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Original Research Article

Clinical utility of serum interleukin-6 in predicting outcomes in pediatric intensive care unit

A. Sai Sneha Reddy[1]*, Harini Venugopal[2]

[1]Department of Pediatrics, Manipal Hospital, Bangalore, Karnataka, India
[2]Department of Pediatrics, Mysore Medical College, Mysore, Karnataka, India

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***Correspondence:**
Dr. A. Sai Sneha Reddy,
E-mail: sneha949154@gmail.com

ABSTRACT

Background: Early identification of critically ill children at high risk of mortality is essential for timely intervention. Biomarkers reflecting the inflammatory response may improve prognostication beyond conventional severity scores. This study evaluated the prognostic utility of serial serum interleukin-6 (IL-6) levels in children requiring intensive care.
Methods: This observational cross-sectional study included 45 children aged 1 month to 18 years admitted to a pediatric intensive care unit. Serum IL-6 levels were measured at admission, 24 hours, and 72 hours. The severity of illness was assessed by the pediatric logistic organ dysfunction-2 (PELOD-2) score. The primary outcome was in-hospital mortality, while secondary outcomes were duration of pediatric intensive care unit stay, hospital stay, and need for respiratory and inotropic support.
Results: Five (11.1%) children died during hospitalization. The median IL-6 levels at 24 hours and 72 hours were significantly higher in non-survivors compared to survivors, with values of 1122 (IQR 1305) pg/ml versus 564 (IQR 153) pg/ml at 24 hours, and 1263 (IQR 626) pg/ml versus 82 (IQR 191) pg/ml at 72 hours, both with p values less than 0.0001. Non-survivors had significantly higher IL-6 levels at 24 and 72 hours than survivors ($p<0.001$). Higher IL-6 levels were also associated with illness severity.
Conclusions: Serial serum IL-6 measurement is a valuable prognostic biomarker in children requiring intensive care. Incorporating serial IL-6 estimation with clinical severity assessment may facilitate early risk stratification and optimize management in the pediatric intensive care unit.

Keywords: Interleukins, PELOD, Prognosis

INTRODUCTION

Critical illness in children is characterized by a complex interaction of infection, inflammation, immune dysregulation, and progressive organ dysfunction, resulting in significant morbidity and mortality. Despite advances in pediatric intensive care, sepsis and multiple organ dysfunction syndrome remain major contributors to adverse outcomes among children admitted to the pediatric intensive care unit (PICU). Early identification is the cornerstone for timely intervention, resource utilization, and improved survival.[1,2]

Pediatric risk of mortality (PRISM), pediatric index of mortality (PIM), and pediatric logistic organ dysfunction-2 (PELOD-2) scores are routinely used to assess illness severity and predict mortality in critically ill children.[3] Although these scoring systems provide valuable prognostic information, they primarily reflect physiological derangements and established organ dysfunction rather than the early inflammatory response. Therefore, there is increasing interest in identifying biomarkers that may complement clinical scoring systems and allow earlier risk stratification.[4,5]

Interleukin-6 (IL-6) is a pro-inflammatory cytokine secreted by monocytes, macrophages, endothelial cells, fibroblasts, and lymphocytes in response to infection and tissue injury.[6] It is key in the acute inflammatory response through induction of hepatic acute-phase protein synthesis and regulation of both innate and adaptive immune responses. A rise in IL-6 levels often precedes the development of overt organ dysfunction and therefore represents a promising biomarker for early prognostication in the critically ill.[7,8]

Previous studies showed that elevated IL-6 concentrations are associated with increased disease severity, septic shock, organ dysfunction, prolonged intensive care stays, and mortality in the critically ill.[9,10] Similar findings have been reported in children, with increased IL-6 levels being linked to severe bacterial infections, sepsis, and poor clinical outcomes. Furthermore, serial measurement of IL-6 appears to provide greater prognostic value than a single baseline measurement by reflecting the dynamic evolution of the inflammatory response during the course of illness.[9,12] Although biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) are widely used in pediatric critical care, their ability to predict disease severity and clinical outcomes remains variable. IL-6 has emerged as a potential adjunctive biomarker because of its early rise following systemic inflammation and its close association with disease progression. However, evidence regarding the prognostic significance of serial IL-6 measurements in critically ill children remains limited, particularly in Indian PICU settings where the burden of infectious diseases is high and data are scarce.

Therefore, the present study was undertaken to evaluate the prognostic significance of serial serum IL-6 levels in critically ill children admitted to the pediatric intensive care unit and to determine the association of serial IL-6 levels with severity of illness as assessed by the PELOD-2 score, requirement for organ support, and mortality.

