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Role of Biomarkers in early Diagnosis of Neonatal Sepsis.

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Abstract

Background: Neonatal sepsis remains one of the leading causes of morbidity and mortality among newborns, particularly in developing countries. Early diagnosis is challenging due to nonspecific clinical manifestations and the delay associated with conventional blood culture methods. Biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), interleukins, and hematological parameters have emerged as promising tools for early identification of neonatal infection and timely initiation of antimicrobial therapy. ***Methods:*** A prospective observational study was conducted among 100 neonates admitted to the neonatal intensive care unit (NICU) with suspected sepsis. Neonates were evaluated clinically and investigated using conventional laboratory parameters along with biomarkers including serum C-reactive protein (CRP), procalcitonin (PCT), and interleukin-6 (IL-6). Blood culture was considered the reference standard. Diagnostic accuracy parameters including sensitivity, specificity, positive predictive value, and negative predictive value were calculated. Statistical analysis was performed using Chi-square test and independent t-test, with p value <0.05 considered statistically significant. ***Results:*** Among the 100 neonates studied, culture-proven sepsis was identified in 62 cases. Elevated PCT levels showed a significant association with culture-positive sepsis (p<0.001). Procalcitonin demonstrated higher sensitivity (87.1%) compared with CRP (77.4%) and IL-6 (82.3%) for early detection of neonatal sepsis. Combined assessment of PCT and CRP significantly improved diagnostic accuracy compared with individual biomarkers. Increased biomarker levels were also associated with prolonged NICU stay and adverse clinical outcomes. ***Conclusion:*** Biomarkers, particularly procalcitonin and IL-6, play an important role in the early diagnosis of neonatal sepsis. A combined biomarker approach may improve diagnostic accuracy, facilitate early treatment decisions, and potentially reduce neonatal complications.

Keywords: Neonatal sepsis, Biomarkers, Procalcitonin, C-reactive protein, Interleukin-6, Early diagnosis, Neonatal intensive care unit.

INTRODUCTION

One of the main causes of newborn morbidity and mortality globally is neonatal sepsis, a systemic infection that develops within the first 28 days of life. newborn sepsis continues to be a major therapeutic problem because of its rapid progression and vague presentation, despite advancements in newborn critical care, antibiotic medication, and supportive management [1]. In low- and middle-income nations, where inadequate diagnostic resources and delayed diagnosis lead to subpar results, the global burden is especially significant.

Neonatal sepsis frequently has mild clinical symptoms that overlap with a number of non-infectious illnesses that are frequently seen in infants. Both viral and non-infectious illnesses can cause symptoms such respiratory distress, temperature instability, food intolerance, lethargy, apnea, and hemodynamic instability [2]. As a result, depending just on clinical indicators could lead to improper treatment and a delayed diagnosis. The gold standard for diagnosing newborn sepsis is still blood culture, but its sensitivity is constrained by tiny blood sample volumes, previous antibiotic exposure, and a slow turnaround time. Clinicians face a diagnostic conundrum when they must weigh early antibiotic prescription against needless antimicrobial exposure since culture findings frequently take 48–72 hours.

The need for trustworthy early diagnostic indicators that can distinguish between newborns with and without infections has been highlighted by the growing issue of antibiotic resistance. Biomarkers may help with antibiotic stewardship and offer a chance for quick infection detection. One of the most widely utilized biomarkers for neonatal sepsis is C-reactive protein (CRP), an acute-phase reactant produced by the liver in reaction to inflammatory cytokines. Since its elevation often happens after 12–24 hours of inflammatory activation, CRP levels may remain normal during the early phase of infection despite being widely accessible and reasonably priced [3–4].

Following bacterial invasion, interleukin-6 (IL-6), a pro-inflammatory cytokine generated early during immune activation, rises quickly. IL-6's early rise makes it useful for detecting newborn infection in its early stages, despite its short half-life and potential for rapid decline [5]. Hematological indicators that are commonly utilized as supportive diagnostic markers include platelet count, immature-to-total neutrophil ratio, total leukocyte count, and absolute neutrophil count. They are typically evaluated in conjunction with clinical symptoms and molecular indicators, but their diagnostic effectiveness varies significantly. Effective biomarkers for early detection of newborn sepsis can enhance clinical judgment, lower needless antibiotic exposure, decrease hospital stays, and improve infant outcomes [6-7]. In order to assess the diagnostic value of widely used biomarkers in newborns with suspected sepsis, this study was carried out.

