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Original Research Article

Relationship between maternal C-reactive protein, cord blood C-reactive protein and early onset neonatal sepsis in a tertiary care centre in North Kerala

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ABSTRACT

Background: Early-onset neonatal sepsis (EONS) remains a major cause of neonatal morbidity and mortality, with diagnosis often delayed due to non-specific presentation. Maternal and neonatal inflammatory markers such as C-reactive protein (CRP) have been explored as early predictors of infection. Objectives were to determine the relationship between maternal CRP, cord blood CRP, and EONS in high-risk mothers, and to evaluate the diagnostic performance of these markers.
Methods: This prospective observational study included 96 high-risk mothers and their neonates at Malabar Medical College, Kozhikode. Maternal serum CRP and cord blood CRP were measured, followed by serial neonatal CRP assessments at 24 and 48 hours of life. Blood culture served as the diagnostic gold standard. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of maternal and cord blood CRP were calculated.
Results: There was no significant association between maternal or cord blood CRP and neonatal sepsis ($p>0.05$). However, serial CRP at 24 and 48 hours showed significant association with confirmed EONS ($p<0.05$). Maternal CRP had sensitivity 85.7%, specificity 22.7%, PPV 23.7%, and NPV 85%. Cord CRP showed sensitivity 4.8%, specificity 100%, PPV 100%, and NPV 78.9%.
Conclusions: Maternal and cord CRP alone are not reliable indicators of early-onset sepsis, but serial neonatal CRP monitoring at 24-48 hours aids in diagnosis. Maternal CRP has good sensitivity and NPV, whereas cord CRP shows high specificity and PPV.

Keywords: C-reactive protein, Early-onset neonatal sepsis, Maternal CRP, Cord blood CRP, Biomarkers

INTRODUCTION

Early-onset neonatal sepsis (EONS), occurring within 72 hours of life, is a leading cause of neonatal morbidity and mortality globally. Despite advances in neonatal care, diagnostic challenges persist due to the nonspecific presentation of EONS. In India, neonatal sepsis accounts for nearly one-quarter of neonatal deaths, with incidence rates as high as 17 per 1000 live births. Rapid and accurate diagnosis is crucial to initiate timely antibiotic therapy and avoid unnecessary antimicrobial exposure. In 2010 worldwide, 7.6 million children less than 5 years old died, predominantly because of infectious causes including sepsis; neonatal deaths (in the first 28 days of life), accounted for 40% of the total lives lost.[1] In 1990, both the United Nations and World Health Organization (WHO), prioritized a two-third reduction in the unacceptable child mortality rate by 2015. Despite major advances in neonatal care and increasing research, in developed countries, 4 out of every 10 infants with sepsis

die or experience major disability, including significant permanent neurodevelopmental impairment.[2] CRP, an acute phase reactant synthesized by hepatocytes, rises rapidly in response to inflammation. Maternal and neonatal CRP levels have been investigated as potential predictors of EONS. However, findings are inconsistent regarding their predictive accuracy. This study aimed to evaluate the relationship between maternal and cord blood CRP with EONS in high-risk deliveries in a tertiary care setting in North Kerala.

METHODS

This was a prospective observational study conducted from January 2021 to July 2022 at Malabar Medical College and Research Centre, Kozhikode, after obtaining institutional ethics approval. Ninety-six high-risk mothers and their neonates were enrolled after informed consent.

High-risk criteria included: maternal fever within two weeks of delivery, meconium-stained amniotic fluid, foul-smelling liquor, prolonged rupture of membranes (>18 hours), prolonged labour (≥24 hours), or multiple unclean vaginal examinations.

Maternal serum CRP was measured within 6 hours before delivery, and cord blood CRP was obtained at birth. Neonatal CRP was measured at 24 and 48 hours of life. CRP estimation was performed using an immunoturbidimetric method (Abbott reagent; cut-off 0.5 mg/L). Neonates were clinically monitored for signs of sepsis, and blood culture was used as the gold standard.

Infants were categorized as: (a) definite sepsis (clinical features + positive blood culture), (b) probable sepsis (clinical features + ≥2 abnormal lab parameters, culture-negative), and (c) no sepsis.

Data were analyzed using SPSS version 20.0. Associations between CRP values and EONS were tested using Fisher's exact test and ROC curve analysis. Statistical significance was set at $p<0.05$.

RESULTS

Majority of the mothers included in the study were multigravida comprising of 66 (68.7%) of the population under study. 67% of the newborns who developed early onset neonatal sepsis were born to multigravida mothers whereas 33% were born to primi mothers. The 46.9% of the mothers delivered by elective LSCS, 10.4% delivered by emergency LSCS whereas 42.7% delivered by normal delivery. Majority of the neonates (86.5%) were born at term, 11.5% were late preterm and 2.1% were early preterm neonates. Among the high-risk mothers, 39.6% had maternal pyrexia less than 2 weeks of delivery, 32.3% had meconium-stained amniotic fluid, 7.3% had prolonged labour, 12.5% had prolonged rupture of membranes, 2.1% had maternal pyrexia and MSAF, 4.2% had maternal pyrexia along with PROM>18 hours, 1% had MSAF and prolonged labor, 1% had MSAF and PROM>18 hours.

Table 1: Maternal risk factors, (n=96).

