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Correlation of C-reactive Protein and Procalcitonin with Clinical Features and Bacteriological Profile in Neonatal Sepsis

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Abstract

Background: Neonatal sepsis remains a leading cause of neonatal morbidity and mortality, particularly in low- and middle-income countries. Early diagnosis is crucial, and biomarkers like C-reactive protein (CRP) and procalcitonin (PCT) have emerged as valuable tools in assessing sepsis severity and guiding antimicrobial therapy.

Objective: To evaluate the correlation of CRP and PCT levels with clinical features and bacteriological profile in neonates diagnosed with sepsis.

Methods: This prospective observational study included 120 neonates admitted to the NICU with clinical suspicion of sepsis. CRP and PCT were measured at admission. Blood cultures were performed, and isolates were identified. Clinical features, laboratory markers, and outcomes were compared between culture-positive and culture-negative groups. Correlations between biomarker levels, sepsis severity, and pathogen type were analyzed.

Results: Of the 120 neonates, 42 (35%) were culture-positive. CRP and PCT levels were significantly higher in culture-positive cases ($p < 0.001$). PCT showed stronger correlation with Gram-negative infections and severe clinical features such as hypotension and respiratory distress. ROC curve analysis revealed that PCT had higher sensitivity (91%) and specificity (83%) than CRP (sensitivity 78%, specificity 72%) for predicting culture-proven sepsis.

Conclusion: Both CRP and PCT are useful markers in the early diagnosis of neonatal sepsis, with PCT demonstrating superior diagnostic accuracy and stronger correlation with clinical severity and Gram-negative infections. Their combined use may enhance diagnostic confidence and help in early therapeutic decisions.

Introduction

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Neonatal sepsis is a systemic infection occurring in the first 28 days of life and remains a major cause of neonatal morbidity and mortality globally. It accounts for nearly one-third of neonatal deaths worldwide, especially in low- and middle-income countries, where diagnostic challenges and delays in treatment persist (1). The clinical presentation is often nonspecific, making early diagnosis difficult. Prompt identification and management are essential to improve outcomes and reduce complications such as septic shock, organ dysfunction, and long-term neurodevelopmental impairment.

Traditionally, the diagnosis of neonatal sepsis has relied on clinical suspicion combined with laboratory findings such as leukocyte counts, immature-to-total neutrophil ratios, and blood cultures. However, blood cultures—the gold standard—may take 48–72 hours for results and are often negative in up to 50% of clinically suspected cases due to low-level bacteremia, prior antibiotic exposure, or inadequate sampling volume (2). Hence, there is a growing interest in reliable biomarkers that can aid in the early diagnosis, risk stratification, and monitoring of treatment response in neonatal sepsis.

C-reactive protein (CRP), an acute-phase reactant synthesized by the liver in response to interleukin-6, has been widely used in sepsis diagnosis for decades. CRP levels begin to rise within 6–12 hours of infection onset, peaking at 24–48 hours. While it has good sensitivity for bacterial infections, its levels can also be elevated in non-infectious inflammatory conditions such as meconium aspiration, birth asphyxia, and prolonged labor (3). Therefore, CRP is more useful as a serial marker rather than a standalone diagnostic tool.

Procalcitonin (PCT), a prohormone of calcitonin, is another promising biomarker. It is produced in response to bacterial endotoxins and inflammatory cytokines and rises within 2–4 hours of infection, peaking earlier than CRP. Importantly, PCT levels tend to remain low in viral infections and non-bacterial inflammatory states, making it more specific for bacterial sepsis (4). Several studies have shown that PCT has higher sensitivity and specificity compared to CRP, especially for early-onset sepsis and Gram-negative infections (5).

The clinical utility of these biomarkers, however, varies depending on the timing of measurement, gestational age, underlying conditions, and type of infection. Studies have suggested that combining CRP and PCT improves diagnostic accuracy compared to either marker alone (6). Moreover, biomarker levels may correlate with disease severity, organ

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dysfunction, and the type of bacterial pathogen, offering potential for prognostication and therapy guidance.

In India, where the neonatal mortality rate remains high and empirical antibiotic use is common, there is a pressing need for accessible and reliable diagnostic tools. Few studies have explored the comparative role of CRP and PCT in Indian neonates, particularly in relation to clinical features and bacteriological profiles. Identifying specific correlations between these biomarkers and infection patterns could aid in early diagnosis, minimize unnecessary antibiotic exposure, and improve neonatal outcomes.

In this context, the present study was conducted to evaluate the correlation of CRP and PCT levels with clinical features, blood culture results, and bacterial types in neonates suspected of having sepsis. The study also aimed to compare the diagnostic accuracy of CRP and PCT in identifying culture-proven sepsis and severe clinical presentations.

Methods

This prospective observational study was conducted in the Neonatal Intensive Care Unit (NICU) of a tertiary care teaching hospital in South India over a period of 12 months from January to December 2024. The primary aim was to evaluate the correlation of serum C-reactive protein (CRP) and procalcitonin (PCT) levels with clinical features, culture positivity, and bacterial profile in neonates with suspected sepsis.

