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Original Research Article

Correlation of C - Reactive Protein with Blood Culture in the Diagnosis of Neonatal Sepsis at a Tertiary Care Hospital: A Retrospective Observational Study

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Abstract

Background: Neonatal sepsis remains a major cause of neonatal morbidity and mortality, particularly in developing countries. Early diagnosis is challenging because clinical manifestations are often nonspecific, while blood culture, the gold standard diagnostic method, requires prolonged incubation time and may yield false-negative results. C-reactive protein (CRP) has been widely utilized as a rapid and cost-effective biomarker for the early detection of neonatal sepsis.

Aim: To evaluate the diagnostic utility of CRP by correlating its results with blood culture findings in neonates with suspected sepsis.

Materials and Methods: A retrospective observational study was conducted in the Department of Microbiology of a tertiary care teaching hospital in Ahmedabad, Gujarat, India, from February 2022 to February 2023. One hundred neonates aged ≤28 days with clinical suspicion of sepsis were included. Blood cultures were processed using the BD BACTEC automated blood culture system, and isolates were identified using the VITEK® 2 Compact system. CRP was assessed by latex agglutination and confirmed quantitatively by nephelometry. Blood culture findings were considered the reference standard for evaluating CRP performance.

Results: Blood culture positivity was observed in 35% of neonates. Among culture-positive cases, 30 (85.71%) were CRP positive and 5 (14.29%) were CRP negative. CRP demonstrated a sensitivity of 85.71%, specificity of 46.15%, positive predictive value of 46.15%, negative predictive value of 85.71%, and diagnostic accuracy of 60%. Gram-negative organisms predominated (54.29%) and were associated with higher mean CRP levels (85.2 mg/L) compared with Gram-positive organisms (42.75 mg/L).

Conclusion: CRP is a useful adjunctive screening marker with high sensitivity and negative predictive value for neonatal sepsis. However, owing to its limited specificity, it should be interpreted alongside clinical findings and blood culture results for accurate diagnosis.

Keywords: Neonatal Sepsis, C-Reactive Protein, Blood Culture, Biomarker, Neonatal Infection, Diagnostic Accuracy.

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Introduction

Neonatal sepsis is a systemic inflammatory response syndrome caused by bacterial, viral, or fungal pathogens occurring during the first 28 days of life.

Despite significant advances in neonatal intensive care, neonatal sepsis remains a major cause of morbidity and mortality worldwide, accounting for approximately one-third of neonatal deaths in low- and middle-income countries. [1-3] Clinical diagnosis of neonatal sepsis is difficult because signs and symptoms such as lethargy, poor feeding, respiratory distress, temperature instability, and irritability are often nonspecific. Blood culture remains the gold standard diagnostic method; however, culture results require 24–72 hours and may be affected by prior antibiotic exposure, inadequate blood volume, or low-grade bacteremia. [4-6] Consequently, several biomarkers including CRP, procalcitonin, interleukin-6, and interleukin-8 have been investigated for early diagnosis. CRP is an acute-phase protein produced by the liver in response to inflammatory mediators and rises within 6–12 hours following infection. Due to its accessibility, low cost, and rapid turnaround time, CRP continues to be widely used in neonatal intensive care units. [7-9] The present study aimed to evaluate the diagnostic utility of CRP by

correlating its results with blood culture findings among neonates suspected of sepsis.

Aims and Objectives: To evaluate the correlation between serum CRP levels and blood culture findings in neonates with suspected sepsis and assess the diagnostic performance of CRP.

Materials and Methods

Study Design and Setting: A retrospective observational study was conducted in the Department of Microbiology at a tertiary care teaching hospital in Ahmedabad, Gujarat, India, over a period of one year from February 2022 to February 2023.

The study included neonates admitted to the Neonatal Intensive Care Unit (NICU) and pediatric wards with clinical suspicion of neonatal sepsis.

