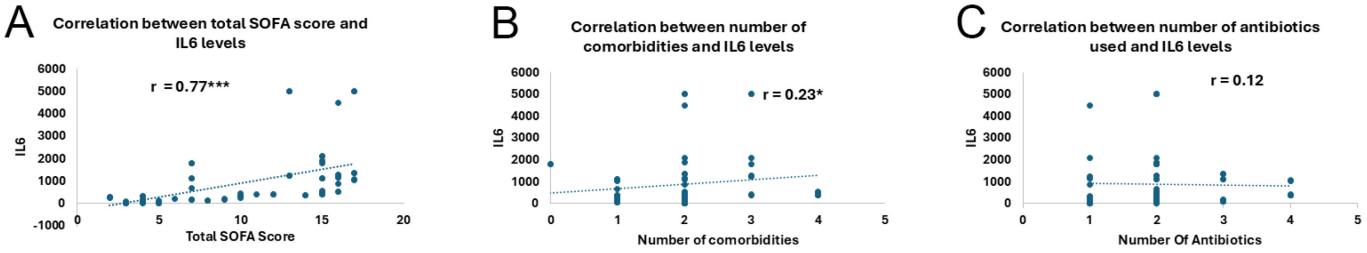
A: respiratory dysfunction score vs IL6 level; **B:** liver dysfunction score vs IL6 level; **C:** central nervous system (CNS) dysfunction score vs IL6 level; **D:** coagulation dysfunction score vs IL6 level; **E:** cardiovascular system (CVS) dysfunction score vs IL6 level; **F:** renal dysfunction score vs IL6 level. r = Spearman's coefficient; **p* = 0.05; ***p* = 0.01; ****p* = 0.001.

dysfunction score (Figure 4C) exhibited a strong positive correlation (r = 0.6, $p < 0.001$) with IL-6 levels. Coagulation dysfunction (Figure 4D) showed a moderate positive correlation (r = 0.47, $p < 0.001$). The cardiovascular system (CVS) dysfunction score (Figure 4E) presented the strongest positive correlation (r = 0.61, $p < 0.001$) among all organ systems. Lastly, renal dysfunction (Figure 4F) also displayed a strong positive correlation (r = 0.64, $p < 0.001$) with IL-6 levels. These results suggest that higher IL-6 levels were associated with more severe organ dysfunction across all systems studied, with the strongest correlations observed in cardiovascular, renal, and central nervous systems.

Figure 5A illustrates the correlation between the total SOFA score and IL-6 levels. There was a strong positive correlation (r = 0.77, $p < 0.001$) between these variables, indicating that higher SOFA scores were associated with higher IL-6 levels. Figure 5B shows the correlation between the number of comorbidities and IL-6 levels. A weak positive correlation (r = 0.23, $p < 0.05$) was observed, suggesting a slight tendency for IL-6 levels to increase with a higher number of comorbidities. Figure 5C depicts the correlation between the number of antibiotics used and IL-6 levels. The correlation coefficient (r = 0.12) indicated a very weak positive correlation, which is likely not statistically significant (asterisks denoting significance levels).

Overall, this study demonstrated that among the factors examined, the total SOFA score had the

Figure 5. Correlation between total SOFA score, total number of comorbidities, total number of antibiotics used and IL6 levels.



A: total SOFA score vs IL6 levels; **B:** number of comorbidities vs IL6 levels; **C:** total number of antibiotics vs IL6 levels. r = Spearman's coefficient; **p* = 0.05; ***p* = 0.01; ****p* = 0.001. SOFA: sequential organ failure assessment.

strongest correlation with IL-6 levels in sepsis patients, while the number of comorbidities showed a weak correlation, and the number of antibiotics used appeared to have little to no significant correlation with IL-6 levels.

Discussion

The results of this prospective observational study provide significant insights into the factors influencing mortality in sepsis patients admitted to the ICU, as well as the relationship between IL-6 levels, SOFA scores, and organ failure. One of the most important findings from this study is the strong association between IL-6 levels and mortality, with a 28.02-fold increase in the odds of mortality for each unit increase in IL-6 levels. This highlights the potential of IL-6 as a powerful biomarker for assessing the severity of sepsis and predicting patient outcomes. The correlation analysis further supports this, revealing strong positive correlations between IL-6 levels and total SOFA score, reinforcing the interrelationship between systemic inflammation and organ dysfunction in sepsis. In addition, there was a strong correlation between specific organ dysfunction scores across multiple organ systems, particularly in the cardiovascular, renal, and central nervous systems. These findings suggest that IL-6 levels reflect the extent of organ dysfunction, which is a critical determinant of mortality in sepsis. The findings underscore the role of IL-6 as not only a predictor of mortality but also as a marker of the extent and severity of organ failure in sepsis. Combining IL-6 levels with SOFA scores will provide a comprehensive assessment of sepsis severity and its impact on patient outcomes.

The findings are consistent with previous research that link higher IL-6 levels with increased mortality [16–19]. For instance, elevated IL-6 levels have been identified as the most powerful predictor of cardiovascular mortality in patients with acute coronary syndrome. Similarly, the study observed that IL-6 levels correlated with cardiovascular dysfunction scores, further supporting its role as a critical biomarker [16]. A multicenter prospective observational study also demonstrated that IL-6; along with other biomarkers like IL-8, IL-10, TNF-α, C-reactive protein (CRP), and procalcitonin; provides a more accurate assessment of mortality when combined with the SOFA score; this observation is similar to the findings of this study [17]. Moreover, a meta-analysis of 28 studies indicated that elevated IL-6 levels are associated with higher risks of cardiovascular and all-cause mortality among dialysis patients, highlighting the significance of IL-6 in renal dysfunction as well [18].

