ORIGINAL ARTICLE

Diagnostic Accuracy of C-reactive Protein in the Diagnosis of Neonatal Sepsis Keeping Blood Culture as Gold Standard

MALIHA MAHMOOD, HABIBULLAH BABAR, AIMAN NIDA

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Correspondence to:

Dr. Maliha Mahmood
Senior Registrar,
Department of Pediatrics,
Balochistan Institute of Child Health Services, Balochistan

E-mail:
malihamahmood36@gmail.com

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ABSTRACT

Objective: To determine the diagnostic accuracy of C-reactive protein in neonatal sepsis keeping blood culture as gold standard.

Study Design: Cross-sectional study.

Place and Duration of Study: This research was conducted in the Department of Pediatrics Medicine at the Balochistan Institute of Child Health Services, Balochistan between October 2021 and March 2022.

Material and Methods: A total of 194 neonates were enrolled in the study, who met the inclusion criteria, from the neonatal intensive care unit (NICU) of the Department of the Pediatric Medicine at the Balochistan Institute of Child Health Services, Balochistan. Their gender, age, weight upon arrival, reason for hospitalization, and length of hospital stay were recorded.

Result: There were 194 neonates who were enrolled in the study. 91 (46.9%) were male and 103 (53.1%) were female. Using a C-reactive protein (CRP) cut-off value of >10 mg/L, the sensitivity of the CRP test in detecting neonatal sepsis, with blood culture as the gold standard, was 56.75%, with specificity, positive predictive value (PPV), and negative predictive value (NPV) of 67.50%, 51.85%, and 71.68%, respectively. The overall accuracy of CRP in diagnosing neonatal sepsis was 63.40%. Diagnostic accuracy was also evaluated in relation to gestational age and birth weight. On average, neonates stayed in the hospital for 4.78 ± 1.67 days.

Conclusion: C-reactive protein is a valuable diagnostic tool for neonatal sepsis, particularly in resource-limited settings where blood culture results are delayed or unavailable. It is most effective when used alongside suggestive clinical features and other diagnostic markers, aiding timely treatment decisions.

Key Words: *Neonatal sepsis, Early onset neonatal sepsis, Late-onset neonatal sepsis, C - reactive protein, Blood culture*

INTRODUCTION

Neonatal sepsis (NS) is a major health threat affecting newborns worldwide. It is a leading cause of illness and death in infants. Sepsis can develop rapidly, and its clinical course can change swiftly, as the symptoms of neonatal sepsis can be mistaken for non-infectious diseases.[1] In routine clinical practice diagnosing neonatal sepsis (NS) accurately often proves

challenging.

Neonatal septicemia is a serious illness but curable if identified early. The most serious signs and symptoms are sometimes vague and are readily mistaken for non-infectious causes. Since diagnostic procedures like blood cultures take time, diagnosing neonatal sepsis accurately is often delayed.[2]

Culture proven sepsis occurs in approximately 2 out of every 1,000 newborns. C-reactive (CRP) along with some other tests like TLC, ANC, and thrombocytopenia are very sensitive in detecting negative cases of neonatal sepsis.[3]

C-reactive protein, an acute-phase protein synthesized by the liver, is produced in response to both inflammatory and infectious triggers. Various prenatal conditions, such as fetal distress, a complicated delivery, and maternal fever, can elevate CRP levels even without a systemic infection. However, due to its limited specificity, CRP is most effective when used in conjunction with another serum biomarker.[4] the objective of conducting this study is to determine the diagnostic accuracy of C-reactive protein in the diagnosis of neonatal sepsis, keeping blood culture as gold standard. In Pakistan, the neonatal mortality rate is about 39 out of 1000 live births, which is quite high compared to other developing countries.[5] Although blood culture is a diagnostic test in evaluating neonatal sepsis, however, its long-awaited results have a major impact on the ongoing treatment of neonatal sepsis in the selection of an appropriate antibiotic timely. C - reactive protein, on the other hand, provides us with real-time early results with a clue for sepsis.[6] We believe that this study will help to determine the value of C-reactive protein in identifying neonatal sepsis. This could ultimately lead to shorter hospital stays and better outcomes for neonates.

MATERIAL AND METHODS

A total of 194 neonates of both genders were enrolled from the neonatal intensive care unit (NICU) of the Pediatrics Department, [Institution Name]. All patients underwent a detailed history and clinical examination and were labeled as having neonatal sepsis as per the operational definition. Neonates were eligible if they were ≤28 days old, had a gestational age between 33 and 42 weeks, and presented with clinical signs suggestive of neonatal sepsis. Both genders were included. Exclusion criteria included neonates with congenital malformations, laboratory-confirmed inborn errors of metabolism, history or clinical evidence of birth asphyxia, hemolytic jaundice, prior antibiotic exposure, or a diagnosis of meconium aspiration syndrome, as these could introduce bias.

