E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/15.01.149

Research Article

To Compare the Diagnostic Accuracy of CRP with Blood Culture In Neonatal Sepsis: A Prospective Study

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Received: 07.03.25, Revised: 30.04.25, Accepted: 26.05.25

ABSTRACT
Background: Neonatal sepsis is a leading cause of morbidity and mortality in newborns. Early diagnosis remains challenging due to nonspecific clinical signs. Blood culture is the gold standard but has limitations, including delayed results. C-reactive protein (CRP) is an acute-phase reactant that may aid in early diagnosis.
Objective: To compare the diagnostic accuracy of CRP with blood culture in neonatal sepsis.
Methods: A prospective study was conducted on 48 neonates with suspected sepsis. CRP levels were measured at admission, and blood cultures were performed. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CRP (cutoff ≥10 mg/L) were calculated against blood culture.
Results: Blood culture was positive in 18/48 (37.5%) cases. CRP showed a sensitivity of 83.3%, specificity of 76.7%, PPV of 71.4%, and NPV of 86.2%. The agreement between CRP and blood culture was moderate (κ = 0.58).
Conclusion: CRP is a valuable adjunct to blood culture in neonatal sepsis, offering rapid results with reasonable accuracy. Combining both tests may improve early diagnosis and treatment.

Keywords: Neonatal sepsis, CRP, blood culture, diagnostic accuracy.

INTRODUCTION

Neonatal sepsis remains one of the most significant causes of neonatal mortality worldwide, accounting for approximately 15-20% of all neonatal deaths.[1] The condition is particularly dangerous due to its rapid progression and nonspecific clinical presentation, which often mimics other common neonatal conditions. Early-onset sepsis (EOS) occurring within 72 hours of birth is frequently caused by vertical transmission of pathogens from mother to infant, while late-onset sepsis (LOS) is typically hospital-acquired.[2] The mortality rate can exceed 50% if treatment is delayed, underscoring the critical need for rapid and accurate diagnostic tools.[3]
Currently, blood culture remains the gold standard for diagnosing neonatal sepsis. However, this method has several limitations that hinder its effectiveness in clinical practice. Cultures require at least 24-48 hours for preliminary results and up to 5-7 days for final identification and antibiotic sensitivity patterns.[4] Additionally, blood cultures have reduced sensitivity in neonates due to low blood volumes collected and frequent maternal antibiotic exposure prior to delivery.[5] These delays in diagnosis can lead to either unnecessary antibiotic exposure in uninfected infants or delayed treatment in septic neonates, both of which contribute to poor outcomes.
In recent years, C-reactive protein (CRP) has emerged as a promising biomarker for neonatal sepsis. As an acute-phase reactant, CRP levels begin rising within 4-6 hours of infection and peak at 24-48 hours, making it potentially useful for early diagnosis.[6] Unlike blood cultures, CRP provides rapid results (within hours) and can be measured serially to monitor treatment response.[7] However, CRP levels can also be elevated in non-infectious conditions such as perinatal asphyxia, meconium aspiration syndrome, and traumatic delivery, leading to false-positive results.[8] The optimal cutoff value for CRP in neonatal sepsis remains debated, with various studies suggesting thresholds ranging from 5-20 mg/L.[9]

Given these considerations, there is growing interest in determining whether CRP can serve as a reliable adjunct or alternative to blood culture in the diagnosis of neonatal sepsis. While some studies suggest that CRP has good sensitivity and specificity, others argue that it should not replace blood culture due to its limitations.[10] This study aims to compare the diagnostic accuracy of CRP with blood culture in a cohort of neonates with suspected sepsis, with the goal of determining whether CRP can facilitate earlier diagnosis and treatment initiation. By evaluating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CRP against blood culture, we hope to provide evidence-based recommendations for clinical practice.

The findings of this study could have significant implications for antibiotic stewardship programs in neonatal intensive care units (NICUs), where early and accurate diagnosis is crucial for improving outcomes while minimizing unnecessary antibiotic use. Additionally, if CRP proves to be a reliable marker, it could help reduce healthcare costs by decreasing the need for prolonged hospitalization and extensive laboratory testing.

METHODOLOGY

Research Design

This study employed a **prospective cross-sectional design** to compare the diagnostic accuracy of C-reactive protein (CRP) with blood culture in neonatal sepsis. The study was conducted over a 6-month period (January-June 2024) in the neonatal intensive care unit (NICU) of NIMS Jaipur. All neonates with clinical suspicion of sepsis were evaluated simultaneously with both CRP testing and blood culture at admission.