METHODS

Study design and setting

This observational cross-sectional study was conducted in PICU, Nitte (Deemed to be university), Mangalore, India and were included in this cross-sectional descriptive study from April 2021 to September 2022. Children receiving steroid therapy or having known immunodeficiency disorders were excluded from the study. After approval of the Institutional Ethics Committee, written informed consent was obtained from the parents or legally authorized representatives of all enrolled children before participation.

Sample size

A time-bound convenience sample of 45 children was enrolled. The sample size was calculated based on previously published literature evaluating the association between serum IL-6 levels and organ dysfunction in critically ill patients, with a confidence level of 95% and a study power of 80%.[13]

Data collection

Demographic characteristics, clinical history, physical examination findings, and laboratory investigations were recorded using a structured case record form. Illness severity was assessed using the PELOD-2 score at admission and subsequently on days 2, 5, 8, 12, 16, and 18 until discharge or death. Clinical outcomes including duration of PICU stay, duration of hospital stay, requirement for respiratory support, inotropic support, renal replacement therapy, and in-hospital mortality were documented.[6,7]

Measurement of serum IL-6

Venous blood samples were collected at admission (0 hour) and subsequently at 24 and 72 hours after PICU admission. Serum was separated by centrifugation and stored according to the manufacturer's recommendations until analysis. Serum IL-6 concentrations were estimated using a commercially available enzyme-linked immunosorbent assay (ELISA) kit following the manufacturer's protocol. Routine laboratory investigations required for diagnosis and clinical management were performed using standard laboratory techniques.

Outcome measures

The primary outcome was in-hospital mortality. Secondary outcomes included duration of PICU stay, duration of hospital stay, need for respiratory support, requirement for inotropic support, need for renal replacement therapy, and severity of organ dysfunction assessed using the PELOD-2 score.[6,7]

Statistical analysis

Comparisons between groups were performed using the Kruskal–Wallis test for continuous variables. Correlation between IL-6 levels and PELOD-2 scores was evaluated using Spearman's correlation coefficient. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the prognostic performance of IL-6 for predicting mortality. A two-tailed p value of <0.05 was considered statistically significant.[9,10]

RESULTS

Baseline characteristics

A total of 45 children admitted to PICU were included in the study. The overall in-hospital mortality was 11.1% (5/45), while 40 (88.9%) children survived. The median (IQR) of IL-6 levels in the study group was 564 (1553) pg/ml (normal 5.4 pg/ml). Baseline characteristics of survivors and non survivors are described in Table 1. The

median age of survivors was 5 years compared with 2 years among non-survivors. Severe pneumonia was the most common indication for PICU admission, whereas mortality was highest among children with sepsis.

Median serum IL-6 concentrations at admission were comparable in both groups. Subsequently, median IL-6 levels were higher in non-survivors than in survivors at 24 hours and 72 hours (Table 2).

Serum IL-6 levels showed a significant positive correlation with illness severity as assessed by PELOD-2 score (Spearman's rho=0.297, p=0.01).

Serial measurements demonstrated distinct trends between survivors and non-survivors. Among non-survivors, serum IL-6 levels progressively increased from admission to 72 hours (Table 2). There was a significant difference in the trend of IL-6 over the first 72 hours in survivors and non-survivors on the Kruskal Wallis H test (p=0.002).

ROC analysis demonstrated that serum IL-6 measured at 72 hours had the best predictive performance for in-hospital mortality, with an area under the curve (AUC) of 0.941 (Figure 1). An IL-6 cut-off value of 787.79 pg/ml at 72 hours predicted mortality with 100% sensitivity and 92% specificity. Children requiring organ support had significantly higher median IL-6 levels than those who did not (1506.2 pg/ml versus 82.9 pg/ml).

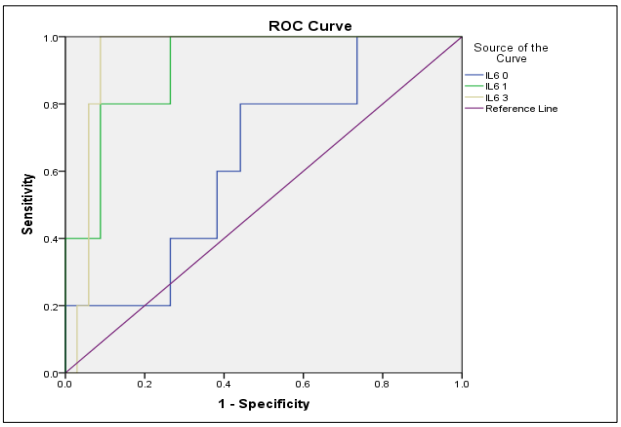

Figure 1: ROC analysis of IL-6 in non-survivors.

