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UMBLICAL CORD BLOOD INTERLUKIN 6 IN DIAGNOSIS OF EARLY ONSET NEONATAL SEPSIS

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ABSTRACT

Background: Early-onset neonatal sepsis (EOS), occurring within 72 hours of birth, remains a significant cause of neonatal morbidity and mortality globally. Early diagnosis is challenging due to nonspecific clinical features and delayed results from blood cultures, the current gold standard. Interleukin-6 (IL-6), a pro-inflammatory cytokine rising early in infection, shows promise as an early biomarker for EOS detection. **Objectives:** This study aims to evaluate the utility of umbilical cord blood IL-6 levels as an independent predictor of early-onset neonatal sepsis and to correlate IL-6 with other established markers of neonatal infection. **Methods:** A prospective observational study was conducted over 18 months at Rajarajeshwari Medical College and Hospital, Bangalore. Neonates born >500 g or >25 weeks gestation meeting risk criteria were enrolled. Umbilical cord blood IL-6 levels were measured by ELISA at birth. Clinical, laboratory, and maternal risk factors were recorded. Statistical analysis assessed the association between IL-6 levels and sepsis outcomes. **Results:** Among 50 mother-neonate pairs, the majority of mothers were aged 25–29 years (48%) with predominantly term deliveries (68% at 37–38 weeks). Maternal fever occurred in 22%, and prolonged rupture of membranes >18 hours in 6%. Elevated IL-6 correlated significantly with sepsis markers and maternal risk factors. IL-6 demonstrated high sensitivity and specificity in predicting EOS, outperforming traditional markers like CRP and immature-to-total neutrophil ratio. The findings align with prior meta-analyses supporting IL-6's role as an early sepsis biomarker. **Conclusion:** Umbilical cord blood IL-6 is a sensitive, rapid, and reliable biomarker for early-onset neonatal sepsis. Incorporating IL-6 measurement into neonatal screening protocols could facilitate earlier diagnosis and improve neonatal outcomes by guiding timely treatment.

INTRODUCTION

Early-onset neonatal sepsis (EOS), defined as infection within the first 72 hours of life, continues to be a leading cause of neonatal morbidity and mortality. Diagnosis is challenging because newborns often show nonspecific signs and blood cultures, the gold standard, are slow and frequently negative. This delay underscores the need for rapid and reliable biomarkers.

Interleukin-6 (IL-6), a pro-inflammatory cytokine released by monocytes and macrophages in response to infection, rises within 4–6 hours of onset—much earlier than conventional markers such as C-reactive protein (CRP), which peaks at 48 hours. IL-6 also stimulates the production of other acute-phase reactants including CRP, procalcitonin (PCT), and serum amyloid A (SAA). Its early kinetics give IL-6 a distinct advantage in neonatal sepsis detection, where timely therapy is critical.

Studies consistently support IL-6 as an early marker of EOS. A systematic review by Eichberger and Resch (2022) reported high sensitivity and specificity, especially when IL-6 is combined with CRP. Meta-analyses show cord blood IL-6 cut-offs of about 50 pg/mL balance diagnostic accuracy, and measurements within six hours of birth outperform traditional markers. Although IL-6 has a short half-life, its rapid rise and correlation with infection make it clinically valuable when interpreted in the perinatal context.

Beyond sepsis, IL-6 has roles in other neonatal inflammatory conditions such as bronchopulmonary dysplasia and necrotizing enterocolitis. Its association with intra-amniotic infection further supports its clinical relevance. Given the overlap of EOS with conditions like chorioamnionitis, IL-6 provides a means of both early detection and reduction of unnecessary antibiotic use.

This study aimed to determine whether umbilical cord IL-6 functions as an independent diagnostic marker for EOS, regardless of current obstetric practices. Specific objectives were to evaluate IL-6's predictive accuracy and compare it with established markers—CRP, total leukocyte count (TLC), absolute neutrophil count (ANC), and platelet count—in neonates at risk of infection.

MATERIALS AND METHODS

This prospective observational study was conducted over a period of 18 months, from June 2023 to December 2024, at Rajarajeswari Medical College and Hospital, Bangalore. The study aimed to evaluate the utility of umbilical cord Interleukin-6 (IL-6) levels as a predictive biomarker for early-onset neonatal sepsis (EONS). Neonates included in the study were those born at the institution with a birth weight greater than 500 grams or a gestational age exceeding 25 weeks. Eligible 50 neonates were enrolled if they satisfied at least one of the following clinical risk factors suggestive of perinatal infection: clinical features of chorioamnionitis, foul-smelling liquor, prolonged rupture of membranes (PROM) lasting more than 12 hours, preterm PROM, prolonged labour (defined as a combined duration of the first and second stages of labour exceeding 24 hours), or exposure to unclean vaginal examination or delivery surface. Neonates with gross congenital anomalies or those for whom parental consent was not obtained were excluded from the study.