Study Population: A total of 100 neonates aged ≤28 days with suspected neonatal sepsis were included in the study. Clinical suspicion of sepsis was based on the presence of one or more signs and symptoms including temperature instability, respiratory distress, poor feeding, lethargy, apnea, irritability, cyanosis, or hemodynamic instability.

Inclusion Criteria

- Neonates aged 0–28 days with clinical suspicion of sepsis.
- Neonates for whom both blood culture and C-reactive protein (CRP) testing were performed.

Exclusion Criteria

- Neonates who had received prolonged antibiotic therapy before sample collection.
- Cases with incomplete laboratory or clinical records.
- Samples showing contamination during culture processing.

Sample Collection: Under strict aseptic precautions, approximately 1–2 mL of venous blood was collected from each neonate before initiation of antimicrobial therapy. The blood sample was divided for microbiological culture and CRP estimation.

Image 1: Blood culture bottle.

Blood Culture Processing: Blood samples were inoculated into pediatric blood culture bottles containing soybean-casein digest broth supplemented with carbon dioxide-generating media and incubated in the BD BACTEC automated blood culture system (Becton Dickinson, USA).

Culture bottles were continuously monitored for microbial growth for up to five days. Bottles flagged positive by the instrument were subjected to Gram staining and subcultured onto: Blood Agar, MacConkey Agar, Chocolate Agar (where indicated),Nutrient Agar. Culture plates were incubated aerobically at 35–37°C for 18–24 hours and examined for bacterial growth.

Identification of Isolates: Preliminary identification was based on: Colony morphology, Gram staining characteristics, Catalase test, Coagulase test, Oxidase test, Conventional biochemical reactions.

For definitive identification, isolates were processed using the VITEK® 2 Compact Automated Identification System (bioMérieux, France) employing Gram-positive and Gram-negative identification cards according to the manufacturer's instructions.

Antimicrobial Susceptibility Testing: Antimicrobial susceptibility testing (AST) was performed using the VITEK® 2 Compact automated system and interpreted according to the latest Clinical and Laboratory Standards Institute

(CLSI) guidelines applicable during the study period.Quality control procedures were performed using standard ATCC reference strains including:

C - Reactive protein Estimation: Qualitative CRP testing was performed using a latex agglutination card method. Visible agglutination within the recommended reaction time was considered positive.

Samples positive by qualitative testing were further subjected to quantitative CRP estimation using nephelometry.

Quantitative CRP values were expressed in mg/L. CRP levels greater than the laboratory reference range were considered indicative of an inflammatory response suggestive of infection.

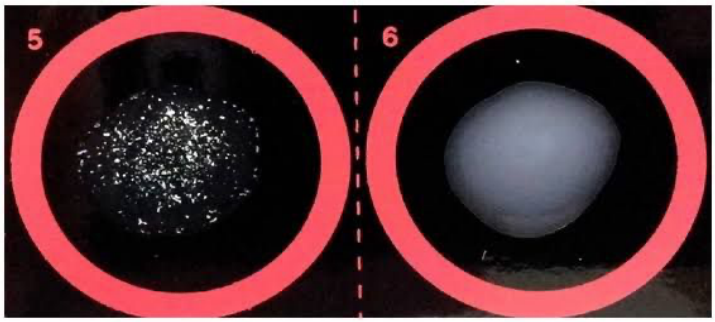

Image 2: CRP testing by latex agglutination test.

Data Collection and Statistical Analysis: Demographic details, laboratory findings, blood culture reports, isolated organisms, and CRP values were retrieved from hospital records and laboratory databases.

Blood culture results were considered the gold standard for diagnosis of neonatal sepsis. Diagnostic performance of CRP was assessed by calculating:

- Sensitivity
- Specificity
- Positive Predictive Value (PPV)
- Negative Predictive Value (NPV)
- Diagnostic Accuracy

Result

A total of 100 neonates with clinically suspected neonatal sepsis were included in the study. Blood culture positivity was observed in 35 (35%) neonates, while 65 (65%) samples were culture negative.

