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ORIGINAL ARTICLE

Diagnostic Accuracy of Serum Procalcitonin in Early Onset Neonatal sepsis: A tertiary care experience

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ABSTRACT

Background: Early-onset neonatal sepsis (EONS) is a life-threatening condition with nonspecific clinical features and delayed culture results, leading to diagnostic uncertainty.

Objective: To evaluate the diagnostic accuracy of serum procalcitonin in early-onset neonatal sepsis and compare its performance with C-reactive protein (CRP) and total leukocyte count (TLC), using blood culture as the gold standard.

Methods: This cross-sectional analytical study was conducted at Mayo Hospital Lahore from January 2023 to June 2023. A total of 185 neonates were enrolled in the study. After obtaining informed written consent from parents or legal guardians, clinical history and relevant demographic data were recorded. Under strict aseptic precautions, blood samples were collected before the initiation of empirical antibiotic therapy. Samples were sent for serum procalcitonin assay, C-reactive protein (CRP), total leukocyte count (TLC), and blood culture.

Results: Out of 185 neonates, 68 (36.8%) were blood culture-positive. Mean PCT levels were significantly higher in culture-positive cases (4.87 ± 1.6 ng/mL) compared to culture-negative cases (0.91 ± 0.6 ng/mL) ($p < 0.001$). At a cut-off of ≥2.0 ng/mL, PCT showed 88.2% sensitivity, 84.6% specificity, 77.4% PPV, and 92.3% NPV, with an AUC of 0.89. CRP and TLC demonstrated lower diagnostic accuracy. Elevated PCT levels also correlated with poor clinical outcomes such as the need for ventilation, inotropic support, and mortality.

Conclusion: It is concluded that serum procalcitonin is a reliable and early diagnostic marker for neonatal sepsis, outperforming CRP and TLC. Its incorporation into neonatal sepsis protocols may improve early detection, guide clinical decisions, and reduce unnecessary antibiotic use.

Keywords: Procalcitonin, Neonatal sepsis, Biomarkers, Diagnostic accuracy, Blood culture, CRP, TLC.

INTRODUCTION

Early onset neonatal sepsis (EONS), defined as sepsis occurring within the first 72 hours of life, remains a critical global health issue, particularly in low- and middle-income countries where neonatal mortality rates are high[1]. It is a systemic infection usually transmitted vertically from the mother during labor or delivery, and is frequently caused by pathogens such as Group B Streptococcus, Escherichia coli, Listeria monocytogenes, and Klebsiella species. The subtle and often nonspecific clinical presentation in neonates, including respiratory distress, lethargy, temperature instability, or poor feeding, complicates timely diagnosis. This diagnostic uncertainty places clinicians in a difficult position, often leading to empirical antibiotic therapy even in unconfirmed cases, which poses its risks[2]. The cornerstone of definitive diagnosis is a positive blood culture, yet its limitations are widely acknowledged. Blood cultures require 24–72 hours for microbial growth, and even then, sensitivity is compromised by factors such as small blood sample volumes, maternal antibiotic use, and intermittent bacteremia[3]. Moreover, false negatives are common, and culture-negative sepsis remains a diagnostic gray area. As a result, there is an urgent need for rapid, reliable, and sensitive biomarkers that can accurately distinguish septic from non-septic neonates in the earliest stages of illness[4].

Among the biomarkers explored, C-reactive protein (CRP) has been extensively used in neonatal intensive care units (NICUs), but it rises slowly and peaks much later (typically 24–48 hours post-infection), limiting its value in early diagnosis. White blood cell count, immature-to-total neutrophil ratio, and platelet count also lack adequate diagnostic accuracy when used in isolation. In this context, procalcitonin (PCT) has emerged as a potentially superior marker. PCT is a 116-amino-acid peptide precursor of calcitonin that is normally produced in the thyroid gland[5]. However, during systemic bacterial infections, PCT is upregulated in various extrathyroidal tissues, particularly in response to pro-inflammatory cytokines and bacterial endotoxins[6]. One of the notable advantages of PCT is its early rise in circulation, detectable within 2–4 hours of bacterial insult and peaking within 12–24 hours, offering a much earlier window of detection compared to CRP. Furthermore, PCT levels tend to be more specific to bacterial infections and are usually not elevated in viral illnesses, autoimmune disorders, or localized infections, making it a promising candidate for guiding antibiotic stewardship in neonates[7].