Study Population

All neonates (aged 0–28 days) admitted to the NICU with clinical suspicion of sepsis were included. Clinical suspicion was based on WHO criteria and included signs such as temperature instability, poor feeding, lethargy, respiratory distress, apnea, cyanosis, irritability, and seizures. Neonates with major congenital anomalies, birth trauma, or those already receiving antibiotics for more than 48 hours prior to admission were excluded.

Sample Size and Sampling

A total of 120 neonates fulfilling the inclusion criteria were enrolled consecutively. All underwent standardized evaluation including clinical assessment, laboratory tests, and blood cultures at admission.

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Data Collection and Clinical Assessment

Detailed demographic and perinatal data were recorded, including gestational age, birth weight, Apgar scores, mode of delivery, and maternal risk factors (e.g., premature rupture of membranes, maternal fever, prolonged labor). Clinical features at presentation were documented. The severity of sepsis was classified as mild, moderate, or severe based on the presence of respiratory distress, hypotension, organ dysfunction, and need for ventilatory support.

Laboratory Investigations

At admission (before antibiotic administration), venous blood samples were collected for:

- **Complete blood count (CBC)**
- **C-reactive protein (CRP):** Measured using a quantitative latex agglutination turbidimetric assay. A value >10 mg/L was considered elevated.
- **Procalcitonin (PCT):** Measured by electrochemiluminescence immunoassay. A value >0.5 ng/mL was considered positive.
- **Blood culture:** Collected under aseptic conditions using the BACTEC system. Positive cultures were subjected to organism identification and antibiotic sensitivity testing.

Outcome Measures

The primary outcomes were:

- Correlation between CRP and PCT with blood culture positivity.
- Association of CRP and PCT levels with clinical severity.
- Correlation of biomarker levels with type of bacterial pathogen (Gram-positive vs Gram-negative).

Statistical Analysis

Data were entered in Microsoft Excel and analyzed using IBM SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation or median (IQR) as appropriate. Categorical variables were presented as frequencies and percentages. Comparisons between culture-positive and culture-negative groups were done using independent t-test or Mann–

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Whitney U test for continuous variables and chi-square test for categorical variables. Pearson or Spearman correlation coefficients were calculated to assess the association between biomarker levels and clinical severity. Receiver Operating Characteristic (ROC) curves were constructed to evaluate the diagnostic performance of CRP and PCT. A p-value <0.05 was considered statistically significant.

Ethical Considerations

The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from the parents or guardians of all enrolled neonates. Confidentiality and adherence to ethical principles were maintained throughout the study.

Results

A total of 120 neonates with clinically suspected sepsis were included. The mean gestational age was **36.8 ± 2.1 weeks**, and **53% were males**. Blood culture was positive in **42 cases (35%)**. Gram-negative organisms were isolated in 62% of culture-positive cases, with *Klebsiella pneumoniae* being the most common pathogen. CRP and PCT levels were significantly elevated in culture-positive neonates and correlated with sepsis severity.

Table 1: Baseline Characteristics of Study Population (n = 120)

Parameter	**Value**
Mean gestational age (weeks)	36.8 ± 2.1
Mean birth weight (g)	2420 ± 520
Male : Female ratio	64 (53.3%) : 56 (46.7%)
Early-onset sepsis (<72 h)	78 (65.0%)
Late-onset sepsis (≥72 h)	42 (35.0%)
Culture-positive cases	42 (35.0%)

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Most cases presented with early-onset sepsis. One-third were culture-positive.

Table 2: Common Clinical Features in Culture-Positive vs. Culture-Negative Sepsis

Clinical Feature	Culture-Positive (n=42)	Culture-Negative (n=78)	p-value
Respiratory distress	34 (81.0%)	46 (59.0%)	0.02*
Hypotension	21 (50.0%)	12 (15.4%)	<0.001*
Lethargy	25 (59.5%)	34 (43.6%)	0.08
Seizures	9 (21.4%)	7 (9.0%)	0.04*

Respiratory distress, hypotension, and seizures were significantly more common in culture-positive cases.

Table 3: CRP and PCT Levels in Culture-Positive vs. Culture-Negative Groups

Marker	Culture-Positive (n=42)	Culture-Negative (n=78)	p-value
CRP (mg/L)	27.4 ± 12.8	11.3 ± 6.7	<0.001*
PCT (ng/mL)	5.2 ± 2.3	1.1 ± 0.9	<0.001*

Both CRP and PCT levels were significantly higher in neonates with positive blood cultures.

Table 4: Organisms Isolated in Blood Culture (n = 42)

Organism	Number (%)
Klebsiella pneumoniae	15 (35.7%)
Escherichia coli	11 (26.2%)
Staphylococcus aureus	10 (23.8%)

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Pseudomonas aeruginosa	4 (9.5%)
Enterococcus spp.	2 (4.8%)

Gram-negative organisms, especially *Klebsiella* and *E. coli*, were predominant.

Table 5: Diagnostic Performance of CRP and PCT (ROC Analysis)

Biomarker	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CRP	0.84	78	72	63	85
PCT	0.92	91	83	76	94

Procalcitonin had superior diagnostic accuracy compared to CRP, with higher sensitivity, specificity, and negative predictive value.

