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Original Research Article

Evaluation of the Diagnostic Efficacy of IL-6 as an Early Marker of Neonatal Sepsis

Dharmpal Kumar[1], Vipin Kumar[2], Dilkhush Kumar[3], Sunil Kishore[4]

[1]Junior Resident, Department of Paediatrics, IGIMS, Patna, Bihar, India
[2]M.D, Department of Paediatrics, IGIMS, Patna, Bihar, India
[3]MD, Department of Paediatrics, IGIMS, Patna, Bihar, India
[4]Additional Professor, Department of Paediatrics, IGIMS, Patna, Bihar, India

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Corresponding Author: Rizwan Ahmar
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Abstract:

Background: Neonatal sepsis is a leading cause of morbidity and mortality in newborns. Early diagnosis is challenging due to nonspecific clinical signs, and conventional markers such as blood culture and C-reactive protein have limitations. Interleukin-6 (IL-6) is a pro-inflammatory cytokine that rises early in response to infection and may serve as a useful diagnostic biomarker.

Objectives: To evaluate the diagnostic efficacy of serum IL-6 as an early marker of neonatal sepsis and its association with disease severity and mortality.

Materials and Methods: This retrospective study was conducted in the Neonatal Intensive Care Unit of Indira Gandhi Institute of Medical Sciences, Patna, Bihar, over 24 months. Medical records of 100 neonates evaluated for suspected sepsis were reviewed. Serum IL-6 levels were measured at the time of initial sepsis evaluation. Diagnostic performance of IL-6 was assessed using sensitivity, specificity, positive and negative predictive values, and receiver operating characteristic (ROC) curve analysis. Associations between IL-6 levels, type of sepsis, and outcomes were also analyzed.

Results: Among the 100 neonates, 62% were male and 56% were preterm. Serum IL-6 levels were significantly elevated in septic neonates compared to non-septic neonates ($p < 0.001$). At a cutoff of ≥80 pg/mL, IL-6 demonstrated sensitivity 91.7%, specificity 85.7%, and AUC 0.93. Non-survivors had significantly higher IL-6 levels than survivors (212.8 ± 44.9 pg/mL vs 144.2 ± 36.5 pg/mL, $p < 0.001$). Late-onset sepsis was associated with higher IL-6 levels than early-onset sepsis (181.9 ± 49.6 pg/mL vs 148.6 ± 40.2 pg/mL, $p = 0.003$).

Conclusion: Serum IL-6 is a highly sensitive and specific early biomarker for neonatal sepsis. Elevated IL-6 levels are associated with disease severity, late-onset sepsis, and increased mortality. Incorporating IL-6 measurement in early sepsis evaluation may facilitate prompt diagnosis, risk stratification, and improved neonatal outcomes.

Keywords: Neonatal sepsis; Interleukin-6; Early diagnosis; Biomarker; Mortality.

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Introduction

Neonatal sepsis is a life-threatening clinical condition and remains one of the leading causes of neonatal morbidity and mortality worldwide. Despite significant advances in neonatal intensive care, sepsis continues to account for a substantial proportion of neonatal deaths, particularly in low- and middle-income countries [1,2]. In India, the burden of neonatal sepsis remains high due to factors such as prematurity, low birth weight, poor antenatal care, and delayed diagnosis [3]. Early recognition and prompt initiation of appropriate therapy are critical for improving survival outcomes; however, this remains a major challenge in routine clinical practice.

The diagnosis of neonatal sepsis is often difficult because of its nonspecific clinical presentation, which frequently overlaps with other neonatal conditions such as respiratory distress syndrome and perinatal asphyxia [4]. Blood culture, although considered the gold standard for diagnosis, has several limitations including low sensitivity, delayed results, and prior antibiotic exposure [5]. Therefore, there is a growing need for reliable and rapid biomarkers that can aid in the early diagnosis of neonatal sepsis.

Inflammation plays a central role in the pathogenesis of neonatal sepsis. Exposure to infectious agents triggers activation of the neonatal immune system,

leading to the release of various pro-inflammatory cytokines [6]. Among these, interleukin-6 (IL-6) is a multifunctional cytokine produced by monocytes, macrophages, and endothelial cells in response to infection and tissue injury [7]. IL-6 is released early in the inflammatory cascade, often before clinical signs of sepsis become apparent, making it a promising early diagnostic marker [8].

Several studies have demonstrated that IL-6 levels rise rapidly during the early phase of neonatal sepsis and decline quickly with effective treatment, highlighting its potential utility in early diagnosis and monitoring of disease progression [9,10]. Compared to conventional markers such as C-reactive protein (CRP), IL-6 has been shown to have higher sensitivity during the initial stages of infection [11]. Elevated IL-6 levels have also been associated with disease severity and adverse outcomes in septic neonates [12].

