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Original Research Article

Importance of C-reactive protein as an early indicator for screening of neonatal sepsis in tertiary care hospital

Dhruvi Dhamsaniya, Aditya Parmar, Hemangini Kharadi, Mansi Bhadresh, Bhadresh Vyas*

Department of Pediatrics, Shri M.P. Shah Medical College, Jamnagar, Gujarat, India

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***Correspondence:**
Dr. Bhadresh Vyas,
E-mail: Bhadreshvyas@yahoo.co.uk

ABSTRACT

Background: Neonatal sepsis remains a leading cause of morbidity and mortality in newborns, especially in resource-limited settings. Early detection is crucial for improving outcomes. This prospective study evaluates the role of C-reactive protein (CRP) as an early screening marker for neonatal sepsis in a tertiary care hospital.
Methods: A total of 220 newborns having risk factors and/or clinical signs of sepsis were included in the study and CRP levels were compared with blood culture results, the diagnostic gold standard.
Results: CRP demonstrated high sensitivity (92.3%) and negative predictive value (NPV) (96.1%), making it reliable for ruling out sepsis. Significant associations were observed between CRP positivity and risk factors such as prematurity, respiratory distress, meconium aspiration, maternal complications, and prolonged hospital stays ($p<0.05$). However, its moderate specificity (58.3%) indicates that CRP should be used alongside clinical findings and blood culture for accurate diagnosis**.**
Conclusions: CRP is a rapid, cost-effective, and sensitive screening tool that can aid in the early detection of neonatal sepsis, facilitating timely intervention and improved clinical outcomes, particularly in resource-constrained settings.

Keywords: Neonatal sepsis, CRP, Blood culture, Prematurity, Low birth weight, Respiratory distress

INTRODUCTION

Neonatal sepsis remains one of the leading causes of morbidity and mortality in neonates, particularly in developing countries like India. It is a clinical syndrome characterized by signs and symptoms of infection during the first 28 days of life, with or without accompanying bacteremia. According to estimates, neonatal sepsis accounts for 30-50% of neonatal deaths in resource-limited settings. Early identification and treatment of sepsis are crucial for improving neonatal survival rates.[1]

Neonatal sepsis is categorized into two types: early onset sepsis (EOS), which occurs within the first 72 hours of life, and late onset sepsis (LOS), which occurs after 72 hours. Risk factors for sepsis include low birth weight, prematurity, prolonged rupture of membranes, maternal peripartum fever, and invasive neonatal procedures.[2,3,12,13]

CRP, an acute phase reactant produced by the liver, is widely used as an inflammatory marker. It rises significantly in response to infection, inflammation, or tissue damage within 4-6 hours and peaks at 48 hours. CRP's high sensitivity makes it a useful screening tool for detecting on- going inflammation in neonates suspected of sepsis. However, elevated CRP levels are not always indicative of sepsis alone, as they can be influenced by other inflammatory conditions such as birth asphyxia and meconium aspiration syndrome (MAS).[4,14]

The present study was conducted to evaluate the role of CRP as an early indicator for screening neonatal sepsis in a tertiary care hospital. The study also aimed to assess the association between CRP values and risk factors like low birth weight, prematurity, and maternal complications, and compare CRP with blood culture results as the gold standard for diagnosing sepsis.

METHODS

This study was conducted to evaluate the role of CRP as an early indicator for screening neonatal sepsis in Guru Gobindsingh hospital, Jamnagar. A prospective observational study was carried out over a period of September 2023 to June 2024, following ethical clearance from the institutional review board. Written informed consent was obtained from the parents or guardians of all participating neonates prior to inclusion.

Study design and population

The study was conducted at the neonatal intensive care unit (NICU) of a tertiary care hospital. A total of 220 neonates admitted to the NICU with clinical suspicion of sepsis were included in the study. Neonates were categorized based on their age of presentation into EOS and LOS. EOS was defined as sepsis occurring within the first 72 hours of life, while LOS was defined as sepsis occurring after 72 hours of life.