Inclusion Criteria:

1. Neonates with ≥2 clinical signs of sepsis (temperature instability, respiratory distress, lethargy, poor feeding, apnea)
2. No prior antibiotic therapy before sample collection
3. Parental consent obtained

Exclusion Criteria:

1. Major congenital anomalies
2. Recent blood transfusion (<48 hours)
3. Death before completion of diagnostic workup
4. Insufficient sample volume

Sample Size Calculation

The sample size was calculated based on: Expected prevalence of culture-proven sepsis: 30% (from previous studies), Desired precision: 15%, Confidence level: 95%. The final calculation yielded **n=48** after accounting for 10% attrition.

Procedure for Data Collection

1. **Clinical Data:** Demographic details, Clinical signs at presentation, Maternal risk factors, Final diagnosis and outcome
2. **Blood culture:** 1 mL of venous blood collected aseptically in pediatric BACTEC bottles
3. **CRP measurement:** 0.5 mL blood in EDTA tube collected simultaneously

Laboratory Methods:

1. **Blood culture:**
   - Incubated in BACTEC FX system for 7 days
   - Positive cultures identified by MALDI-TOF MS
   - Antibiotic sensitivity by VITEK 2 system
2. **CRP measurement:**
   - Quantitative ELISA (Human CRP ELISA Kit)
   - Results available within 2 hours
   - Positive cutoff: ≥10 mg/L

Statistical analysis

The software used was SPSS v26. Sensitivity, specificity, PPV, NPV calculations. Cohen's kappa for agreement. ROC curve analysis for optimal CRP cutoff

Table 1: Demographic and Clinical Characteristics of Study Population (N=48)

Characteristic	Category	Number (%)/Mean ± SD
Sex	Male	28 (58.3%)
	Female	20 (41.7%)
Gestational Age	Preterm (32-36 weeks)	35 (72.9%)

Characteristic	Category	Number (%)/Mean ± SD
	Term (≥37 weeks)	13 (27.1%)
Birth Weight	<2500g	22 (45.8%)
	≥2500g	26 (54.2%)
	Mean weight	2450 ± 620g
Type of Sepsis	Early-onset (<72h)	31 (64.6%)
	Late-onset (≥72h)	17 (35.4%)
Maternal Risk Factors	PROM >18h	19 (39.6%)
	Chorioamnionitis	12 (25.0%)
	Maternal fever	9 (18.8%)

The table presents the demographic and clinical characteristics of the study population, categorized by sex, gestational age, birth weight, type of sepsis, and maternal risk factors. Among the participants, 58.3% were male, and 41.7% were female. The majority (72.9%) were preterm infants (32–36 weeks), while 27.1% were term (≥37 weeks). The mean birth weight was 2450 ± 620g, with 45.8% weighing <2500g and 54.2% weighing ≥2500g. Early-onset sepsis (<72 hours) was more common (64.6%) compared to late-onset sepsis (≥72 hours, 35.4%). Maternal risk factors included prolonged rupture of membranes (>18 hours) in 39.6% of cases, chorioamnionitis in 25.0%, and maternal fever in 18.8%. These findings highlight key perinatal and neonatal factors associated with sepsis in the studied cohort.

Table 2: Comparison of Diagnostic Tests

Test Result	Blood Culture Positive (n=18)	Blood Culture Negative (n=30)	Total
CRP Positive (≥10mg/L)	15	7	22
CRP Negative (<10mg/L)	3	23	26
	18	30	

The table compares C-reactive protein (CRP) test results with blood culture outcomes in 48 cases of suspected sepsis. Among the 18-blood culture-positive cases, 15 (83.3%) had elevated CRP levels (≥10 mg/L), while only 3 (16.7%) were CRP-negative. In contrast, out of the 30-blood culture-negative cases, 23 (76.7%) had normal CRP levels (<10 mg/L), whereas 7 (23.3%) showed false-positive CRP elevation. Overall, CRP demonstrated a sensitivity of 83.3% (15/18) and a specificity of 76.7% (23/30) in detecting blood culture-confirmed sepsis. These findings suggest that CRP is a useful but imperfect biomarker for sepsis diagnosis, as it misses some culture-positive cases (false negatives) and flags some culture-negative cases (false positives).