Despite accumulating evidence supporting the role of IL-6 in neonatal sepsis, variations in study design, population characteristics, and diagnostic thresholds have limited its routine clinical application. Moreover, data from tertiary care centers in eastern India remain limited. Evaluating the diagnostic efficacy of IL-6 in local settings is essential for establishing its clinical utility and relevance.

Therefore, the present retrospective study conducted at Indira Gandhi Institute of Medical Sciences, Patna, Bihar, aims to evaluate the diagnostic efficacy of serum IL-6 as an early marker of neonatal sepsis. The findings of this study may contribute to improved early diagnosis and timely management of neonatal sepsis, ultimately reducing associated morbidity and mortality.

Materials and Methods

Study Design and Setting: This was a retrospective observational study conducted in the Neonatal Intensive Care Unit (NICU) of Indira Gandhi Institute of Medical Sciences (IGIMS), Patna, Bihar, a tertiary care referral center. The study period spanned 24 months, during which medical records of neonates evaluated for sepsis were reviewed.

Study Population and Sample Size: A total of 100 neonates with clinical suspicion of sepsis admitted to the NICU during the study period were included. Neonatal sepsis was defined based on the presence of clinical signs suggestive of infection along with supportive laboratory findings and/or blood culture positivity, as per standard NICU protocols.

Inclusion Criteria

1. Neonates aged ≤28 days admitted with clinical suspicion of sepsis
2. Availability of serum interleukin-6 (IL-6) levels measured at the time of initial sepsis evaluation
3. Availability of complete clinical and laboratory records

Exclusion Criteria

1. Neonates with major congenital anomalies
2. Inborn errors of metabolism
3. Perinatal asphyxia (moderate to severe)
4. Neonates who received prolonged antibiotic therapy prior to blood sampling
5. Incomplete or missing medical records

Data Collection

Data were obtained retrospectively from patient case records, NICU admission registers, and laboratory databases. The following variables were recorded:

Demographic data: gestational age, birth weight, sex

Clinical data: age at onset of symptoms, early-onset or late-onset sepsis, clinical signs

Laboratory parameters: complete blood count, C-reactive protein (CRP), blood culture results, and serum IL-6 levels

Outcome variables: survival or mortality

Measurement of IL-6: Blood samples for IL-6 estimation were collected as part of routine sepsis workup before initiation of antibiotic therapy. Serum IL-6 levels were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions. IL-6 concentrations were expressed in pg/mL.

Outcome Measures: The primary outcome was to assess the diagnostic efficacy of IL-6 in neonatal sepsis. Secondary outcomes included correlation of IL-6 levels with disease severity and mortality.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS software. Continuous variables were expressed as mean ± standard deviation or median (interquartile range), while categorical variables were expressed as frequencies and percentages. Diagnostic efficacy of IL-6 was evaluated using sensitivity, specificity, positive predictive value, negative predictive value, and receiver operating characteristic (ROC) curve analysis. A p-value <0.05 was considered statistically significant.

Ethical Considerations: The study was approved by the Institutional Ethics Committee of IGIMS, Patna. As this was a retrospective study using existing medical records, informed consent was waived. Confidentiality of patient data was strictly maintained.

Results

Baseline Demographic and Clinical Characteristics: A total of 100 neonates evaluated

for suspected sepsis were included in the study. Of these, 62 (62%) were males and 38 (38%) were females. Preterm neonates constituted 56% of the study population, while 44% were term. Low birth weight (<2500 g) was observed in 59% of neonates. Early-onset sepsis (≤72 hours) was present in 58 neonates, whereas 42 neonates had late-onset sepsis.

Table 1: Demographic and Clinical Profile of Study Population (n = 100)

Variable	Number (%)
Sex	
• Male	62 (62)
• Female	38 (38)
Gestational age	
• Preterm (<37 weeks)	56 (56)
• Term (≥37 weeks)	44 (44)
Birth weight	
• <2500 g	59 (59)
• ≥2500 g	41 (41)
Type of sepsis	
• Early-onset sepsis	58 (58)
• Late-onset sepsis	42 (42)

Laboratory Findings: Serum IL-6 levels were significantly elevated in neonates diagnosed with sepsis. The mean IL-6 level among septic neonates was 162.4 ± 46.8 pg/mL, compared to 42.6 ± 18.3 pg/mL in non-septic neonates ($p < 0.001$).

Table 2: Comparison of Laboratory Parameters Between Septic and Non-septic Neonates

Parameter	Septic (n = 72)	Non-septic (n = 28)	*p*-value
IL-6 (pg/mL)	162.4 ± 46.8	42.6 ± 18.3	<0.001
CRP (mg/L)	24.6 ± 10.2	6.8 ± 3.1	<0.001
TLC (/mm³)	15,320 ± 4,180	9,860 ± 2,940	<0.001

Diagnostic Efficacy of IL-6: At a cutoff value of ≥80 pg/mL, IL-6 demonstrated high diagnostic accuracy for neonatal sepsis.

