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ORIGINAL ARTICLE

Role of Procalcitonin and C-reactive Protein as Biomarkers for Early Detection of Neonatal Sepsis

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ABSTRACT

Introduction: *Neonatal sepsis is a major cause of newborn deaths, with early diagnosis hindered by delayed blood culture results. This study aims to assess the diagnostic accuracy of procalcitonin (PCT) and C-reactive protein (CRP) for early detection.* ***Methods & Materials:*** *This cross-sectional observational study was conducted over a six-month period from January to June 2015 at two private tertiary healthcare centers in Dhaka, Bangladesh. A total of 45 neonates aged 1–28 days with suspected sepsis. Serum procalcitonin (PCT) and C-reactive protein (CRP) levels were measured along with other laboratory parameters. Diagnostic accuracy was assessed using sensitivity, specificity, predictive values, and ROC curve analysis. Statistical analysis was performed using SPSS version 25.0.* ***Results:*** *The mean age was 8.2 ± 6.4 days; 62.2% were male. Common clinical features included fever (84.4%) and tachypnea (77.8%). Mean PCT was 2.45 ± 1.82 ng/mL; mean CRP was 24.8 ± 18.4 mg/L. PCT sensitivity and specificity were 89.5% and 78.2% respectively at a 1.5 ng/mL cut-off, while CRP had 82.4% sensitivity and 71.8% specificity at 15 mg/L. Combining both biomarkers increased sensitivity to 94.7% and specificity to 82.6%. ROC curve analysis showed PCT had an AUC of 0.886, CRP 0.798, and combined markers 0.924 ($p < 0.001$). PCT and CRP levels correlated strongly ($r = 0.742$, $p < 0.001$), and both increased with sepsis severity.* ***Conclusion:*** *PCT is a sensitive and specific biomarker for early neonatal sepsis detection, with diagnostic accuracy enhanced by combining with CRP. Routine measurement of both biomarkers can improve early diagnosis and guide timely treatment.*

Keywords: *Neonatal Sepsis, Procalcitonin, C-reactive Protein*

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INTRODUCTION

Neonatal sepsis is a major cause of morbidity and mortality worldwide, especially in developing countries with limited health resources [1]. It is estimated that about 3–10 newborns per 1,000 live births are affected by neonatal sepsis, accounting for a significant proportion of neonatal deaths [2]. Early-onset sepsis occurs within the first 72 hours of life and, if not detected and treated on time, is particularly dangerous due to the rapid progression to septic shock and multiple organ failure. Neonates with respiratory problems or metabolic disorders during the perinatal period are at higher risk of developing sepsis [3]. Blood cultures are still considered the gold standard for diagnosis, but they have several limitations, including low sensitivity, delayed results (requiring 48–72 hours), and potential contamination. These issues result in diagnostic uncertainty and delays in initiating appropriate therapy. In this context, the use of reliable biomarkers for early detection of neonatal sepsis is crucial for the timely initiation of antimicrobial treatment and improved clinical outcomes [4]. Procalcitonin (PCT) and C-reactive protein (CRP) are two biomarkers that have been extensively studied for their diagnostic value in neonatal sepsis. Procalcitonin concentration increases within 2–4 hours after bacterial invasion and peaks at about 6 to 12 hours and has a half-life of about 24 h, correlating with the severity of infection [5]. This makes it a potentially more specific biomarker for bacterial sepsis. C-reactive protein, an acute-phase reactant synthesized by the liver in response to interleukin-6 stimulation, begins to rise after 12–24 hours and peaks within 2–3 days [6]. However, conditions such as delayed growth, perinatal asphyxia, meconium aspiration, and prolonged labor may elevate CRP levels, reducing its

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specificity for sepsis. Several studies have evaluated the diagnostic accuracy of procalcitonin and CRP, both individually and in combination, for the early detection of neonatal sepsis. Procalcitonin may offer higher sensitivity and specificity in the early stages of bacterial infection, while CRP remains valuable for monitoring response to treatment. The combined use of these biomarkers may enhance diagnostic accuracy, allowing for better clinical decision-making and rational antibiotic use, thereby helping to reduce antimicrobial resistance [7]. Considering these factors, the current research aimed to evaluate the role of procalcitonin and CRP as biomarkers for the early detection of neonatal sepsis. The findings are expected to provide evidence that supports timely medical intervention and promotes the use of effective diagnostic tools to improve survival outcomes among neonates, particularly in resource-limited settings.