The sample size was calculated using a sensitivity and specificity calculator (Open EPI software), with a confidence level (1-α) of 95% and desired precision (d) of 0.09. Based on an expected sensitivity of 77.6% from a prior study in a similar Pakistani population,[7] a minimum of 83 diseased cases was required. Accounting for an estimated 43% prevalence of positive blood cultures[7] and to ensure adequate power for specificity estimates, a total sample of 194 was enrolled.

Blood samples were collected under strict aseptic conditions at admission. Samples were immediately transferred to the hospital laboratory to measure CRP levels, with a cut-off of >10 mg/L considered positive, based on its established balance of sensitivity and specificity in neonatal sepsis diagnostics.[8,9] Concurrently, another sample was sent for blood culture using various culture media to confirm neonatal sepsis. CRP levels were repeated 24 to 48 hours after the initial collection. All laboratory procedures were supervised by a pathologist.

Data were analyzed using SPSS statistical software (version 26). Numerical data (e.g., age, weight, length of stay) were reported as mean ± standard deviation, and qualitative variables (e.g., gender) as n (%). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the CRP test were calculated using 2x2 contingency tables. Stratification by age and gender was performed to assess the impact of these effect modifiers on outcome variables.

RESULTS

The study included 194 neonates, with 91 (46.9%) males and 103 (53.1%) females. The mean weight was 2.53 ± 0.54 kg. All neonates underwent sepsis evaluation through laboratory investigations, including CRP and blood culture. Of the 194 neonates, 81 had positive CRP (>10

mg/L), and 74 had positive blood culture results. The diagnostic accuracy of CRP was evaluated against blood culture, the gold standard. The main 2x2 contingency table for CRP vs. blood culture is presented below **table 1**:

TABLE 1: Comparison of CRP and Blood Culture Outcomes (2×2 Contingency table)

CRP result	Blood culture positive	Blood culture negative	Total
Positive (>10 mg/L)	42	39	81
Negative	32	81	113
Total	74	120	194

Diagnostic Accuracy: Sensitivity = 56.75%, specificity = 67.50%, PPV = 51.85%, NPV = 71.68%, accuracy = 63.40%

The diagnostic accuracy of CRP was also stratified by gender, gestational age, and birth weight. NPV = 69.09%, accuracy = 60.19%

TABLE 2: Assessment of CRP diagnostic accuracy according to gender

Gender	CRP	Blood Culture Positive	Blood Culture Negative	Total
	Positive	18	15	33
Male	Negative	15	43	58
	Total	33	58	91
Female	**CRP**	**Blood Culture Positive**	**Blood Culture Negative**	**Total**
	Positive	24	24	48
	Negative	17	38	55
	Total	41	62	103

Diagnostic accuracy male: Sensitivity = 54.54%, specificity = 74.13%, PPV = 54.54%, NPV = 74.13%, accuracy = 67.03%

Diagnostic accuracy female: Sensitivity = 58.53%, specificity = 61.29%, PPV = 50.00%,

TABLE 3: Assessment of CRP diagnostic accuracy according to gestational age

Gestational age (GA)	CRP	Blood Culture		
		Positive	Negative	Total
	Positive	16	13	29
33-37 weeks	Negative	8	15	23
	Total	**24**	**28**	**52**
	Positive	14	22	36
> 37-40 weeks	Negative	12	51	63
	Total	**26**	**73**	**99**

Diagnostic Accuracy 33-37 Weeks: Sensitivity = 66.66%, specificity = 53.57%, PPV = 55.17%, NPV = 65.21%, accuracy = 59.61%

Diagnostic Accuracy >37-40 Weeks: Sensitivity = 53.84%, specificity = 69.86%, PPV = 38.88%, NPV = 80.95%, accuracy = 65.65%

TABLE 4: Assessment of CRP diagnostic accuracy according to birth weight low (<2.5 kg): Normal (≥2.5 kg):

Birth weight	CRP	Blood culture		
		Positive	Negative	Total
Low (<2.5 kg)	Positive	11	20	31
	Negative	12	35	47
	Total	**23**	**55**	**78**
Normal (≥2.5 kg)	Positive	31	19	50
	Negative	20	46	66
	Total	**51**	**65**	**116**

Diagnostic Accuracy Low weight (<2.5 kg): Sensitivity = 47.82%, specificity = 63.63%, PPV = 35.48%, NPV = 74.46%, accuracy = 58.97%

Diagnostic Accuracy Normal Weight (≥2.5kg): Sensitivity = 60.78%, specificity = 70.76%, PPV = 62.00%, NPV = 69.69%, accuracy = 66.37%

On average, neonates stayed in the hospital for 4.78 ± 1.67 days.