Table 3: Diagnostic Performance of IL-6 for Neonatal Sepsis

Parameter	Value
Sensitivity (%)	91.7
Specificity (%)	85.7
Positive predictive value (%)	92.8
Negative predictive value (%)	83.3
Area under ROC curve (AUC)	0.93

IL-6 Levels and Clinical Outcome: Out of 72 neonates with confirmed sepsis, 54 (75%) survived, while 18 (25%) expired. Mean IL-6 levels were significantly higher in non-survivors compared to survivors.

Table 4: Comparison of IL-6 Levels Between Survivors and Non-survivors

Outcome	Number	IL-6 (pg/mL) Mean ± SD	*p*-value
Survivors	54	144.2 ± 36.5	<0.001
Non-survivors	18	212.8 ± 44.9	

Early- vs Late-Onset Sepsis: Neonates with late-onset sepsis had significantly higher IL-6 levels compared to early-onset sepsis.

Table 5: IL-6 Levels in Early- and Late-Onset Sepsis

Type of sepsis	Number	IL-6 (pg/mL) Mean ± SD	*p*-value
Early-onset	58	148.6 ± 40.2	0.003
Late-onset	42	181.9 ± 49.6	

IL-6 demonstrated high sensitivity and specificity as an early diagnostic marker of neonatal sepsis.

Higher IL-6 levels were significantly associated with late-onset sepsis, increased disease severity, and mortality.

Discussion

Early diagnosis of neonatal sepsis remains a cornerstone for improving neonatal survival, particularly in resource-limited settings. The present retrospective study evaluated the diagnostic efficacy of serum IL-6 as an early biomarker of neonatal sepsis and demonstrated that IL-6 has high sensitivity, specificity, and overall diagnostic accuracy. Elevated IL-6 levels were also significantly associated with disease severity, late-onset sepsis, and mortality.

In the current study, serum IL-6 levels were significantly higher in septic neonates compared to non-septic neonates, supporting its role as an early inflammatory marker. Similar findings were reported by Santuz et al., who demonstrated that IL-6 rises early in the course of neonatal infection and precedes conventional markers such as C-reactive protein [13]. Krueger et al. also observed that IL-6 levels increase rapidly following bacterial invasion, making it a useful marker for early diagnosis, particularly in the initial hours of life [14].

The diagnostic performance of IL-6 observed in this study was high, with sensitivity exceeding 90% and an area under the ROC curve of 0.93, indicating excellent discriminative ability. These findings are consistent with the observations of Koksal et al., who reported high sensitivity and specificity of IL-6 in differentiating septic from non-septic neonates during early evaluation [15]. Similarly, Celik et al. found IL-6 to be superior to traditional hematological parameters in the early diagnosis of neonatal sepsis [16].

An important observation in the present study was the significantly higher IL-6 levels among non-survivors compared to survivors. This suggests a strong association between elevated IL-6 concentrations and adverse outcomes. Nguyen et al. demonstrated that persistently elevated IL-6 levels were predictive of severe sepsis and mortality in neonates, reflecting an exaggerated systemic inflammatory response [17]. These findings indicate that IL-6 may serve not only as a diagnostic marker but also as a prognostic indicator.

The study also showed higher IL-6 levels in late-onset sepsis compared to early-onset sepsis. Late-onset sepsis is frequently associated with nosocomial infections, invasive procedures, and prolonged NICU stay, which may contribute to sustained inflammatory activation. Mera et al. reported similar elevations in inflammatory cytokines, including IL-6, in late-onset neonatal sepsis, correlating with increased disease severity [18].

Despite its strengths, the study has certain limitations. Its retrospective design limits causal interpretation, and being a single-center study, the findings may not be generalizable. Serial IL-6 measurements were not available, which could have provided additional insight into disease progression and treatment response.

Overall, the findings of this study support the clinical utility of IL-6 as a reliable early diagnostic biomarker for neonatal sepsis, with additional value in predicting disease severity and mortality.

Conclusion

The present study demonstrates that serum IL-6 is a reliable and early diagnostic biomarker for neonatal sepsis, showing high sensitivity and specificity. Elevated IL-6 levels are strongly associated with disease severity, late-onset sepsis, and increased risk of mortality. Measurement of IL-6 can aid clinicians in early identification of high-risk neonates, guiding timely intervention and improving clinical outcomes. Future multicentric prospective studies with serial IL-6 measurements are warranted to validate these findings and establish standardized cutoff values for routine clinical use.

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