Demographic Characteristics: Among the 35 culture-confirmed cases of neonatal sepsis, male neonates constituted the majority with 22 (62.86%) cases, whereas female neonates accounted for 13 (37.14%) cases, indicating a higher susceptibility among male neonates.

Correlation between CRP and Blood Culture: Out of the 100 neonates studied, CRP positivity was observed in 65 cases. Among the 35 blood culture-positive cases, 30 were CRP positive and 5 were CRP negative. Of the 65 blood culture-negative cases, 35 were CRP positive while 30 were CRP negative.

Table 1: Correlation of CRP with Blood Culture Findings

CRP Status	Blood Culture Positive	Blood Culture Negative	Total
Positive	30	35	65
Negative	5	30	35
Total	35	65	100

Diagnostic Performance of CRP: Using blood culture as the reference standard, CRP demonstrated a sensitivity of 85.71% and specificity of 46.15%. The positive predictive value (PPV) and negative predictive value (NPV) were 46.15% and 85.71%, respectively. The overall diagnostic accuracy of CRP was found to be 60%.

Table 2: Diagnostic Performance of CRP in Neonatal Sepsis

Parameter	Value (%)
Sensitivity	85.71
Specificity	46.15
Positive Predictive Value	46.15
Negative Predictive Value	85.71
Diagnostic Accuracy	60.00

Distribution of Organisms and CRP Levels: Among the 35 culture-positive isolates, Gram-negative bacteria accounted for 19 (54.29%) isolates, while Gram-positive bacteria accounted for 16 (45.71%) isolates. CRP positivity was observed in 18 of 19 Gram-negative infections and 12 of 16 Gram-positive infections. The mean CRP concentration was substantially higher in Gram-negative infections (85.2 mg/L) compared to Gram-positive infections (42.75 mg/L), suggesting a more pronounced inflammatory response associated with Gram-negative bacterial sepsis.

Table 3: CRP Levels in Relation to Type of Organism Isolated

Organism Group	Blood Culture Positive (n)	CRP Positive (n)	Mean CRP (mg/L)
Gram-negative bacteria	19	18	85.2
Gram-positive bacteria	16	12	42.75

Comparison of CRP Positivity among Culture-Positive Cases: Among the blood culture-positive neonates, CRP positivity was detected in 85.71% (30/35) of cases, demonstrating a strong correlation between elevated CRP levels and microbiologically confirmed sepsis.

Conversely, 14.29% (5/35) of culture-positive neonates had negative CRP results, indicating that CRP alone may fail to identify a small proportion of septic neonates.

Discussion

Neonatal sepsis remains a significant cause of neonatal morbidity and mortality worldwide, particularly in developing countries where timely diagnosis and treatment remain major challenges. Despite advances in neonatal intensive care, early diagnosis continues to be difficult because clinical manifestations are often nonspecific and may overlap with other neonatal conditions. [1-3] Blood culture remains the gold standard for diagnosis; however, its utility is limited by delayed turnaround time, prior antibiotic exposure, low-grade bacteremia, and inadequate blood volume collection. [4-6] consequently, biomarkers such as C-reactive protein (CRP) have been extensively evaluated as adjunctive tools for the early diagnosis of neonatal sepsis. [7-10]

In the present study, blood culture positivity was observed in 35% of neonates with suspected sepsis. Similar findings have been reported by Monga et al. [11] and Gupta et al. [13] who observed culture positivity rates comparable to the present study. Other Indian studies have reported blood culture positivity ranging from 25% to 45%, depending on patient population, microbiological techniques employed, and antibiotic exposure prior to sampling. [14-16] The culture positivity observed in our study therefore falls within the expected range reported in the literature.