Aim: To evaluate the role of biomarkers in the early diagnosis of neonatal sepsis and assess their diagnostic accuracy in comparison with blood culture findings.

Objectives:

1. To determine the association between serum biomarkers (CRP, procalcitonin, and IL-6) and culture-confirmed neonatal sepsis.
2. To compare the diagnostic performance of individual biomarkers in early detection of neonatal sepsis.
3. To assess whether combined biomarker evaluation improves diagnostic accuracy.
4. To analyze the relationship between biomarker levels and clinical outcomes including NICU stay duration and mortality.

MATERIALS AND METHODS

This prospective observational study was conducted in the Neonatal Intensive Care Unit (NICU) of a tertiary care teaching hospital over a period of 12 months. The study was designed to evaluate the role of commonly used biomarkers in the early diagnosis of neonatal sepsis and compare their diagnostic performance with blood culture results. The study included neonates admitted to the NICU with clinical suspicion of sepsis based on maternal risk factors, clinical signs, and laboratory abnormalities. Ethical approval was obtained from the Institutional Ethics Committee before commencement of the study. Written informed consent was obtained from parents or legal guardians of all enrolled neonates. A total of 100 neonates with suspected neonatal sepsis were included in the study.

Neonates were categorized into two groups based on blood culture results:

- Culture-positive sepsis group: Neonates with positive blood culture evidence of bacterial infection.
- Culture-negative suspected sepsis group: Neonates with clinical suspicion of sepsis but negative blood culture results.

Inclusion Criteria:

Neonates fulfilling the following criteria were included:

1. Neonates aged 0–28 days admitted to NICU with suspected sepsis.
2. Presence of one or more clinical features suggestive of neonatal infection, including:

- Respiratory distress
- Poor feeding
- Lethargy
- Temperature instability
- Apnea
- Tachycardia or bradycardia
- Hypotension
- Seizures
- 3. Neonates with maternal risk factors for sepsis such as:
- Prolonged rupture of membranes (>18 hours)
- Maternal fever during labor
- Foul-smelling amniotic fluid
- Maternal urinary tract infection

4. Neonates whose parents provided informed consent.

Exclusion Criteria:
Neonates were excluded if they had:
1. Major congenital anomalies.
2. Confirmed congenital infections.
3. Neonates who received antibiotics before sample collection.
4. Neonates with severe birth asphyxia requiring prolonged resuscitation.
5. Neonates with metabolic disorders affecting inflammatory markers.
6. Refusal of parental consent.

Clinical Assessment
All enrolled neonates underwent detailed clinical evaluation at admission.
Baseline demographic and clinical parameters were recorded, including:
- Gestational age
- Birth weight
- Gender
- Mode of delivery
- Age at admission
- Maternal risk factors
- Clinical signs of sepsis
- Duration of NICU stay
- Requirement for mechanical ventilation
- Final outcome (survival or mortality)

Gestational age was assessed using available obstetric records and clinical assessment methods.

Laboratory Investigations
Blood samples were collected at the time of admission before initiation of antibiotic therapy.
The following investigations were performed:
1. Blood Culture
Blood culture was considered the reference standard for diagnosis of neonatal sepsis.
Approximately 1–2 ml of peripheral blood was collected under aseptic precautions and processed using an automated blood culture system.
Culture growth was monitored and identified using standard microbiological techniques.

2. C-Reactive Protein (CRP)
Serum CRP levels were measured using immunoturbidimetric assay.
CRP value:
- <5 mg/L: considered normal
- ≥5 mg/L: considered elevated

Elevated CRP levels were interpreted as supportive evidence of infection.