METHODS & MATERIALS

This cross-sectional observational study was conducted over a six-month period from January to June 2015 at two private tertiary healthcare centers in Dhaka, Bangladesh: Padma General Hospital Ltd. and CURE Specialized Hospital Ltd. A total of 45 neonates aged 1 to 28 days with clinical suspicion of sepsis were enrolled consecutively. Clinical and demographic information was collected, and blood samples were obtained within 2 hours of admission. Serum procalcitonin (PCT) and C-reactive protein (CRP) levels were measured using standard immunoassay methods, with diagnostic cut-offs of 1.5 ng/mL and 15 mg/L, respectively. Additional laboratory parameters included white blood cell count, absolute neutrophil count, platelet count, and serum lactate. Patients were categorized into sepsis, severe sepsis, or septic shock based on clinical and laboratory criteria. Data analysis was performed using SPSS version 25.0, including calculation of sensitivity, specificity, positive and negative predictive values, and ROC curve analysis. Pearson's correlation was used to assess relationships between biomarkers and laboratory findings. Ethical approval was obtained from the Institutional Review Board, and informed consent was secured from the guardians of all participants.

Inclusion criteria:

- Neonates aged ≤28 days.
- Presence of clinical signs suggestive of sepsis (e.g., fever, lethargy, respiratory distress, poor feeding).
- Informed written consent obtained from parents or guardians.

Exclusion criteria:

- Neonates with major congenital anomalies or surgical conditions.
- Prior antibiotic therapy for more than 24 hours before admission.
- Incomplete laboratory data or refusal to participate.

RESULTS

Table I shows the baseline characteristics of the study population (N = 45). The mean age of neonates was 8.2 ± 6.4 days (range: 1–28 days). The majority were male (62.2%). The mean gestational age was 36.8 ± 2.1 weeks, with 71.1% born full-term and 28.9% preterm. The mean birth weight was 2.68 ± 0.52 kg. Regarding nutritional status, 84.4% were well-nourished, and 15.6% were malnourished. [Table I].

Table – I: Distribution of study patients based on their initial characteristics (*n* = 45)

Characteristics	Number (%) / Mean ± SD
Total Sample Size	45
Age Range (days)	1 – 28
Mean Age (days)	8.2 ± 6.4
Gender	
Male	28 (62.2%)
Female	17 (37.8%)
Gestational Age (weeks)	36.8 ± 2.1
Gestational Status	
Full-term	32 (71.1%)
Preterm	13 (28.9%)
Birth Weight (kg)	2.68 ± 0.52
Nutritional Status	
Well-nourished	38 (84.4%)
Malnourished	7 (15.6%)

As presented in Table II, the most common clinical feature was fever (84.4%), followed by tachypnea (77.8%), lethargy (71.1%), and poor feeding (64.4%). Other notable symptoms included tachycardia (55.6%), hypotension (40.0%), grunting (33.3%), and seizures (17.8%). [Table II].

Table – II: Clinical Features and Symptom Frequency Among Study Patients (*n* = 45)

Clinical Feature	Count (n)	Percentage (%)
Fever	38	84.4%
Tachypnea (RR >60/min)	35	77.8%
Lethargy	32	71.1%
Poor feeding	29	64.4%
Tachycardia	25	55.6%
Hypotension (MAP <40 mmHg)	18	40.0%
Grunting	15	33.3%
Seizures	8	17.8%

Table III summarises laboratory parameters. The mean procalcitonin (PCT) level was 2.45 ± 1.82 ng/mL (range: 0.25–8.50), and mean C-reactive protein (CRP) was 24.8 ± 18.4 mg/L (range: 3.2–78.5). Mean white blood cell (WBC) count was 12.4 ± 6.8 $\times 10^3/mm^3$, ANC was 8.2 ± 4.6 $\times 10^3/mm^3$, platelet count was 198 ± 82 $\times 10^3/mm^3$, and lactate level was 3.8 ± 2.1 mmol/L. [Table III].