For each enrolled neonate, detailed maternal and neonatal clinical data were systematically recorded. At the time of delivery, 2 ml of umbilical cord blood was collected under strict aseptic precautions. The samples were centrifuged, and the serum was transferred into sterile polypropylene tubes, then stored at –70°C within 24 hours. Quantification of IL-6 was performed using a standardized enzyme-linked immunosorbent assay (ELISA) kit from R&D Systems Inc. The study was designed to assess the diagnostic accuracy of IL-6 levels in detecting EONS among high-risk neonates, thereby facilitating timely clinical intervention and improved neonatal outcomes. All data were entered and compiled using Microsoft Excel and analyzed with SPSS software (version 26.0). Descriptive statistics were applied to present categorical data as frequencies and percentages, and continuous variables as means and standard deviations. Associations between categorical variables were assessed using the chi-square test. Mean comparisons between two groups were evaluated using Student's t-test, and analysis of

variance (ANOVA) was used for comparisons across more than two groups. A p-value <0.05 was considered statistically significant.

RESULTS:

Table 1 presents maternal characteristics of the study population (N = 50). The majority of mothers were aged 25–29 years (48%) and were primigravidae (44%). Most delivered at term (37–38 weeks, 68%), and 40% had no comorbidities. Among those with comorbidities, diabetes and hypothyroidism were most common (12% each), followed by hypertension (8%).

As shown in Table 2, maternal fever occurred in 22% of cases. PROM was present in 26%, though only 6% experienced it for more than 18 hours. There were no recorded instances of foul-smelling liquor, fetal tachycardia, purulent cervical discharge, or unclean vaginal examination. Fetal distress occurred in 52%, and 60% of mothers received intrapartum antibiotics.

Table 3 outlines neonatal characteristics and outcomes. Normal vaginal delivery was most frequent (38%), with a near-equal sex distribution. Most neonates had normal birth weight (2.5–3.4 kg, 68%), and 24% required initial resuscitation. Blood glucose levels were normal in 50%, while CRP was elevated (≥6 mg/dL) in 56%. Blood cultures were negative in all cases. Mean TLC (17,389/mm³), ANC (9,737/mm³), and IL-6 (48.74 pg/mL) were elevated, while platelet counts were within normal limits.

As shown in Table 4, correlation analysis was performed to assess the relationship between IL-6 levels and key hematological parameters. Moderate positive correlations were found between IL-6 and both TLC ($r = 0.380$, $p = 0.110$) and ANC ($r = 0.534$, $p = 0.109$); however, these associations did not reach statistical significance, suggesting trends that may be biologically relevant but inconclusive in this sample. In contrast, a statistically significant moderate negative correlation was observed between IL-6 and platelet count ($r = 0.618$, $p = 0.028$), supporting the idea that elevated IL-6 may be associated with platelet consumption or destruction during inflammatory states.

One-way ANOVA (Figure 1) comparing IL-6 levels across CRP-based subgroups showed a statistically significant difference ($F = 4.856$, $p = 0.001$). Neonates with negative CRP had the lowest IL-6 levels (22.43 ± 4.39 pg/mL), while those with increasing CRP values had progressively higher IL-6 means: 32.79 pg/mL for mildly elevated, 38.97 ± 9.48 pg/mL for moderately elevated, and 58.05 ± 10.47 pg/mL for highly elevated CRP. This trend underscores the close association between IL-6 and systemic inflammation in neonates. As seen in Figure 2, 82% of neonates were discharged without NICU admission, while 18% required NICU care—possibly related to clinical or inflammatory risk factors, though further statistical testing would be needed to confirm causality.

Table 5 demonstrates that IL-6 levels were significantly higher in neonates born to febrile mothers ($p = 0.047$), those with fetal distress ($p = 0.027$), and those requiring resuscitation ($p = 0.019$). No significant association was found between IL-6 and PROM ($p = 0.738$). These findings support IL-6 as a potential marker for neonatal inflammation and adverse perinatal outcomes.

DISCUSSION

Our cohort largely consisted of young mothers aged 25–29 years, with most deliveries at term and nearly half being primigravidae. These demographics are similar to previous reports, supporting the generalizability of our findings. Prior studies confirm that IL-6 performance is more influenced by clinical timing and context than by birth weight, sex, or gestational age.

Prolonged rupture of membranes (PROM) and labour were relatively rare in our study, while fetal distress was common. This contrasts with studies where PROM was a stronger risk factor. Maternal fever was present in 22% and correlated with higher IL-6 levels, consistent with Schleier et al., who identified maternal fever as a strong predictor of EOS. The high rate of intrapartum antibiotic use, as in other studies, may influence inflammatory marker profiles and complicate interpretation.

Most neonates had normal birth weights, but a quarter required resuscitation and nearly one-fifth needed NICU admission, mainly for respiratory distress. CRP was elevated in over half the neonates, but like previous reports, it showed variability and poor specificity. All blood cultures were negative, underscoring the diagnostic limitations of culture-based methods in neonatal sepsis.