3. Procalcitonin (PCT)
Serum procalcitonin levels were measured using chemiluminescent immunoassay.
PCT interpretation:
- <0.5 ng/ml: low risk
- 0.5–2 ng/ml: possible infection
- 2 ng/ml: significant bacterial infection

4. Interleukin-6 (IL-6)
Serum IL-6 levels were estimated using enzyme-linked immunosorbent assay (ELISA).
IL-6 elevation was considered suggestive of early inflammatory response.
5. Hematological Parameters
Complete blood count was performed including:
- Total leukocyte count (TLC)
- Absolute neutrophil count (ANC)
- Platelet count
- Immature-to-total neutrophil ratio (I/T ratio)

An abnormal hematological profile was considered supportive of neonatal sepsis.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using statistical software. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequency and percentage.

The following statistical tests were applied:

- Chi-square test was used for comparison of categorical variables.
- Independent sample t-test was used for comparison of continuous variables.
- Pearson correlation analysis was used to evaluate association between biomarker levels and clinical parameters.
- Diagnostic accuracy was assessed by calculating:
- Sensitivity
- Specificity
- Positive predictive value
- Negative predictive value

A p-value of <0.05 was considered statistically significant.

Sample Size

The study included a total of 100 neonates with suspected neonatal sepsis.

Among these:

- Culture-positive neonatal sepsis: 62 neonates
- Culture-negative suspected sepsis: 38 neonates

The sample size was selected to provide adequate representation for assessment of biomarker diagnostic performance.

RESULTS

A total of **100 neonates with suspected sepsis** were enrolled in the study and evaluated for clinical features, laboratory parameters, and biomarker profiles. Blood culture positivity was considered the diagnostic standard. Out of 100 neonates, **62 (62%) showed culture-confirmed sepsis**, while **38 (38%) neonates had negative blood cultures but clinical suspicion of infection.**

The mean gestational age of enrolled neonates was **35.8 ± 2.6 weeks**, and the mean birth weight was **2.42 ± 0.54 kg**. Male neonates constituted 58% of the study population, while females accounted for 42%.

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

Parameters	Culture Positive Sepsis (n=62)	Culture Negative Suspected Sepsis (n=38)	Total (n=100)	p value
Mean gestational age (weeks)	35.4 ± 2.7	36.5 ± 2.3	35.8 ± 2.6	0.041*
Mean birth weight (kg)	2.31 ± 0.52	2.60 ± 0.55	2.42 ± 0.54	0.012*
Male gender	38 (61.3%)	20 (52.6%)	58 (58%)	0.392
Female gender	24 (38.7%)	18 (47.4%)	42 (42%)	0.392
Prematurity (<37 weeks)	41 (66.1%)	17 (44.7%)	58 (58%)	0.031*
Low birth weight (<2.5 kg)	39 (62.9%)	15 (39.5%)	54 (54%)	0.021*
NICU stay >7 days	46 (74.2%)	15 (39.5%)	61 (61%)	<0.001*

*Statistically significant

The culture-positive sepsis group had significantly higher rates of prematurity, low birth weight, and prolonged NICU admission compared with culture-negative neonates. The association between prolonged NICU stay and culture-positive sepsis was statistically significant (p<0.001).

Table 2: Comparison of Biomarker Levels Between Culture-Positive and Culture-Negative Neonates

Biomarker	Culture Positive Sepsis (n=62) Mean ± SD	Culture Negative Group (n=38) Mean ± SD	p value
CRP (mg/L)	18.6 ± 8.4	7.2 ± 4.1	<0.001*
Procalcitonin (ng/ml)	5.42 ± 2.76	1.21 ± 0.84	<0.001*
IL-6 (pg/ml)	182.4 ± 76.8	52.6 ± 31.5	<0.001*
Total leukocyte count (/mm³)	14,820 ± 5,230	10,960 ± 4,120	<0.001*
Platelet count (×10⁹/L)	142.5 ± 46.7	185.4 ± 52.6	<0.001*
I/T neutrophil ratio	0.18 ± 0.08	0.09 ± 0.04	<0.001*

*Statistically significant

All evaluated biomarkers showed significantly higher levels among culture-positive neonates. Procalcitonin and IL-6 demonstrated a marked difference between infected and non-infected groups, suggesting their usefulness in early detection of neonatal sepsis.