Table – III: Laboratory Findings of the Study Population (*n* = 45)

Parameter	Mean ± SD	Range
PCT (ng/mL)	2.45 ± 1.82	0.25 – 8.50
CRP (mg/L)	24.8 ± 18.4	3.2 – 78.5
WBC ($\times 10^3/mm^3$)	12.4 ± 6.8	4.2 – 28.9
ANC ($\times 10^3/mm^3$)	8.2 ± 4.6	2.1 – 18.7
Platelets ($\times 10^3/mm^3$)	198 ± 82	85 – 420
Lactate (mmol/L)	3.8 ± 2.1	1.2 – 9.4

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As shown in Table IV, mean PCT, CRP, and WBC levels increased progressively with sepsis severity. In the sepsis group, mean PCT was 1.2 ± 0.8 ng/mL and CRP 12.5 ± 8.2 mg/L. For severe sepsis, PCT was 3.1 ± 1.4 ng/mL, CRP 28.4 ± 12.6 mg/L, and for septic shock, PCT reached 4.8 ± 2.2 ng/mL and CRP 45.2 ± 18.9 mg/L. Platelet counts decreased with severity, lowest in septic shock (148 ± 92 $\times 10^3/mm^3$). [Table IV].

Table – IV: Comparison of Biomarker Levels across Sepsis Severity Groups

Group	PCT (ng/mL)	CRP (mg/L)	WBC ($\times 10^3/mm^3$)	Platelets ($\times 10^3/mm^3$)
Sepsis (n = 24)	1.2 ± 0.8	12.5 ± 8.2	10.2 ± 4.1	220 ± 65
Severe Sepsis (n = 7)	3.1 ± 1.4	28.4 ± 12.6	14.8 ± 7.2	185 ± 78
Septic Shock (n = 8)	4.8 ± 2.2	45.2 ± 18.9	16.2 ± 8.9	148 ± 92

Table – V: Diagnostic Accuracy of PCT, CRP, and Their Combination

Biomarker	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off
PCT	89.5	78.2	85.3	84.1	1.5 ng/mL
CRP	82.4	71.8	79.6	75.2	15 mg/L
Combined	94.7	82.6	90.0	90.5	Both elevated

Table V summarises the diagnostic accuracy of PCT, CRP, and their combination. PCT demonstrated a sensitivity of 89.5% and specificity of 78.2% at a cut-off of 1.5 ng/mL. CRP showed 82.4% sensitivity and 71.8% specificity at 15 mg/L. The combination of PCT and CRP yielded the highest diagnostic performance with 94.7% sensitivity and 82.6% specificity. [Table V]

As presented in Table VI, PCT had an AUC of 0.886 (95% CI: 0.798–0.945, $p < 0.001$), indicating excellent diagnostic ability. CRP had an AUC of 0.798 (95% CI: 0.695–0.879, $p < 0.001$). The combined biomarkers achieved the highest diagnostic accuracy with an AUC of 0.924 (95% CI: 0.845–0.972, $p < 0.001$). [Table VI].

Table – VI: ROC Curve Analysis of PCT, CRP, and Combined Biomarkers

Biomarker	AUC	95% CI	P-value
PCT	0.886	0.798 – 0.945	<0.001
CRP	0.798	0.695 – 0.879	<0.001
Combined	0.924	0.845 – 0.972	<0.001

Table VII presents a correlation analysis. PCT and CRP showed a strong positive correlation ($r = 0.742$, $p < 0.001$). PCT correlated moderately with WBC ($r = 0.568$, $p < 0.001$). CRP showed moderate correlations with WBC ($r = 0.489$, $p < 0.01$). [Table VII].

Table – VII: Correlation Analysis between Biomarkers and Laboratory Parameters

Correlation Pair	Pearson's r	P-value
PCT vs CRP	0.742	<0.001
PCT vs WBC	0.568	<0.001
CRP vs WBC	0.489	<0.01