A male predominance was observed among culture-positive neonates, accounting for 62.86% of cases. Similar observations have been reported by Singel et al. [12] and Bizzarro et al. [17] Male neonates are believed to be more susceptible to neonatal infections due to genetic and immunological factors, including the presence of several immune-regulatory genes on the X chromosome. [17]

CRP demonstrated a sensitivity of 85.71% in the present study, indicating that the majority of culture-confirmed septic neonates were correctly identified by CRP testing. Comparable sensitivity values have been reported by Monga et al. [11] and Chiesa et al. [10] These findings support the usefulness of CRP as an effective screening marker for neonatal sepsis, particularly in resource-limited settings where advanced molecular diagnostic techniques may not be readily available.

The negative predictive value of CRP in the present study was 85.71%, suggesting that a negative CRP result is useful in excluding neonatal sepsis. Similar conclusions have been drawn by Benitz[7] and Hofer et al. [9], who reported that CRP is particularly valuable for ruling out bacterial infection and assisting clinicians in decisions regarding discontinuation of empirical antibiotic therapy. A high negative predictive value is clinically important because it may help reduce unnecessary antibiotic exposure, hospital stay, and associated healthcare costs.

Despite its high sensitivity, CRP demonstrated a relatively low specificity (46.15%) and positive predictive value (46.15%) in the present study. Similar findings have been reported by Ng and Lam [8] and Chiesa et al. [10] Elevated CRP concentrations may also occur in several noninfectious inflammatory conditions such as birth asphyxia, meconium aspiration syndrome, prolonged rupture of membranes, maternal fever, respiratory distress syndrome, and traumatic delivery. [9] Therefore, CRP should not be used as a standalone diagnostic test but rather as an adjunct to clinical assessment and microbiological investigations.

An important finding of the present study was the predominance of Gram-negative bacterial isolates (54.29%) over Gram-positive isolates (45.71%). Similar observations have been reported by Shah et al. [16] and Muley et al. [15], who documented Gram-negative organisms as the predominant etiological agents of neonatal septicemia in tertiary

care centers. Gram-negative pathogens remain important causes of neonatal bloodstream infections and are frequently associated with severe disease and poor clinical outcomes. [5,16]

The mean CRP level among Gram-negative infections (85.2 mg/L) was considerably higher than that observed among Gram-positive infections (42.75 mg/L). Similar findings have been reported by Pourcyrous et al. [18] and Ng and Lam [8] These observations may be explained by the strong inflammatory response induced by Gram-negative bacterial endotoxins, which stimulate the release of cytokines such as interleukin-6 and tumor necrosis factor-alpha, resulting in increased hepatic synthesis of CRP. [18]

Therefore, quantitative CRP estimation may provide an indirect indication of the likely etiological group of pathogens even before culture results become available.

The overall diagnostic accuracy of CRP in the present study was 60%. Although this finding supports the utility of CRP as an adjunctive diagnostic marker, blood culture remains indispensable for definitive diagnosis, organism identification, and antimicrobial susceptibility testing.[4] Modern automated systems such as the BD BACTEC blood culture system and VITEK® 2 Compact have significantly improved pathogen recovery, identification, and antimicrobial susceptibility reporting, thereby facilitating prompt and targeted antimicrobial therapy. [19,20]

Overall, the findings of the present study suggest that CRP is a valuable, rapid, inexpensive, and readily available biomarker for the early screening of neonatal sepsis. However, owing to its limited specificity, CRP should always be interpreted in conjunction with clinical findings and blood culture results. Future studies incorporating larger sample sizes and additional biomarkers such as procalcitonin and interleukin-6 may further improve the diagnostic accuracy of neonatal sepsis. [8,9]

Conclusion

CRP demonstrated high sensitivity and negative predictive value in the diagnosis of neonatal sepsis and can serve as a useful adjunctive screening biomarker. However, due to its limited specificity, CRP should not replace blood culture, which remains the gold standard for definitive diagnosis. Early use of CRP alongside clinical assessment and microbiological investigations may facilitate prompt diagnosis and timely initiation of appropriate antimicrobial therapy, thereby reducing neonatal morbidity and mortality. [4,7,8,9]

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