Inclusion and exclusion criteria

Neonates with risk factors or clinical features suggestive of sepsis, such as lethargy, poor feeding, temperature instability, respiratory distress, history of meconium aspiration were included in the study. Neonates with congenital malformations and neonates who received antibiotics before admission to our setup were excluded from the study.

Data collection

Detailed clinical history, including maternal risk factors (e.g., prolonged rupture of membranes, maternal fever, and leaking per vaginum), birth history, and neonatal risk factors (e.g., prematurity and low birth weight), was collected for all participants. Thorough physical examinations performed to document signs of sepsis.

Blood samples were collected from all neonates under sterile conditions for CRP measurement and blood culture analysis. CRP levels were measured using a semi-quantitative latex agglutination method. A CRP value greater than 10 mg/L was considered positive. Blood culture was performed as gold standard to confirm sepsis.

Statistical analysis

Data were analyzed using statistical software. Descriptive statistics, such as mean, median, and standard deviation, were used to summarize demographic and clinical characteristics. Sensitivity, specificity, positive predictive value (PPV), and NPV of CRP were calculated, using blood culture results as the reference standard. The association between CRP levels and risk factors, such as low birth weight, prematurity, and maternal complications, was evaluated using chi-square tests. A $p<0.05$ was considered statistically significant.

Study flow

The flow of the study is summarized as follows: Screening of neonates admitted to the NICU with suspected sepsis, collection of maternal and neonatal risk factor data, measurement of CRP levels and performance of blood cultures, correlation of CRP results with blood culture and analysis of diagnostic parameters.

This systematic approach ensured comprehensive data collection, reliable analysis, and meaningful conclusions regarding the role of CRP as an early indicator for neonatal sepsis.

RESULTS

Demographic characteristics

A total of 220 neonates were included in the study. Out of these, 123 (55.9%) were male and 97 (44.1%) were female. Of the total neonates, 119 (54%) were born at term (≥ 37 weeks of gestation), while 101 (46%) were preterm. Table 1 summarizes the demographic characteristics of the study population.

Table 1 presents the demographic characteristics of study population. Total of 220 neonates included, with 55.9% male and 44.1% females. In this study 58.6% of neonates were term, while 41.4% of neonates are preterm.

Table 1: demographic characteristics of the study population, (n=220).

Variables	N (%)
Male	123 (55.9)
Female	97 (44.1)
Term	119 (54)
Preterm	101 (46)

Figure 1 visually highlights the gestational age distribution, emphasizing that preterm neonates constituted 41.4% of the study population. Neonates born at less than 28 weeks accounted for a small proportion (4.5%), indicating their higher risk of complications.

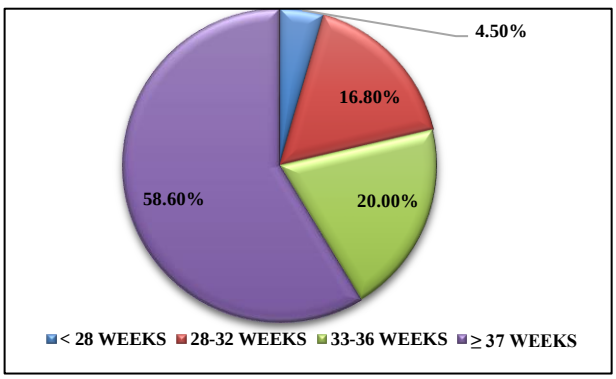

Figure 1: Gestational age distribution: proportion of term and preterm neonates.

Predictive value of CRP over culture

Table 2 presents the predictive value of CRP in comparison to blood culture results. CRP showed a sensitivity of 92.3%, a specificity of 58.3%, a PPV of 40.7%, and a NPV of 96.1%.

Table 2 highlights the high sensitivity (92.3%) and NPV (96.1%) of CRP, making it a reliable tool for ruling out neonatal sepsis. These findings indicate that CRP is a useful screening marker for identifying neonates unlikely to have sepsis, thereby minimizing unnecessary antibiotic use. However, the lower PPV (40.7%) and specificity (58.3%) suggest that CRP alone cannot confirm sepsis and must be interpreted alongside clinical symptoms and confirmatory tests like blood culture.