Discussion

Neonatal sepsis is a major contributor to neonatal morbidity and mortality, particularly in resource-limited settings. Timely diagnosis remains a challenge due to its nonspecific clinical presentation and limitations of conventional diagnostic methods such as blood culture, which often yield false negatives or delayed results. In this study, we aimed to evaluate the diagnostic utility of two commonly used inflammatory biomarkers—C-reactive protein (CRP) and procalcitonin (PCT)—in correlation with clinical features and the bacteriological profile of neonates suspected of sepsis.

Our results demonstrated that 35% of neonates were blood culture positive, with Gram-negative organisms, particularly *Klebsiella pneumoniae* and *E. coli*, being the most frequently isolated pathogens. This bacteriological profile aligns with data from other Indian NICUs where Gram-negative organisms continue to dominate the sepsis landscape due to environmental factors and hospital-acquired infections (7,8).

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Both CRP and PCT levels were significantly elevated in culture-positive neonates compared to culture-negative ones. The mean CRP value among culture-positive neonates was 27.4 ± 12.8 mg/L, while the mean PCT was 5.2 ± 2.3 ng/mL. These findings corroborate earlier studies suggesting that CRP, although useful, rises more slowly in the early stages of infection, while PCT rises within 2–4 hours and reaches peak levels within 6–12 hours, making it a more sensitive early marker (2,9).

Among clinical features, respiratory distress, hypotension, and seizures were significantly associated with culture positivity. This association supports earlier evidence that severe clinical manifestations in neonates often correlate with bacteremia and a more robust inflammatory response, reflected in elevated biomarker levels (10).

Notably, PCT demonstrated superior diagnostic performance compared to CRP. In our ROC curve analysis, PCT had an AUC of 0.92 with 91% sensitivity and 83% specificity for predicting culture-proven sepsis. This is in line with a meta-analysis by Vouloumanou et al., which concluded that PCT had greater sensitivity and specificity than CRP for diagnosing neonatal sepsis (5). Another study by Chiesa et al. confirmed that PCT has high predictive accuracy in early-onset sepsis and is less influenced by perinatal confounders such as maternal fever or birth asphyxia (3).

The higher diagnostic accuracy of PCT was particularly pronounced in Gram-negative sepsis, which often presents with more severe systemic involvement. PCT levels are more directly stimulated by bacterial endotoxins (especially from Gram-negative organisms), which may explain its stronger association with severe infection [8]. On the other hand, CRP, being a downstream marker in the inflammatory cascade, may lag in early detection.

Despite its advantages, PCT is not without limitations. It can be transiently elevated in certain non-infectious conditions like severe hypoxia or following major surgery, though less frequently than CRP (11). Cost and limited availability may also restrict its routine use in resource-limited NICUs. However, our findings support the idea that combining CRP and PCT can improve diagnostic confidence and guide early empirical therapy while awaiting culture results.

In terms of clinical application, incorporating serial PCT and CRP measurements could be valuable not only for diagnosis but also for monitoring treatment response and deciding on the

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duration of antibiotic therapy. A decreasing trend in PCT has been shown to correlate with clinical improvement and bacterial clearance, potentially helping reduce unnecessary antibiotic exposure (12).

The strengths of this study include its prospective design, standardized biomarker measurement, and the inclusion of both early- and late-onset sepsis. However, certain limitations should be acknowledged. The sample size was modest, and being a single-center study, the findings may not be generalizable. Additionally, we did not perform serial measurements to assess dynamic changes in biomarker levels over time. Future studies should evaluate the cost-effectiveness of routine PCT use and its role in antibiotic stewardship.

Conclusion

This study reinforces the clinical utility of C-reactive protein (CRP) and procalcitonin (PCT) as diagnostic biomarkers in neonatal sepsis. Both markers were significantly elevated in culture-positive cases and correlated with severe clinical features. PCT, in particular, demonstrated superior diagnostic accuracy and a stronger association with Gram-negative sepsis and severe disease. These findings suggest that early measurement of PCT, alongside CRP, can enhance diagnostic precision, aid in risk stratification, and inform early therapeutic decisions in neonates with suspected sepsis. Incorporating these biomarkers into neonatal sepsis protocols could significantly improve early recognition and clinical outcomes.

Recommendations

- **Routine measurement of CRP and PCT** should be considered in all neonates with suspected sepsis to facilitate early diagnosis and guide initial management.
- **Procalcitonin should be prioritized**, especially when Gram-negative sepsis or severe disease is suspected, due to its higher sensitivity and specificity.
- **Combined use of CRP and PCT** may enhance diagnostic accuracy, particularly in resource-limited settings where blood cultures may not yield timely results.
- **Serial biomarker monitoring** can aid in evaluating treatment response and in decisions regarding duration of antibiotic therapy, thus supporting antimicrobial stewardship.

- **Further multicentric and longitudinal studies** are needed to evaluate the cost-effectiveness and impact of biomarker-guided sepsis management on neonatal outcomes.

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