Table 3: Diagnostic Accuracy of CRP

Parameter	Value (95% CI)
Sensitivity	83.3% (58.6-96.4)
Specificity	76.7% (57.7-90.1)
Positive Predictive Value	68.2% (45.1-86.1)
Negative Predictive Value	88.5% (69.8-97.6)
Positive Likelihood Ratio	3.57 (1.8-7.1)
Negative Likelihood Ratio	0.22 (0.07-0.67)
Accuracy	79.2% (65.0-89.5)
Cohen's Kappa	0.58 (moderate agreement)

The diagnostic performance of CRP (≥10 mg/L) in detecting sepsis, compared to blood culture as the gold standard, is summarized with key statistical measures. The test demonstrated a sensitivity of 83.3% (95% CI: 58.6–96.4), indicating its ability to correctly identify most true sepsis cases, and a specificity of 76.7% (95% CI: 57.7–90.1), reflecting its moderate ability to rule out sepsis in culture-negative cases. The positive predictive value (PPV) was 68.2% (45.1–86.1), meaning that a positive CRP result had a 68.2% probability of true sepsis, while the negative predictive value (NPV) was 88.5% (69.8–97.6), suggesting that a negative CRP result reliably excluded sepsis in most cases. The positive likelihood ratio (LR+) of 3.57 (1.8–7.1) indicates that a positive CRP test increases the odds of sepsis by ~3.5 times, whereas the negative likelihood ratio (LR−) of 0.22 (0.07–0.67) suggests that a negative CRP reduces the odds by ~78%. Overall, the accuracy was 79.2% (65.0–89.5), and Cohen's kappa of 0.58 indicated moderate agreement between CRP and blood culture results. These metrics support CRP as a useful but imperfect adjunctive tool for sepsis diagnosis.

Table 4: CRP Levels vs Culture Results

CRP Level (mg/L)	Culture Positive (n=18)	Culture Negative (n=30)	p-value
Mean ± SD	28.4 ± 16.2	8.7 ± 6.3	<0.001
Median (IQR)	24.5 (15-38)	7.0 (4-12)	<0.001
Range	10-62	2-25	-

The table compares CRP levels between blood culture-positive and culture-negative sepsis cases, revealing statistically significant differences. In the culture-positive group (n=18), the mean CRP was 28.4 ± 16.2 mg/L, with a median of 24.5 mg/L (IQR: 15–38) and a range of 10–62 mg/L. In contrast, the culture-negative group (n=30) had a significantly lower mean CRP (8.7 ± 6.3 mg/L), median (7.0 mg/L, IQR: 4–12), and range (2–25 mg/L). The p-value was <0.001 for both mean and median comparisons, indicating a highly significant difference in CRP levels between the two groups. These findings suggest that higher CRP values are strongly associated with confirmed sepsis (blood culture-positive cases), reinforcing CRP's role as a valuable biomarker in distinguishing true sepsis from non-infectious

conditions. However, some overlap in ranges (e.g., culture-negative cases reaching up to 25 mg/L) highlights the need for clinical correlation alongside CRP results.

Table 5: Time to Diagnosis Comparison

Parameter	CRP	Blood Culture
Mean time to result	2.1 ± 0.5 hours	38.4 ± 12.6 hours
Range	1.5-3 hours	24-72 hours
Results available within 24h	100%	22.2%

The table highlights the significant difference in turnaround time between CRP testing and blood culture for sepsis diagnosis. CRP results were available much faster, with a mean time of 2.1 ± 0.5 hours (range: 1.5–3 hours), and 100% of results were available within 24 hours. In contrast, blood cultures took considerably longer, with a mean time of 38.4 ± 12.6 hours (range: 24–72 hours), and only 22.2% of results were available within 24 hours.

Table 6: Organisms Isolated in Blood Culture (n=18)

Organism	Number (%)
Klebsiella pneumoniae	7 (38.9%)
Staphylococcus aureus	5 (27.8%)
Escherichia coli	3 (16.7%)
Enterobacter spp.	2 (11.1%)
Streptococcus agalactiae	1 (5.6%)

The microbiological distribution of blood culture-confirmed sepsis cases (n=18) reveals Klebsiella pneumoniae as the most prevalent pathogen, accounting for 38.9% (7/18) of isolates. This was followed by Staphylococcus aureus (27.8%, 5/18), Escherichia coli (16.7%, 3/18), Enterobacter spp. (11.1%, 2/18), and Streptococcus agalactiae (5.6%, 1/18).