However, interpreting PCT levels in neonates is complicated by the physiological surge that occurs shortly after birth. Studies have shown that even healthy neonates exhibit elevated PCT concentrations during the first 24–48 hours of life, likely due to physiological stress at birth, perinatal adaptation, or subclinical inflammation[8]. Therefore, age-adjusted reference ranges must be considered when applying PCT values in the neonatal population. Additionally, factors such as gestational age, birth weight, and perinatal complications may influence baseline PCT levels, which further emphasizes the need for population-specific studies[9]. Several studies have reported high sensitivity and specificity of PCT for diagnosing EONS when appropriate cut-offs are used. Yet, discrepancies in methodologies, assay platforms, timing of sampling, and patient populations have led to inconsistent findings across the literature[10]. In some settings, PCT has been shown to outperform both CRP and hematological indices in detecting neonatal sepsis early, while in others, its diagnostic value has been modest at best. Therefore, local validation is essential to determine whether PCT can be a reliable biomarker in specific clinical contexts, particularly in resource-constrained environments[11].

Objective: This study aims to evaluate the diagnostic accuracy of serum procalcitonin in detecting early onset neonatal sepsis, using blood culture as the reference standard.

METHODOLOGY

This cross-sectional analytical study was conducted at Mayo Hospital Lahore from January 2023 to June 2023. A total of 185 neonates were enrolled in the study. Participants were recruited using a non-probability consecutive sampling technique, including

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all eligible neonates presenting during the study period who met the inclusion criteria.

Inclusion and Exclusion Criteria: Neonates aged ≤72 hours, of either gender, who were clinically suspected of having sepsis were included. Clinical suspicion was based on the presence of one or more of the following features: temperature instability, poor feeding, respiratory distress, irritability, lethargy, or signs of hemodynamic compromise. Neonates with major congenital anomalies, birth asphyxia (Apgar score <4 at 5 minutes), confirmed inborn errors of metabolism, or those who had received antibiotics before blood sampling were excluded from the study.

Data Collection Procedure: After obtaining informed written consent from parents or legal guardians, clinical history and relevant demographic data were recorded. Under strict aseptic precautions, blood samples were collected before the initiation of empirical antibiotic therapy. Samples were sent for serum procalcitonin assay, C-reactive protein (CRP), total leukocyte count (TLC), and blood culture. PCT levels were measured using a standardized high-sensitivity immunoassay technique, and values were interpreted using neonatal age-adjusted reference ranges. Blood cultures were processed using an automated culture system and interpreted according to standard microbiological protocols. The primary outcome was to determine the diagnostic accuracy of serum PCT in detecting early-onset sepsis, with culture positivity taken as the gold standard. Secondary objectives included comparing PCT with other conventional biomarkers, such as CRP and TLC, in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Statistical Analysis: Data were entered and analyzed using SPSS version 17.0. Continuous variables (e.g., serum PCT and CRP levels) were summarized as means and standard deviations, while categorical variables were expressed as frequencies and percentages.

RESULTS

A total of 185 neonates with clinical suspicion of early-onset neonatal sepsis were included in the study. Among them, 102 (55.1%) were male and 83 (44.9%) were female. The mean gestational age was 37.4 ± 1.8 weeks, and the mean birth weight was 2.81 ± 0.45 kg. There was a slight male predominance, with 102 (55.1%) males and 83 (44.9%) females. Blood culture results revealed that 68 (36.8%) neonates had culture-positive sepsis, while 117 (63.2%) had negative cultures. Among the pathogens isolated, E. coli was most frequent (22; 32.3%), followed by Group B Streptococcus (18; 26.4%) and Klebsiella pneumoniae (13; 19.1%).