Table 2: Predictive value of CRP over blood culture.

Predictive value	Value
Sensitivity	92.6%
Specificity	64.2%
PPV	26.6%
NPV	98.4%

The results emphasize that while CRP is effective for initial screening due to its high sensitivity, caution must be exercised when relying solely on CRP for diagnosis. Combining CRP results with other biomarkers and clinical indicators can improve diagnostic accuracy for neonatal sepsis.

A study conducted by Celik et al found-out sensitivity, specificity, PPV and NPV of CRP as 97%, 67%, 39%, 99% which is similar to our study.[5]

Association between CRP and blood culture

Table 3 shows the association between CRP positivity and blood culture results. Among neonates with CRP positivity (n=94), 25 (26.6%) had a positive blood culture, while 69 (73.4%) had a negative blood culture. In contrast, among neonates with CRP negativity (n=126), only 2 (1.6%) had a positive blood culture. The association was highly significant (p<0.001).

Table 3 highlights the strong association between CRP positivity and blood culture positivity, with CRP showing a sensitivity of 92.6% in detecting sepsis.

Table 3: Association between CRP and blood culture results.

CRP result	Culture positive (%)	Culture negative (%)	Total	P value
Positive	25 (26.6)	69 (73.4)	94	<0.001
Negative	2 (1.6)	124 (98.4)	126	
Total	27 (12.3)	193 (87.7)	220	

Figure 2 visually illustrates the association between CRP positivity and blood culture results. The data emphasizes the utility of CRP as a highly sensitive screening tool for neonatal sepsis, even though its specificity remains moderate.

Hisamuddin et al study had neonates with risk factors, 65% CRP positive rate and out of that 60% blood culture positivity. Rest of the 35% CRP negative neonates had 90% blood culture negativity.[6]

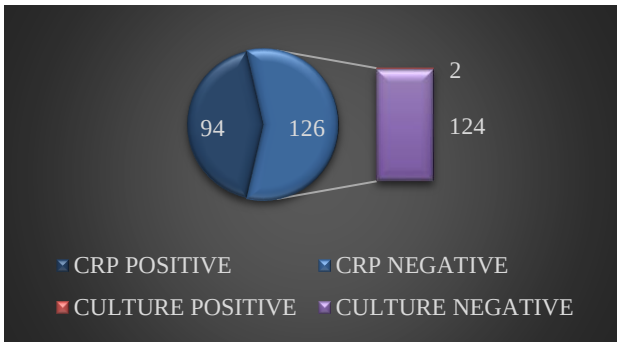

Figure 2: Association of CRP positivity with blood culture results.

Association of gestational age with CRP and blood culture positivity

Table 4 shows the association of gestational age with CRP and blood culture positivity. The proportion of neonates with a positive CRP result decreased with increasing gestational age, from 70.0% in neonates born before 28 weeks to 32.6% in neonates born at term (≥37 weeks). The proportion of neonates with a positive blood culture result also decreases with increasing gestational age, from 40% in neonates born before 28 weeks to 9.3% in neonates born at >37 weeks. Blood culture positivity is less than CRP positivity but overall, prematurity is directly associated with increased chances of sepsis. The association between gestational age and CRP positivity is statistically significant (p=0.001). Association between gestational age and blood culture positivity is statistically significant (p=0.003).

Table 4 demonstrates a clear trend: CRP positivity and blood culture positivity were higher among neonates born at earlier gestational ages. This highlights the vulnerability of preterm neonates to infections, particularly those born before 32 weeks.

Association of respiratory distress with CRP and blood culture positivity

Table 5 presents the association between respiratory distress, CRP positivity, and blood culture results. Among neonates with respiratory distress (n=116), CRP positivity was observed in 69 (59.5%) cases, while blood culture positivity was found in 24 (20.6%) cases. In neonates without respiratory distress (n=104), CRP

positivity was observed in 25 (24.0%) cases, and blood culture positivity was seen in 12 (11.5%) cases.