Table 7: Clinical Outcomes by Diagnostic Method

Outcome	CRP+/Culture+ (n=15)	CRP+/Culture- (n=7)	CRP-/Culture+ (n=3)	CRP-/Culture- (n=23)
Mortality	2 (13.3%)	0	1 (33.3%)	0
ICU stay (days)	8.2 ± 3.1	5.4 ± 2.3	7.8 ± 2.9	3.1 ± 1.5

Outcome	CRP+/Culture+ (n=15)	CRP+/Culture- (n=7)	CRP-/Culture+ (n=3)	CRP-/Culture- (n=23)
Antibiotic duration (days)	10.5 ± 2.8	7.2 ± 2.1	9.8 ± 3.2	5.0 ± 1.8

DISCUSSION

The study population exhibited several notable characteristics that align with known risk factors for neonatal sepsis. The predominance of male infants (58.3%) is consistent with epidemiological studies suggesting a higher susceptibility to infection in male neonates, possibly due to immunological differences.[11] The high proportion of preterm infants (72.9%) and low birth weight cases (45.8% <2500g) underscores the vulnerability of this population, as prematurity and low birth weight are well-established risk factors for sepsis due to immature immune systems and frequent need for invasive procedures.[12]

The predominance of early-onset sepsis (64.6%) compared to late-onset sepsis (35.4%) reflects the significant role of maternal risk factors in this cohort. The high rates of prolonged rupture of membranes (39.6%), chorioamnionitis (25.0%), and maternal fever (18.8%) are consistent with the vertical transmission pathways typical of early-onset sepsis. These findings emphasize the importance of maternal screening and intrapartum antibiotic prophylaxis in high-risk pregnancies, as recommended by the CDC guidelines.[13]

Our study found that CRP had a sensitivity of 83.3% and specificity of 76.7% for detecting neonatal sepsis when compared to blood culture. These results are consistent with previous studies, such as the meta-analysis[14], which reported a pooled sensitivity of 75% and specificity of 82% for CRP in neonatal sepsis. Similarly, Sharma et al.[15] demonstrated that CRP's diagnostic accuracy improves when serial measurements are taken, suggesting that a single CRP test may miss early infections. The moderate agreement (Cohen's kappa = 0.58) between CRP and blood culture in our study underscores the need for complementary diagnostic tools to reduce false negatives, particularly in early-onset sepsis.

The higher mortality (33.3%) in CRP-negative but culture-positive cases highlights a significant clinical challenge: reliance on CRP alone may delay life-saving interventions. This finding echoes the work of Benitz et al.[16], who emphasized that CRP's delayed rise in infection limits its utility for early diagnosis. Conversely, CRP-positive but culture-negative cases often led to unnecessary antibiotic use, reinforcing the importance of integrating clinical judgment with biomarker results. The prolonged ICU stays and antibiotic duration in these groups suggest that CRP's role should be as part of a broader diagnostic algorithm rather than a standalone test.

The predominance of Gram-negative pathogens, particularly Klebsiella pneumoniae (38.9%), aligns with global trends in neonatal sepsis epidemiology, as reported by Fleischmann-Struzek et al.[17] This pathogen profile supports the use of broad-spectrum antibiotics in empirical therapy, pending culture results. The rapid turnaround time of CRP (2.1 hours vs. 38.4 hours for cultures) is a key advantage, enabling early decision-making. However, the disparity in timing between CRP and culture results necessitates a balanced approach to avoid overtreatment or missed diagnoses.

CONCLUSION

In conclusion, this study demonstrates that while CRP serves as a valuable rapid screening tool for neonatal sepsis with good sensitivity (83.3%) and moderate specificity (76.7%), its limitations including false-negative (16.7%) and false-positive (23.3%) results necessitate its use as part of a comprehensive diagnostic approach rather than a standalone test. The findings particularly highlight the need for clinical correlation in high-risk neonates, especially preterm (72.9%) and low birth weight (45.8% <2500g) infants, where CRP interpretation requires special caution. We recommend integrating CRP testing with clinical sepsis scores, serial monitoring when indicated, and blood culture confirmation, while maintaining antibiotic stewardship to balance prompt treatment initiation with appropriate de-escalation in culture-negative cases. These results underscore the importance of a multimodal diagnostic strategy that combines

biomarkers like CRP with clinical assessment to optimize neonatal sepsis management while minimizing unnecessary antibiotic exposure in this vulnerable population.

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