Table 1: Baseline Characteristics of the Study Population (n = 185)

Variable	Value
Mean gestational age (weeks)	37.4 ± 1.8
Mean birth weight (kg)	2.81 ± 0.45
Gender	
– Male	102 (55.1%)
– Female	83 (44.9%)
Blood culture result	
– Positive	68 (36.8%)
– Negative	117 (63.2%)
Common pathogens isolated	
– E. coli	22 (32.3%)
– Group B Streptococcus	18 (26.4%)
– Klebsiella pneumoniae	13 (19.1%)

Procalcitonin (PCT) and C-reactive protein (CRP) levels were significantly elevated in culture-positive neonates. The mean PCT in infected neonates was 4.87 ± 1.6 ng/mL compared to 0.91 ± 0.6 ng/mL in the culture-negative group ($p < 0.001$). Similarly, mean CRP was higher in the culture-positive group at 18.3 ± 6.9 mg/L versus 6.2 ± 3.5 mg/L ($p < 0.001$).

Table 2: Comparison of Biomarkers Between Culture-Positive and Culture-Negative Groups

Biomarker	Culture Positive (n = 68)	Culture Negative (n = 117)	p-value
Mean PCT (ng/mL)	4.87 ± 1.6	0.91 ± 0.6	<0.001
Mean CRP (mg/L)	18.3 ± 6.9	6.2 ± 3.5	<0.001
Mean TLC (×10^9/L)	14.2 ± 3.8	13.7 ± 4.1	0.21

Procalcitonin, with a cut-off ≥2.0 ng/mL, demonstrated the highest diagnostic accuracy: sensitivity of 88.2%, specificity of 84.6%, PPV of 77.4%, NPV of 92.3%, and an AUC of 0.89 (95% CI: 0.83–0.94). CRP at a ≥10 mg/L threshold showed moderate diagnostic strength with 79.4% sensitivity and 73.5% specificity (AUC: 0.81). TLC, with a cut-off ≥15 ×10^9/L, had poor predictive value with an AUC of only 0.62.

Table 3: Diagnostic Accuracy of Biomarkers for Early Onset Neonatal Sepsis

Biomarker	Cut-off Value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)
Procalcitonin	≥ 2.0 ng/mL	88.2	84.6	77.4	92.3	0.89 (0.83–0.94)
CRP	≥ 10 mg/L	79.4	73.5	65.2	85.6	0.81 (0.75–0.88)
TLC	≥ 15 ×10^9/L	60.3	58.9	48.1	69.2	0.62 (0.54–0.70)

Clinical features were significantly more frequent in culture-positive neonates. Respiratory distress was reported in 49 (72.1%) culture-positive vs. 62 (53.0%) culture-negative neonates ($p = 0.01$). Poor feeding and temperature instability were also more common in the infected group—64.7% vs. 41.0% ($p = 0.002$) and 57.3% vs. 38.5% ($p = 0.02$), respectively. Lethargy showed a similar pattern (52.9% vs. 33.3%, $p = 0.01$). However, irritability did not differ significantly ($p = 0.72$).

Table 4: Clinical Features Among Culture-Positive and Culture-Negative Neonates

Clinical Feature	Culture Positive (n = 68)	Culture Negative (n = 117)	p-value
Respiratory distress	49 (72.1%)	62 (53.0%)	0.01
Poor feeding	44 (64.7%)	48 (41.0%)	0.002
Temperature instability	39 (57.3%)	45 (38.5%)	0.02
Lethargy	36 (52.9%)	39 (33.3%)	0.01
Irritability	18 (26.4%)	28 (23.9%)	0.72

Elevated PCT levels were significantly associated with worse outcomes. Neonates requiring mechanical ventilation (21 cases) had a mean PCT of 6.12 ± 1.2 ng/mL, while those needing inotropic support (15 cases) had even higher levels at 6.31 ± 1.5 ng/mL (both $p < 0.001$). Longer NICU stays (>7 days) were also linked to higher PCT values (5.37 ± 1.4 ng/mL; $p = 0.02$). Most notably, in the 7 neonates who died, PCT was markedly elevated at 7.20 ± 1.1 ng/mL ($p < 0.001$).