Table 5 shows a strong association between respiratory distress and CRP positivity, with significantly higher CRP and blood culture positivity rates observed in neonates presenting with respiratory distress. The higher positivity rates in neonates with respiratory distress reinforce its role as an important clinical indicator for sepsis screening.

Association of meconium aspiration with CRP and blood culture positivity

Table 6 shows the association of meconium aspiration with CRP positivity and blood culture results. Among neonates with meconium aspiration (n=21), CRP positivity was observed in 14 (66.7%) cases, while blood culture positivity was noted in 3 (14.2%) cases. In contrast, among neonates without meconium aspiration (n=199), CRP positivity was seen in 80 (40.2%) cases, and blood culture positivity was found in 33 (16.5%) cases.

Table 6 highlights that CRP positivity was significantly higher in neonates with meconium aspiration compared to those without. However, blood culture positivity did not show a significant difference between the two groups. The higher CRP positivity suggests an inflammatory response, while blood culture positivity remained low.

Association of CRP and duration of stay in hospital

Table 6 presents the association between CRP positivity and the duration of hospital stay. Among neonates with CRP positivity (n=94), 66 (70.3%) had a prolonged hospital stay of more than 7 days.

In contrast, among neonates with CRP negativity (n=126), 69 (54.8%) had a prolonged hospital stay. The difference was statistically significant (χ^2=6.2, p=0.012).

Table 7 indicates that CRP positivity is significantly associated with prolonged hospital stays, suggesting that neonates with elevated CRP levels may have more severe infections requiring extended treatment.

Table 4: Association of gestational age with CRP and blood culture positivity.

Gestational age (weeks)	CRP positive, N (%)	CRP negative, N (%)	Positive blood culture, N (%)	Negative blood culture, N (%)	Total
<28	7 (70.0)	3 (30.0)	4 (40)	6 (60)	10
28-32	23 (62.2)	14 (37.8)	10 (27)	27 (73)	37
33-36	22 (50.0)	22 (50.0)	10 (22.7)	34 (77.3)	44
≥ 37	42 (32.6)	87 (67.4)	12 (9.3)	117 (90.7)	129
Total	94	126	36	184	220
	X^2=15.02, df= 3, p=0.001		X^2=13.67, df= 3, p=0.003		

Table 5: Association of respiratory distress with CRP and blood culture positivity.

Respiratory distress	CRP positive, N (%)	CRP negative, N (%)	Positive blood culture, N (%)	Negative blood culture, N (%)	Total
Yes	69 (59.5)	47 (40.5)	24 (20.6)	92 (79.4)	116
No	25 (24.0)	79 (76.0)	12 (11.5)	92 (88.5)	104
Total	94	126	36	184	220
	X^2=28.13, df=1, p<0.0001		X^2=3.84, df=1, p=0.05		

Table 6: Association of meconium aspiration with CRP and blood culture positivity.

Meconium aspiration	CRP positive, N (%)	CRP negative, N (%)	Positive blood culture, N (%)	Negative blood culture, N (%)	Total
Yes	14 (66.7)	7 (33.3)	3 (14.2)	13 (85.7)	21
No	80 (40.2)	119 (59.8)	33 (16.5)	171 (83.5)	199
Total	94	126	36	184	220
	X^2=5.37, df=1, p=0.020		X^2=0.018, df=1, p=0.893		

Table 7: Association of CRP and duration of stay in hospital.

Hospital stays	<7 days, N (%)	>7 days, N (%)	Total
CRP +ve	28 (29.7)	66 (70.3)	94
CRP -ve	57 (45.2)	69 (54.8)	126
Total	85	135	220

DISCUSSION

Higher CRP positivity rates were associated with neonates having respiratory distress, meconium aspiration, birth asphyxia, low birth weight, prematurity and maternal history of PROM >18 hours.