Table 1: Baseline characteristics of study population.

Variable	Total cases (n=45)	Survivors (n=40)	Non-survivors (n=5)	P value
Age (years) median (IQR)	5 (7)	5 (7)	2 (13)	0.106
Sex, N (%)				
Male	31	29 (72)	2 (40)	0.109
Female	14	11 (27)	3 (60)	
Sepsis	2	0	2	<0.001
Severe pneumonia	14	12	2	0.5
Gastrointestinal infections	9	9	0	0.25
Genitourinary infections	5	5	0	0.34
Central nervous system infections	11	10	1	0.596
Musculoskeletal	3	3	0	0.526
Inborn error of metabolism	1	1	0	0.45

Table 2: Comparison of IL-6 values at admission, 24 hours, 72 hours of PICU stay among survivors and non-survivors.

Biomarker	Non-survivors (n=5) Median (IQR)	Survivors (n=40) Median (IQR)	P value (Mann-Whitney test)
IL-6 (pg/ml)			
At admission	1122 (1305)	564 (153)	0.317
24 hours	1506 (630)	138 (945)	0.002*
72 hours	1263 (626)	82 (191)	0.001*
PELOD 2, N (predicted death rate%)	6 (83.6)	2 (0.3)	<0.001*

*Statistically significant p value (<0.05)

DISCUSSION

The present study evaluated the serial serum IL-6 levels as prognostic marker in critically ill children admitted to PICU. The study demonstrated persistently increased IL-6 levels, particularly at 24 and 72 hours after admission and they were significantly associated with morbidity, increased requirement for organ support and mortality. These support the role of IL-6 as a biomarker for earlier detection of systemic inflammation and morbidity in critically ill children.

The overall mortality observed in our study was 11.1%, which is comparable to previously published reports from

PICU in developing countries.[14,15] Differences in mortality rates reported across studies may be attributed to variations in patient demographics, disease severity, referral patterns, and availability of intensive care resources.[16]

Children who did not survive had significantly higher serum IL-6 concentrations at both 24 and 72 hours than survivors. Similar observations have been reported by Huang et al, who demonstrated significantly elevated IL-6 levels among children with sepsis, and by Bian et al, who showed that IL-6 concentrations correlated with the severity of bacterial infections.[8,11] Studies in adult patients with sepsis have likewise reported that persistently elevated IL-6 levels are associated with septic shock, multiple organ dysfunction, and increased mortality.[9,10]

An important finding of the present study was the progressive decline in IL-6 concentrations among survivors, whereas persistently elevated or increasing levels were observed among non-survivors. This suggests that serial measurement provides greater prognostic value than a single baseline estimation by reflecting the dynamic inflammatory response during the course of illness. Similar conclusions have been reported in previous studies evaluating serial measurements of cytokines in critically ill patients.[17,18]

Serum IL-6 levels were significantly positively correlated with the PELOD-2 score, and higher IL-6 concentrations were associated with more severe organ dysfunction.[6,19] This observation is consistent with previous reports demonstrating that inflammatory biomarkers complement clinical severity scores in predicting adverse outcomes in pediatric critical illness.[7,13]

Receiver operating characteristic analysis in the present study demonstrated the excellent discriminatory ability of IL-6 measured at 72 hours for predicting in-hospital mortality. These results are in line with systematic reviews and meta-analyses that have found IL-6 to be a useful diagnostic and prognostic biomarker in sepsis.[12,17] IL-6 should not replace validated clinical scoring systems, but might be useful in combination with PELOD-2 for early risk stratification and timely therapeutic decision-making.

The strengths of the present study include prospective serial measurement of IL-6 and correlation with an established organ dysfunction score. However, there are some limitations to acknowledge. This was a single-center study with a relatively small sample size, which may limit the generalizability of the findings. In addition, the heterogeneous etiologies of critical illness may have influenced cytokine responses.[20,21] Larger multicenter studies are required to validate these findings, establish standardized pediatric reference values, and determine clinically useful IL-6 cut-off concentrations.[22,23]

Overall, the findings of this study suggest that serial serum IL-6 measurement is a useful adjunct to conventional clinical assessment and may facilitate early identification of critically ill children at increased risk of adverse outcomes.

CONCLUSION

Serial measurement of serum IL-6 is a valuable prognostic biomarker in critically ill children admitted to the pediatric intensive care unit. Persistently elevated IL-6 levels at 24 and 72 hours were significantly associated with increased illness severity, greater requirement for organ support, and higher in-hospital mortality. Serial IL-6 estimation demonstrated excellent predictive performance for mortality and showed a positive correlation with the PELOD-2 score.

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