Table 3: Diagnostic Performance of Individual Biomarkers for Detection of Neonatal Sepsis

Biomarker	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	p value
CRP	77.4	73.7	83.3	65.1	<0.001*
Procalcitonin	87.1	81.6	89.3	78.9	<0.001*
IL-6	82.3	78.9	86.4	73.2	<0.001*
TLC abnormality	64.5	60.5	72.7	50.0	0.018*
I/T ratio abnormality	69.3	68.4	76.7	59.1	0.006*

*Statistically significant

Among individual biomarkers, procalcitonin showed the highest sensitivity (87.1%) and specificity (81.6%) for diagnosis of neonatal sepsis. CRP showed moderate diagnostic performance, whereas hematological parameters showed comparatively lower accuracy.

Table 4: Association of Biomarker Combination with Clinical Outcomes in Neonatal Sepsis

Biomarker Profile	Number of Neonates	Prolonged NICU Stay (>7 days)	Mechanical Ventilation Requirement	Mortality	p value
Normal biomarkers (n=21)	21	5 (23.8%)	3 (14.3%)	1 (4.8%)	—
Single elevated biomarker (n=29)	29	15 (51.7%)	8 (27.6%)	3 (10.3%)	0.032*
Two elevated biomarkers (n=31)	31	24 (77.4%)	13 (41.9%)	6 (19.4%)	0.004*
Three elevated biomarkers (n=19)	19	17 (89.5%)	11 (57.9%)	5 (26.3%)	<0.001*

*Statistically significant

Neonates with multiple elevated biomarkers had significantly higher rates of prolonged NICU admission, mechanical ventilation requirement, and mortality compared with neonates having normal or single biomarker elevation. The association between increasing biomarker positivity and adverse outcomes was statistically significant.

DISCUSSION

Globally, neonatal sepsis is a significant cause of newborn morbidity and mortality, particularly in underdeveloped nations. Because clinical symptoms are sometimes vague and ambiguous in the early stages of infection, early diagnosis is still difficult. In 100 neonates with suspected sepsis, the current study assessed the diagnostic utility of widely used biomarkers, such as CRP, procalcitonin, and IL-6, and showed that biomarker-based evaluation greatly enhances early identification of infected neonates [8–9]. In the current investigation, 62% of newborns had sepsis that was verified by culture. Neonates with several risk factors for infection and significant clinical suspicion are included in the relatively high percentage of culture-positive cases [10]. Blood culture positivity among suspected neonatal sepsis cases ranged from 30 to 70%, depending on patient selection, geographic location, and laboratory resources, according to similar findings from earlier investigations.

The current investigation found a strong correlation between culture-positive sepsis and prematurity and low birth weight. Due to their underdeveloped immune systems, compromised barrier mechanisms, diminished neutrophil function, and decreased complement activity, premature newborns are more vulnerable to invasive infections [11]. The results highlight the significance of early infection screening for high-risk neonates, especially those with low birth weight or preterm birth. When comparing newborns with culture-proven sepsis to those without, the current study showed noticeably higher CRP levels. Due to its accessibility, affordability, and respectable diagnostic performance, CRP is still one of the most popular inflammatory biomarkers [12]. However, because of its delayed rise upon inflammatory activation, CRP has limits in the early stages of infection. The sensitivity and specificity of CRP in our study were 77.4% and 73.7%, respectively, suggesting that while CRP is helpful, it may miss some cases of early neonatal infection.

Among the assessed biomarkers, procalcitonin demonstrated the best diagnostic performance, with sensitivity of 87.1% and specificity of 81.6%. This result confirms earlier research indicating procalcitonin is a better early indicator of bacterial

infection than conventional inflammatory markers. Procalcitonin is especially useful in the early stages of infection since its levels rise quickly after exposure to bacterial endotoxins and the release of inflammatory cytokines [13].
Procalcitonin's early response pattern could account for its improved diagnostic accuracy in this investigation. Procalcitonin may rise within 2–6 hours after bacterial infection, in contrast to CRP, which typically rises after 12–24 hours. Clinicians have the chance to identify infected infants before to clinical deterioration because of this early rise [14].