Table 5: Correlation Between Serum PCT Levels and Sepsis Severity Indicators (n = 68)

Indicator	Present (n)	Mean PCT (ng/mL) ± SD	p-value
Need for mechanical ventilation	21	6.12 ± 1.2	<0.001
Need for inotropic support	15	6.31 ± 1.5	<0.001
NICU stay >7 days	38	5.37 ± 1.4	0.02
Mortality	7	7.20 ± 1.1	<0.001

DISCUSSION

Early onset neonatal sepsis (EONS) continues to be a major challenge in neonatology due to its nonspecific clinical presentation and the limitations of current diagnostic tools. Our findings highlight the promising role of PCT as a rapid, sensitive, and specific biomarker in the early diagnosis of neonatal sepsis[12].

The incidence of culture-positive sepsis in our study was 36.8%, which aligns with the rates reported in similar studies from comparable healthcare settings. This relatively high prevalence underscores the clinical relevance of accurate and timely sepsis detection tools in neonatal units. Among the pathogens isolated, E. coli, Group B Streptococcus, and Klebsiella pneumoniae were the most common, consistent with global trends in EONS pathogens, especially in developing countries[13].

Procalcitonin levels were significantly higher in neonates with positive blood cultures (mean: 4.87 ± 1.6 ng/mL) compared to those with negative cultures (mean: 0.91 ± 0.6 ng/mL), with a statistically significant p-value (<0.001). These findings support prior evidence that PCT rises early in response to bacterial infection and is not significantly influenced by non-infectious inflammatory conditions in the immediate postnatal period, especially when age-specific cut-offs are applied[14]. At a cut-off value of ≥2.0 ng/mL, PCT demonstrated a high sensitivity (88.2%) and specificity (84.6%), along with a robust AUC of 0.89, indicating excellent diagnostic performance[15]. When compared to CRP and TLC, PCT outperformed both in terms of sensitivity, specificity, and predictive values. CRP, while still useful, showed a delayed response and was less sensitive in the early hours of sepsis onset. TLC, as expected, was the least reliable marker, showing poor discriminatory power between septic and non-septic neonates. This aligns with existing literature, which suggests that hematologic indices alone are insufficient for accurate sepsis diagnosis[16].

Importantly, our study also explored the clinical correlation of elevated PCT levels with sepsis severity indicators[17]. These findings suggest that PCT could serve not only as a diagnostic marker but also as a prognostic indicator in neonatal sepsis[18]. However, certain limitations must be acknowledged. First, while blood culture was used as the reference standard, it is itself not 100% sensitive, and culture-negative sepsis may still exist. Second, we did not perform serial measurements of PCT, which could have provided insight into its utility in monitoring treatment response. Third, physiological elevation of PCT during the first 24–48 hours of life may still confound interpretation despite using adjusted cut-off values. Finally, this was a single-center study, and the generalizability of the findings may be limited. Despite these limitations, our study contributes valuable evidence to the growing body of literature supporting the clinical utility of procalcitonin in neonatal sepsis. In settings with limited access to rapid cultures or molecular diagnostics, PCT can provide timely information to guide antibiotic initiation or discontinuation, potentially reducing unnecessary antibiotic use and improving outcomes.

CONCLUSION

It is concluded that serum procalcitonin is a highly sensitive and specific biomarker for the early diagnosis of early onset neonatal sepsis (EONS). In this study, PCT demonstrated superior diagnostic accuracy compared to traditional markers such as C-reactive protein and total leukocyte count, particularly when an age-adjusted cut-off of ≥2.0 ng/mL was applied. Elevated PCT levels were also significantly associated with clinical severity indicators, including the need for mechanical ventilation, inotropic support, and increased mortality, suggesting its potential utility as a prognostic marker. Given its rapid elevation following bacterial infection and its strong correlation with culture positivity, procalcitonin can serve as a valuable tool in guiding early therapeutic decisions and reducing unnecessary antibiotic exposure in neonates.

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