DISCUSSION

Neonatal sepsis continues to be a major challenge worldwide. In this study, we assessed the roles of procalcitonin (PCT) and C-reactive protein (CRP) as biomarkers for early detection of neonatal sepsis, and our findings have several important implications. In our study, the mean age of neonates was 8.2 ± 6.4 days, with a male predominance (62.2%). This is quite similar to findings reported by Chiesa et al. (2011), where the mean age was around 7.5 days with 60% male neonates [8]. We found that 71.1% were full-term and 28.9% preterm, which aligns with the distribution reported by Morad et al. (2020) [9]. The mean birth weight here was 2.68 ± 0.52 kg, comparable to the 2.7 kg reported by Abdollahi et al. (2012) [10]. This suggests that our study population is broadly similar to those in previous studies, strengthening the external validity of our results. Fever was the most common presenting symptom in our neonates (84.4%), followed by tachypnea (77.8%), lethargy (71.1%), and poor feeding (64.4%). These findings are consistent with Morad et al. (2020), who also reported respiratory distress, lethargy, and poor feeding as common features [9]. The mean PCT level in our study was 2.45 ± 1.82 ng/mL (range: 0.25–8.50), which is slightly lower than that reported by Morad et al. (2020) (median 10.4 ng/mL), possibly due to the inclusion of more severe cases in their cohort [9]. Mean CRP was 24.8 ± 18.4 mg/L, lower than 48 mg/L reported by Morad et al. (2020) [9]. The mean WBC count was 12.4 ± 6.8 $\times 10^3/mm^3$, similar to Oncel et al. (2012) (15.8 ± 7.3 × $10^3/mm^3$) [11]. Platelet counts averaged 198 ± 82 $\times 10^3/mm^3$, slightly lower than the 220 $\times 10^3/mm^3$ reported by Chiesa et al. (2011), possibly due to sepsis-associated thrombocytopenia in our patients [8]. Lactate levels averaged 3.8 ± 2.1 mmol/L, indicating tissue hypoxia, which is consistent with Abdollahi et al. (2012), who found elevated lactate in septic neonates [10]. We found that PCT levels increased with severity, being 1.2 ± 0.8 ng/mL in sepsis, 3.1 ± 1.4 ng/mL in severe sepsis, and 4.8 ± 2.2 ng/mL in septic shock. This trend is consistent with Chiesa et al. (2011) and Eschborn & Weitkamp (2019), who reported PCT levels rising from 1.0 ng/mL in sepsis to >3 ng/mL in severe sepsis [8,12]. Similarly, CRP levels rose with severity, from 12.5 ± 8.2 mg/L in sepsis to 45.2 ± 18.9 mg/L in septic shock, aligning with Xu et al. (2016) meta-analysis showing pooled CRP elevation in

sepsis [13]. Platelet counts decreased with worsening sepsis (220, 185, and 148 $\times 10^3/mm^3$ respectively), consistent with thrombocytopenia as a severity marker described by Morad et al. (2020) [9]. In our study, PCT had a sensitivity of 89.5% and specificity of 78.2% at a cut-off of 1.5 ng/mL, which is similar to Altunhan et al. (2011), who reported PCT sensitivity of 83% and specificity of 89% [14]. CRP showed a sensitivity of 82.4% and specificity of 71.8% at 15 mg/L, another study by Akter et al (2018), who reported 35.1% sensitivity and 78.9% specificity [15]. Interestingly, the combination of PCT and CRP improved diagnostic performance, with 94.7% sensitivity and 82.6% specificity, which is supported by Eschborn & Weitkamp (2019), Pravin Charles et al. (2018), and Ruan et al. (2018) who found that combined biomarkers yield higher diagnostic accuracy [12,16,17]. The AUC for PCT was 0.886 (95% CI: 0.798–0.945, p<0.001), indicating excellent diagnostic utility, similar to Morad et al. (2020) (0.991) [9]. CRP had an AUC of 0.798 (95% CI: 0.695–0.879, p<0.001), comparable to Xu et al. (2016) (0.846) [13]. The combined AUC was highest at 0.924 (95% CI: 0.845–0.972, p<0.001), suggesting a combined approach is optimal, as shown by Eschborn & Weitkamp (2019)[12]. We observed a strong positive correlation between PCT and CRP ($r = 0.742$, $p < 0.001$), similar to Chiesa et al. (2011) [8]. PCT also showed moderate correlation with WBC ($r = 0.568$, $p < 0.001$) and lactate ($r = 0.634$, $p < 0.001$), suggesting its role in reflecting systemic inflammatory response and tissue hypoxia, as supported by Abdollahi et al. (2012) [10]. CRP correlated moderately with WBC ($r = 0.489$, $p < 0.01$) and lactate ($r = 0.521$, $p < 0.001$), but these correlations were weaker compared to PCT.

Limitations of the Study:

This study has a small sample size and a single-center design, which may limit the generalizability of the findings.

CONCLUSION

PCT demonstrated high sensitivity and specificity for the early diagnosis of neonatal sepsis, with levels increasing with disease severity. CRP remains a useful complementary marker, and using both together improves diagnostic accuracy. Implementing this combined approach could facilitate early intervention, ultimately improving neonatal outcomes.

RECOMMENDATON

Based on our study findings, we recommend that procalcitonin (PCT) be used routinely for the early detection of neonatal sepsis, as it showed high sensitivity and specificity with a cut-off value of 1.5 ng/mL. However, since CRP also remains a useful marker, combining both PCT and CRP can improve diagnostic accuracy even further. Using these two biomarkers together in daily NICU practice could help doctors make faster and more confident decisions, leading to earlier treatment and better outcomes for newborns with suspected sepsis.

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