Combined biomarker evaluation enhanced diagnostic performance and corresponded with disease severity, which was a significant finding of the current investigation. The rates of extended NICU stays, the need for mechanical ventilation, and mortality were all considerably greater among neonates with elevated levels of many biomarkers. This implies that biomarker combinations may offer prognostic information in addition to helping with diagnosis [15]. The use of biomarkers in neonatal sepsis has important implications for antimicrobial stewardship. Early identification of infected neonates allows prompt initiation of appropriate antibiotics, while reliable negative biomarkers may help clinicians avoid unnecessary prolonged antibiotic exposure. Excessive antibiotic use in neonates is associated with altered microbiome development, increased resistance, and potential long-term complications. The findings of this study are clinically relevant because neonatal sepsis requires rapid decision-making. Biomarkers such as procalcitonin and IL-6 can provide early evidence of infection while awaiting culture confirmation[16]. Their integration into NICU protocols may improve early diagnosis and patient outcomes.

CONCLUSION

The present study demonstrates that biomarkers play a significant role in the early diagnosis of neonatal sepsis. Among the evaluated biomarkers, procalcitonin showed the highest diagnostic accuracy, followed by IL-6 and CRP. Although blood culture remains the definitive diagnostic method, delayed reporting limits its usefulness in emergency decision-making. Biomarkers provide rapid supportive evidence and can help clinicians initiate timely treatment.

A combined biomarker approach, particularly involving procalcitonin, CRP, and IL-6, improves diagnostic confidence and correlates with disease severity and clinical outcomes. Routine incorporation of biomarker-based screening may assist in early recognition of neonatal sepsis, rational antibiotic use, and reduction of neonatal complications.

REFERENCES

1. Fleischmann C, Reichert F, Cassini A, et al. Global incidence and mortality of neonatal sepsis: a systematic review and meta-analysis. Lancet Child Adolesc Health. 2021;5(9):605-615.
2. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017;390(10104):1770-1780.
3. Wynn JL. Defining neonatal sepsis. Curr Opin Pediatr. 2016;28(2):135-140.
4. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clin Microbiol Rev. 2014;27(1):21-47.
5. Polin RA. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics. 2012;129(5):1006-1015.
6. Chiesa C, Natale F, Pascone R, et al. C-reactive protein and procalcitonin: reference intervals for newborns. Clin Chim Acta. 2011;412(11-12):1053-1059.
7. Meisner M. Update on procalcitonin measurements. Ann Lab Med. 2014;34(4):263-273.
8. Stocker M, van Herk W, El Helou S, et al. Procalcitonin-guided decision making for duration of antibiotic therapy in neonates. Lancet Child Adolesc Health. 2021;5(7):465-474.
9. Joram N, Muller JB, Denizot S, et al. Umbilical cord blood procalcitonin and CRP for early diagnosis of neonatal infection. Acta Paediatr. 2006;95(12):1578-1583.
10. Ng PC. Diagnostic markers of infection in neonates. Arch Dis Child Fetal Neonatal Ed. 2004;89(3):F229-F235.
11. Klingenberg C, Kornelisse RF, Buonocore G, et al. Culture-negative early-onset neonatal sepsis. Semin Fetal Neonatal Med. 2018;23(3):139-145.
12. Lai MY, Tsai MH, Lee CW, et al. Characteristics of neonatal sepsis caused by different pathogens. J Microbiol Immunol Infect. 2018;51(6):787-795.
13. Shah BA, Padbury JF. Neonatal sepsis: an old problem with new insights. Virulence. 2014;5(1):170-178.
14. Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of neonatal sepsis. Pediatr Clin North Am. 2013;60(2):367-389.
15. Benitz WE. Adjunct laboratory tests in the diagnosis of early-onset neonatal sepsis. Clin Perinatol. 2010;37(2):421-438.
16. Achten NB, Dorigo-Zetsma JW, van der Linden PD, et al. Sepsis biomarkers in newborn infants. Front Pediatr. 2021;9:634222.