PPV = positive predictive value. NPV = negative predictive value

DISCUSSION

Neonatal sepsis remains a diagnostic challenge due to its rapid progression and nonspecific symptoms. Blood culture, the gold standard, has a low yield, necessitating reliable surrogate tests like CRP. This study evaluated CRP's diagnostic accuracy in a Pakistani NICU setting, where timely diagnosis is critical due to high neonatal mortality and limited laboratory resources.

The rationale for focusing on CRP lies in its rapid availability and ability to guide empirical antibiotic therapy in resource-limited settings. Unlike blood cultures, which may take days, CRP results are available within hours, enabling prompt treatment decisions.[10] This is particularly vital in Pakistan, where delays in blood culture results and high antimicrobial resistance rates underscore the need for accessible biomarkers. CRP's moderate sensitivity and specificity, when combined with clinical judgment and other markers, can reduce unnecessary antibiotic use, addressing the global challenge of antimicrobial stewardship.[11,12]

In our study, CRP (cut-off >10 mg/L) demonstrated a sensitivity of 56.75% and specificity of 67.50%, with an overall accuracy of

63.40%. These findings align with prior studies, though variations exist. For instance, Effat et al. reported a higher sensitivity (76.92%) but lower specificity (53.49%),[13] while Chacha et al. found a sensitivity of 40% at presentation, increasing to 90% with serial testing.[14] Hisamuddin et al. noted a sensitivity increase from 22% to 61% over time.[13] These differences may reflect variations in cut-off values, timing of CRP measurements, or population-specific factors like gestational age and infection prevalence. Recent meta-analyses report pooled sensitivities of 69-77% and specificities of 77-83% for CRP, with improved performance through serial testing.[15,16] Emerging biomarkers like procalcitonin or resistin may offer superior accuracy in some contexts,[17,18] but CRP remains widely accessible and cost-effective.

Stratification by gender, gestational age, and birth weight revealed variations in CRP performance. Notably, neonates with gestational ages of 33-37 weeks showed a higher sensitivity (66.66%) but lower specificity (53.57%), possibly due to higher rates of obstetric interventions in this group, which may elevate CRP levels non-specifically (e.g., due to intrauterine growth restriction). Low-birth-weight neonates (<2.5 kg) had lower sensitivity (47.82%) and specificity (63.63%), suggesting that CRP's diagnostic utility may be reduced in this subgroup. These findings highlight the importance of context-specific cut-offs and serial measurements, as supported by recent studies on CRP dynamics and ratios with other markers like platelets.[19,20]

The study's novelty lies in providing local data from a Pakistani NICU, stratifying CRP accuracy by gestational age and birth weight, and reinforcing its utility in resource- constrained settings. Limitations include the lack of quantitative CRP data for Receiver Operating Characteristic (ROC) analysis to determine an optimal cut-off specific to this population. Future studies should incorporate serial CRP measurements and compare CRP with emerging biomarkers to enhance diagnostic precision.

CONCLUSION

Our study found that CRP, using a cut-off of >10 mg/L, has a sensitivity of 56.75%, specificity of 67.50%, and accuracy of 63.40% in detecting neonatal sepsis, with blood culture as the gold standard. Its rapid availability makes it a valuable tool in resource-limited settings like Pakistan, where blood culture delays are common. CRP is most effective when used with clinical and other inflammatory markers to guide antibiotic therapy, reducing neonatal morbidity and mortality. Further research into serial CRP measurements and novel biomarkers could enhance early sepsis detection, particularly in resource-constrained environments.

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Authors' affiliation

Dr. Maliha Mahmood,
Senior Registrar,
Department of Pediatrics, Balochistan Institute of Child Health Services, Balochistan

Prof. Habibullah Babar,
Professor of Pediatrics, CEO's
Department of Pediatrics, Balochistan Institute of Child Health Services, Balochistan

Aiman Nida
PGR,
Department of Pediatrics, Balochistan Institute of Child Health Services, Balochistan

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Authors’ contribution

MM: Proposed topic basic study design, material and methods and manuscript.
HB: Literature review & referencing and quality insurer.
AN: Data collection, statistical analysis and interpretation of result etc.

All the authors have approved the final manuscript draft and accept the responsibility of research integrity.