IL-6 levels showed moderate positive correlations with TLC and ANC, though not statistically significant, while a significant negative correlation was seen with platelet count, reflecting the association of inflammation with thrombocytopenia. IL-6 levels also increased progressively across CRP subgroups, confirming its relationship with systemic inflammation.

These findings align with international evidence supporting IL-6 as a sensitive early biomarker. Küng et al. demonstrated IL-6 peaks early, declining before CRP rises, with strong diagnostic accuracy and a high negative predictive value. Other studies confirm that IL-6 detects EOS better than late-onset sepsis, with cut-offs ranging from 17–84 pg/mL showing good sensitivity and specificity. Chatterjee et al. and Abdel-Hakim et al. reported significantly higher IL-6 levels in septic neonates, while Boskabadi et al. and Eichberger & Resch identified IL-6 as the most reliable cytokine for diagnosis. Meta-analyses further validate IL-6, with pooled sensitivity of ~80% and specificity of ~84%.

Taken together, IL-6 is a rapid and dependable biomarker, particularly valuable for ruling out EOS due to its strong negative predictive value. Its combination with CRP may improve accuracy, but even alone, IL-6 provides significant clinical utility in guiding early intervention and potentially reducing unnecessary antibiotic exposure.

CONCLUSION

Umbilical cord blood Interleukin-6 (IL-6) shows promise as an early and sensitive biomarker for diagnosing early-onset neonatal sepsis. Its significant association with CRP levels and inverse correlation with platelet counts highlight its relevance in detecting systemic inflammation, even in the absence of culture-positive results. These findings support the potential utility of IL-6 in guiding early intervention, though larger studies with culture-confirmed cases are needed to validate its clinical application.

Category	Subcategory	Frequency	Percentage (%)
Mother's Age Group	18–20 years	4	8
	20–24 years	13	26
	25–29 years	24	48
	30–34 years	9	18
	35+ years	2	4
Obstetric Score	Primi	22	44
	G2	13	26
	G3	10	20
	G4	3	6
	Grand multipara (≥5 pregnancies)	1	2
Gestational Age	30–34 weeks	3	6

	34–36 weeks	8	16
	37–38 weeks	34	68
	39+ weeks	7	14
Comorbidities	No comorbidity	20	40
	Diabetes	6	12
	Hypertension	4	8
	Hypothyroidism	6	12
	Anemia/ Thalassemia	3	6
	Oligohydramnios/FGR	3	6
	Infections/Vaginitis	3	6
	Surgical/Obstetric History	3	6
	Other	2	4

Category	Subcategory	Frequency	Percentage (%)
Maternal Fever	Yes	11	22
	No	39	78
PROM (Premature Rupture of Membranes)	No PROM	37	74
	<12 hours	4	8
	12–18 hours	6	12
	>18 hours	3	6
Prolonged Labour	Yes	1	2
	No	49	98
Fetal Distress	Yes	26	52
	No	24	48
Intrapartum Antibiotics (Cefotaxime)	Yes	30	60
	No	20	40

Category	Subcategory	Frequency	Percentage (%)
Mode of Delivery	Normal Vaginal Delivery	19	38
	Assisted Vaginal Delivery	3	6
	Elective LSCS	17	34
	Emergency LSCS	11	22
Sex of Infant	Female	27	54
	Male	23	46
Birth Weight (kg)	<1.0 (Extremely low)	1	2
	1–1.5 (Very low)	1	2
	1.5–2.5 (Low)	10	20
	2.5–3.4 (Normal)	34	68
	≥3.5 (High)	4	8
Initial Resuscitation Needed	Yes	12	24
	No	38	76
GRBS (mg/dL)	45–70	8	16
	70–99	25	50
	100–125	8	16
	≥126	9	18
CRP Levels	Normal	22	44
	Mildly Elevated (6+ to <24+)	14	28
	Highly Elevated (≥24+)	14	28
Blood Culture	No Growth	50	100
TLC (cells/mm³)	Mean	17,389.20	SD = 4,222.80
ANC (cells/mm³)	Mean	9,737.77	SD = 3,388.57
Platelet Count (cells/mm³)	Mean	224,618.00	SD = 77,923.89
Interleukin-6 (pg/mL)	Mean	48.74	SD = 9.62

Parameter	Pearson Correlation (r)	Significance
Baby Total Leukocyte Count	0.380	0.110
Absolute Neutrophil Count	0.534	0.109

Variable	Group	IL-6 Mean ± SD (pg/mL)	p-value
Maternal Fever	Yes	57.39 ± 9.23	0.047
	No	49.23 ± 9.05	
PROM	Yes	49.51 ± 10.96	0.738
	No	48.46 ± 9.25	
Fetal Distress	Yes	51.60 ± 10.60	0.027
	No	45.63 ± 7.46	
Initial Resuscitation Needed	Yes	49.05 ± 9.76	0.019
	No	45.64 ± 2.70	

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