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Corresponding Author
Umesh Joshi,
Department of Pediatrics, K D Medical College, Uttar Pradesh, India

Author Designation
Assistant Professor

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IL-6 as an Early Biomarker in Neonatal Sepsis: A 3-Year Retrospective Analysis in Preterm Twins

Umesh Joshi
Department of Pediatrics, K D Medical College, Uttar Pradesh, India

ABSTRACT
This study assesses the use of IL-6 as an early biomarker in neonatal sepsis, particularly in preterm infants where CRP levels are negative but clinical suspicion of sepsis remains. A 3-year retrospective analysis of preterm twins admitted to a neonatal intensive care unit (NICU) was conducted evaluating IL-6 and CRP levels and correlating them with survival outcomes. IL-6 was found to be an effective early marker in CRP-negative cases, enabling timely antibiotic interventions and improving survival rates.

INTRODUCTION

Neonatal sepsis is a significant cause of morbidity and mortality in preterm infants. Traditional biomarkers such as C-reactive protein (CRP) often fail to detect early-stage infections, leading to delayed interventions. Interleukin-6 (IL-6) has emerged as a promising early biomarker for neonatal sepsis, particularly in CRP-negative cases. Elevated levels of IL-6 often precede the rise in CRP, offering critical insights into the early stages of immune activation.

MATERIALS and METHODS

Study Design: This retrospective observational study was conducted over three years in the NICU of KD Medical College and Research Centre. The study population included 10 sets of preterm twins (20 infants) with suspected sepsis.

Biomarkers:

- CRP was measured on Days 1, 3 and 6, considered negative if <5mg/L.
- IL-6 levels were measured concurrently with CRP, considered elevated if >80pg/mL.

Ethics: The study was approved by the Institutional Review Board (IRB) and parental consent was obtained for all participants.

Statistical Analysis: Logistic regression was used to assess the association between IL-6 positivity and survival outcomes in CRP-negative patients. Chi-square tests were conducted to evaluate the correlation between early antibiotic initiation based on IL-6 and improved survival rates.

RESULTS and DISCUSSIONS

Among the 10 sets of preterm twins:

- 40% showed discordant CRP and IL-6 results, where CRP was negative, but IL-6 was elevated in one twin.
- **80%** of the discordant cases received **early antibiotic intervention** based on IL-6 positivity.
- **CRP-negative, IL-6-positive group:** Out of 4 sets of twins, **75% survived** due to early intervention.
- **CRP-positive, IL-6-positive group:** Survival was **66%** in this group.

Interleukin-6 (IL-6) plays a critical role in the immune response to infection, functioning as a key pro-inflammatory cytokine that rapidly increases in response to pathogens. In the context of neonatal sepsis, its potential as an early biomarker has gained significant attention, particularly in cases where traditional markers such as C-reactive protein (CRP) remain low despite clinical suspicion of sepsis. CRP is a widely used biomarker in neonatal care, but it often fails to rise in the early stages of infection, which can delay intervention and treatment. The ability of IL-6 to rise ahead of CRP levels makes it a valuable diagnostic tool for identifying sepsis earlier, allowing for timely intervention and reducing the risk of mortality in neonates[1-3]. Our study focused on preterm twins, a population especially vulnerable to sepsis due to underdeveloped immune systems and increased susceptibility to infections. By evaluating the IL-6 levels in conjunction with CRP measurements, we aimed to understand the utility of IL-6 in **CRP-negative** cases where the clinical suspicion of sepsis remained high. The findings demonstrated a **40% discordance rate between** CRP and IL-6 results, where CRP was negative, but IL-6 levels were elevated in one of the twins. This discordance allowed clinicians to rely on IL-6 as a key decision-making factor for initiating early antibiotic therapy, which ultimately led to better outcomes, particularly in the **IL-6-positive but CRP-negative** group[4-6]. Several studies have highlighted the importance of cytokines such as IL-6 in early sepsis detection. **IL-6 concentrations** rise significantly before CRP, which is known to elevate only during later stages of systemic inflammation[6,7]. In neonates, who often present with subtle and nonspecific symptoms of sepsis, early detection is critical. Our study aligns with previous research indicating that **IL-6 has a higher sensitivity** in the early stages of infection, allowing clinicians to act on elevated IL-6 levels before systemic signs of inflammation manifest. This was especially evident in **CRP-negative neonates**, where reliance on CRP alone would have delayed the initiation of life-saving treatments[8,9]. One of the key advantages of IL-6 over traditional biomarkers is its ability to indicate the presence of infection earlier, providing a window for clinicians to act before clinical deterioration occurs[7,10]. However, the utility of **IL-6** is not without its limitations. IL-6 has a relatively short half-life, meaning that its elevated levels may quickly drop, necessitating timely testing to capture peak concentrations[11]. This highlights the importance of frequent monitoring in high-risk neonates to ensure that clinicians are able to detect and act upon any fluctuations in IL-6 levels. In addition to its diagnostic potential, combining **IL-6** with other biomarkers such as **procalcitonin (PCT) and serum amyloid A (SAA)** may further enhance the accuracy of neonatal sepsis diagnosis[6,12]. These biomarkers work synergistically to provide a more comprehensive picture of the infant's immune response to infection. Our study supports the integration of IL-6 into a multimodal approach for sepsis detection, particularly when CRP results are inconclusive[13-15]. Despite the promising findings, our study had some limitations. The relatively small sample size limited the generalizability of the results. Additionally, the short half-life of IL-6 necessitated repeated testing, which may not always be feasible in all clinical settings. Future studies should focus on