A study was conducted by Belachew et al to determine the association between gestational age and neonatal sepsis. The analysis of this study revealed that neonatal sepsis was significantly associated with the gestational age of newborn with OR 3.36 (95% CI: 2.50, 4.54). Preterm babies were 3.36 more likely to develop neonatal sepsis than term babies.[7]

Rego et al conducted a study to find out diagnostic value of CRP as a marker to predict neonatal sepsis in neonates born with respiratory distress. Study concluded that CRP can predict sepsis early but poor specificity limits its potential benefit as a diagnostic tool. Sensitivity of CRP increases when it is used with other markers of inflammation like IL-6.[8]

Negative CRP results have even more significance in ruling out sepsis. Negative CRP was almost always associated with negative blood culture results and it almost always rules out sepsis. Not giving antibiotics in CRP negative newborns can help reducing unnecessary use of antibiotics and prevent further chances of antibiotics resistance in future.

Hofer et al in their study found out that high CRP values were closely linked to a more severe course of MAS during early phase of disease. These findings reflect the role of inflammation in the pathogenesis of MAS.[9]

Even if blood culture positivity rates are low in MAS in comparison to CRP, a study by Mohamed et al revealed that CRP was markedly elevated in patients with MAS with septicaemia in comparison to MAS without septicaemia.[10]

CRP has a good sensitivity and NPV but it has low specificity and PPV for sepsis when compared to blood culture. CRP has been the most widely used biomarker for neonatal sepsis specially in resource limited settings. With detailed history and clinical examination, results of CRP can be interpretated more efficiently. With cheaper cost and faster results CRP still remains a useful marker for neonatal sepsis.

Hisamuddin et al study had neonates with risk factors, around 65% CRP positive rate and out of that 60% blood culture positivity. Rest of the 35% CRP negative neonates had 90% blood culture negativity.[11]

Positive CRP was also found to be a good predictor for a longer hospital stay, need for invasive ventilation and requirement of inotropes.

Early identification of sepsis with CRP can help clinicians in decision making for initiation of antibiotics and prevent neonatal morbidity and mortality to a significant extent.

Limitation of this study is that, when blood culture results were analysed, it was found that not all the conditions with higher CRP were having blood culture positivity. Newborns with meconium aspiration and birth asphyxia were having falsely high CRP results which could be due to ongoing inflammatory process and not neonatal sepsis. CRP is an inflammatory marker and it was elevated in all inflammatory processes but it cannot differentiate septicaemia from other non-septicaemic inflammatory conditions like meconium aspiration. Using CRP alone without any other marker or detailed history can lead to falsely high prediction of sepsis and unnecessary usage of antibiotics. So clinical judgement based on history and simultaneous use of other laboratory parameters like TLC, ANC etc. for decision making for antibiotics initiation.

CONCLUSION

This study highlights the importance of CRP as a reliable early indicator for screening neonatal sepsis in a tertiary care hospital. The findings demonstrate that CRP has high sensitivity (92.3%) and NPV (96.1%), making it particularly effective in ruling out sepsis and guiding early clinical decisions. The association of CRP positivity with risk factors such as prematurity, low birth weight, respiratory distress, meconium aspiration, and maternal complications emphasizes its relevance in identifying at-risk neonates. Furthermore, CRP positivity showed a strong correlation with blood culture results, which remains the gold standard for diagnosing sepsis, reinforcing CRP's role as a valuable adjunctive tool. Incorporating CRP measurement into routine clinical practice, alongside other diagnostic markers, can enhance the accuracy and efficiency of neonatal sepsis management in resource-limited settings.

Recommendations

The diagnostic utility of CRP should be interpreted in the context of a comprehensive clinical evaluation and employing serial CRP assays. CRP response can be influenced by gestational age. CRP is a nonspecific biomarker, as it elevates in conditions other than sepsis as well. Therefore, it should be used in conjunction with additional markers such as procalcitonin and other sepsis screening markers. Incorporating these recommendations into clinical practice can enhance the diagnostic and prognostic utility of CRP while ensuring judicious use of antibiotics in management of suspected neonatal sepsis.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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