While most studies have shown a positive correlation between IL-6 levels and mortality, some have reported conflicting results, with IL-6 failing to predict mortality in certain populations [20–23]. Despite these discrepancies, this study demonstrates the situation in the Indian population, where there are very few studies and most have focused on coronavirus disease 2019 (COVID-19) [22–24]. Combining SOFA scores with IL-6 levels provides a reliable predictor of mortality in sepsis patients, underscoring the value of IL-6 as a critical biomarker in assessing organ dysfunction and patient outcomes.

In this study, diabetes mellitus and cardiopulmonary diseases were the most common comorbidities. A study conducted by Dremsizov *et al.* showed similar findings, indicating that diabetes is associated with alterations in the immune system, making patients more susceptible to nosocomial infections, secondary infections, and subsequently sepsis [25]. However, none of the comorbidities, except for CKD, showed a significant difference in mortality. The relevance was limited even in CKD, as most CKD patients had multiple other comorbidities. Therefore, the number of comorbidities in relation to mortality were analyzed. Interestingly, while the number of comorbidities was significantly different between survivors and non-survivors in the univariate analysis, it did not emerge as an independent predictor of mortality in the multivariate analysis. This suggests that although comorbidities contribute to the overall clinical picture, their direct impact on mortality may be less pronounced when accounting for other factors such as IL-6 levels and organ dysfunction.

This study reported a mortality rate of 39%, which is higher than the 23.4% reported in the ‘second Indian intensive care case mix and practice patterns study’ [26]. The latter study included 5,222 patients from 141 ICUs across India. While both studies found that non-survivors had more comorbidities than survivors, there was a notable difference in antibiotic use patterns. The ‘case mix’ study reported that clinically improved patients received more antibiotics compared to non-survivors, whereas in this study the observation was the opposite. This discrepancy may be attributed to this study's focus exclusively on sepsis patients, as opposed to the broader ICU population in the ‘case mix’ study.

The number of antibiotics used emerged as a significant factor associated with mortality, with an odds ratio of 4.08 in the multivariate analysis. This finding likely reflects the complexity and severity of infections in non-survivors; as these patients likely

required broader-spectrum or multiple antibiotics due to persistent or worsening infections, multidrug-resistant organisms, or inadequate initial antimicrobial coverage. necessitating more aggressive antimicrobial therapy.

However, the weak correlation between the number of antibiotics and IL-6 levels suggests that the relationship between antibiotic use and outcomes may be influenced by factors beyond inflammation alone. While IL-6 serves as a marker of inflammatory burden and host response, the number of antibiotics may reflect other aspects of disease complexity such as resistant organisms, polymicrobial infections, or treatment failures; necessitating sequential antibiotic modifications. There may be other mechanisms such as direct organ damage from the infectious process, metabolic derangements, immunological exhaustion, or potential adverse effects from multiple antibiotics which might have resulted in mortality. The timing of antibiotic administration relative to the inflammatory response, along with the immunomodulatory effects of different antibiotic classes, may further explain this lack of correlation. This finding underscores the complexity of severe infections, where both inflammatory burden and infection complexity independently contribute to mortality risk through separate mechanisms.

The 'intensive care case mix and practice patterns study' [26] did not include IL-6 levels in their analysis. They did, however, identify SOFA score as a predictor of ICU mortality, which aligns with the findings of this study. The significant association found between IL-6 levels and mortality highlights the importance of such studies in the Indian population, and suggests the potential value of incorporating serum IL-6 measurements into routine diagnostic practices in ICU settings.

The ROC curve analysis of the multivariate model demonstrated good predictive performance, indicating that the combination of IL-6 levels, SOFA scores, and antibiotic use provides a robust tool for assessing mortality risk in sepsis patients. The high sensitivity and specificity of this model suggest its potential utility in guiding clinical decision-making and resource allocation in the ICU.

Given the strong correlation between IL-6 levels and mortality in this study, it is important to consider the potential therapeutic implications. IL-6 receptor inhibitors, such as tocilizumab and sarilumab, have gained attention in recent years for their potential in managing severe inflammatory conditions especially in COVID-19 [27–29]. The timing of administration, patient selection, and potential side effects (such as increased risk of secondary infections) are important considerations for the use of IL-6 receptor inhibitors. The findings of this study which demonstrate a strong correlation between IL-6 levels and organ dysfunction scores, could potentially aid in identifying patients who might benefit most from IL-6 targeted therapies.

Conclusions

This was a single-center study with 72 patients and therefore generalizability of the findings is limited. Further, while SOFA and IL-6 are analyzed, other inflammatory markers (e.g., CRP, procalcitonin, etc.) which could have been confounding factors, were not included for comparison. The IL-6 levels were measured only at the time of admission. Serial measurements would improve prediction accuracy.

Future research should focus on multicentric prospective trials evaluating the efficacy of IL-6 receptor inhibitors in sepsis patients, particularly in the Indian context, where genetic and environmental factors may influence treatment responses. Additionally, studies investigating the optimal timing and dosing of these inhibitors, as well as their integration with standard sepsis care, would be valuable in refining treatment protocols.

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Conflict of interest

No conflict of interest is declared.

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