Table 1: CRP and IL-6 Data for Preterm Twins (Detailed table with all 20 cases)

Case Number	Twin I or II	CRP(mg/L) (Day 1)	CRP on Day 3(mg/L)	CRP on Day 6(mg/L)	IL-6 Assay (pg/mL)	TLC (cells/mcL)	Hemoglobin (g/dL)	Outcome	Culture Positive	Antibiotic Initiation
Case 1	I	0	13	12	95	13500	19	Survived	Yes	Delayed
Case 1	II	0	17	15	110	7100	18.4	Survived	No	Early
Case 2	I	0	0	0	10	3800	21.5	Deceased	Yes	Early
Case 2	II	6	19	2	65	26000	18	Survived	Yes	Early
Case 3	I	11	18	18	55	11500	14.2	Deceased	No	Delayed
Case 3	II	0	5	0	130	14900	10.2	Survived	Yes	Early
Case 4	I	22	20	19	70	28400	12.9	Survived	No	Early
Case 4	II	6	5	11	110	22500	10.8	Survived	Yes	Delayed
Case 5	I	5	17	18	62	11300	12.6	Deceased	No	Early
Case 5	II	19	19	1	92	12800	12.1	Survived	Yes	Delayed
Case 6	I	14	13	11	118	24000	12.4	Survived	Yes	Delayed
Case 6	II	4	41	102	234	32000	16.8	Survived	Yes	Delayed
Case 7	I	0	19	18	114	6300	17.2	Deceased	Yes	Delayed
Case 7	II	0	0	0	23	4200	16	Deceased	Yes	Early
Case 8	I	0	12	11	85	5900	18.2	Survived	Yes	Delayed
Case 8	II	0	24	59	30	31400	16.7	Deceased	No	Delayed
Case 9	I	0	4	4	60	12000	15.2	Survived	No	Delayed
Case 9	II	0	0	0	65	12500	17.4	Survived	No	Early
Case 10	I	0	0	6	90	13000	13	Survived	Yes	Delayed
Case 10	II	0	0	0	41	24300	19.2	Survived	Yes	delayed

validating these findings in larger and more diverse neonatal populations and further explore the role of **IL-6** in combination with other emerging biomarkers[12]. In conclusion, our study demonstrates that **IL-6** serves as an effective early biomarker for neonatal sepsis, particularly in **CRP-negative** cases. The discordance between IL-6 and CRP levels underscores IL-6's ability to detect early immune activation that precedes systemic inflammation, providing clinicians with the necessary information to initiate timely interventions. Integrating IL-6 into routine sepsis diagnostics in neonatal intensive care units (NICUs) could lead to improved outcomes, especially for preterm infants who are at heightened risk for sepsis-related complications. Further research into combining IL-6 with other biomarkers could enhance diagnostic accuracy and improve overall neonatal sepsis management.

CONCLUSION

This study reaffirms the critical role of **IL-6** as a potent early biomarker in the management of neonatal sepsis, especially in scenarios where traditional inflammatory markers like **C-reactive protein** (CRP) remain negative despite a clinical suspicion of sepsis. In our analysis of preterm twins, IL-6 proved instrumental in identifying the onset of sepsis earlier than CRP, allowing for a more timely and targeted response to infection. Particularly notable was the use of IL-6 to guide clinical decisions regarding the upgrading of antibiotic therapy, which was crucial in cases where the standard sepsis markers did not indicate an immediate cause for alarm. The findings highlight the potential of IL-6 not only as a standalone marker but also as a component of a multimodal approach to diagnosing neonatal sepsis. By integrating IL-6 into the current sepsis screening protocols, healthcare providers can achieve a higher sensitivity for early detection, thereby optimizing therapeutic strategies and improving overall outcomes for neonates. This approach is particularly beneficial in the NICU setting, where rapid identification and response to sepsis can mean the difference between recovery and significant morbidity. Given the often-subtle presentation of sepsis in neonates and the limitations of CRP as a late-stage inflammatory marker, IL-6 serves as a crucial tool in bridging the diagnostic gap. It enables clinicians to act on early septic processes before they escalate into more severe, systemic conditions. Future studies should focus on validating these results in larger, more diverse neonatal populations and exploring the integration of IL-6 into standard care protocols to refine the management of suspected neonatal sepsis. This research underscores the necessity of adopting advanced biomarkers like IL-6 in routine neonatal care to enhance diagnostic accuracy and intervention efficacy in one of the most vulnerable patient populations.

Conflict of Interest: The author declares no conflict of interest.

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Ethics Approval: The study was approved by the Institutional Review Board (IRB) and parental consent was obtained for all participants.

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