Maternal risk	N	Percentage (%)
Maternal pyrexia<2 weeks of delivery	38	39.6
MSAF	31	32.3
Prolonged labour	7	7.3
Prom more than 18 hours	12	12.5
Both maternal fever and MSAF	2	2.1
Both maternal fever and prom more than 18 hours	4	4.2
Both MSAF and prolonged labour	1	1
Both MSAF and prom more than 18 hours	1	1
Total	96	100

Majority of the newborns with early onset neonatal sepsis were male babies comprising 54.5% of the neonate's with EONS. The 25% of the neonates with signs of sepsis had positive CRP at 24 hours of life whereas 72% of them had negative CRP. The 14.6% of the neonates had positive CRP at 48 hours of life, whereas majority of the neonates of the high-risk mothers had negative CRP. Blood culture of neonates with positive blood culture among newborns with positive CRP (CORD CRP/24 hour CRP/48 hour CRP). Only 9% of the neonates had positive blood culture. Majority of the neonates did not have sepsis (78%), 19.8% had probable sepsis and 2.1% of neonates had definite sepsis.

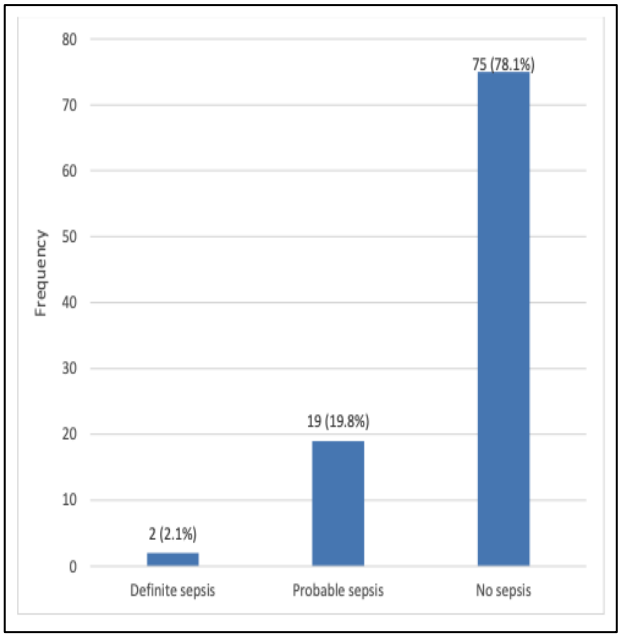

Figure 1: Neonates with definite sepsis, probable sepsis and no sepsis, (n=96).

A total of 21 neonates (21.9%) developed early-onset sepsis. Among them, 33% were born to primigravida and 67% to multigravida mothers. Maternal fever and meconium-stained amniotic fluid were the predominant risk factors.

There was no statistically significant association between maternal CRP (>1 mg/l) and neonatal sepsis (p=0.236) or between cord CRP (>0.5 mg/l) and sepsis (p=0.79). However, neonatal serum CRP at 24 and 48 hours showed strong association (p<0.05).

Table 2: Association between cord CRP and early onset neonatal sepsis, (n=96).

Cord blood CRP	Sepsis Yes	Sepsis No	Chi-square value	P value
Positive	1 (100%)	0 (0%)	3.609	0.219
Negative	20 (21.1%)	75 (78.9%)		

The above table shows fisher exact test to show the association between cord CRP and early onset neonatal sepsis. No association was found between maternal CRP and early onset neonatal sepsis (p>0.05).

Table 3: Association between 24-hour CRP and neonatal sepsis, (n=96).

CRP 24 hour	Sepsis Yes	Sepsis No	Chi-square value	P value
Positive	18 (75%)	6 (25%)	52.846	<0.001
Negative	3 (4.2%)	69 (95.8%)		

The above table shows fisher exact test to show the association between 24-hour CRP and early onset neonatal sepsis. Association was found between 24-hour CRP and early onset neonatal sepsis (p<0.05).

Table 4: Association between 48-hour CRP and early onset neonatal sepsis, (n=96).

Cord blood CRP 48 hour	Sepsis Yes	Sepsis No	Chi-square value	P value
Positive	14 (100%)	0 (0%)	58.537	<0.001
Negative	7 (8.5%)	75 (91.5%)		

Table depicting fisher exact test to show association between 48-hour CRP and early onset neonatal sepsis. Association was found between 48-hour CRP and early onset neonatal sepsis (p<0.05).

Out of the 21 neonates who were diagnosed with sepsis, 85.7% (n=18) of them have maternal CRP of more than 1. Hence sensitivity of maternal CRP in detecting neonatal sepsis was 85.7%. Out of the 75 neonates who were diagnosed with no sepsis, only 22.7% (n=17) of them have maternal CRP of less than 1. Hence specificity of maternal CRP in detecting no sepsis was 22.7%. Among the 76 neonates who had maternal CRP of more than 1, 23.7% (n=18) were diagnosed with sepsis. Maternal CRP have PPV of 23.7% in detecting neonatal sepsis. Among the 20 neonates who had maternal CRP of less than 1, 85% (n=17) were diagnosed with no sepsis. Maternal CRP have NPV of 85% in detecting no neonatal sepsis.

Table 5: Diagnostic performance of CRP in predicting EONS.

Marker	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Maternal CRP	85.7	22.7	23.7	85.0
Cord blood CRP	4.8	100	100	78.9

DISCUSSION

This study demonstrated that maternal and cord blood CRP levels were not significantly associated with EONS, aligning with findings from Van de Laar et al who reported limited diagnostic value of CRP in isolation.[3] However, serial neonatal CRP at 24 and 48 hours showed a strong correlation with confirmed sepsis, consistent with the work of Puello Ávila et al.[4]

The present prospective cohort study was conducted among 96 mothers who had high antenatal risk factors and their neonates having risk of developing early onset neonatal sepsis. Among 96 neonates included in the study, 30 (31.3%) were born to primi mothers, and 66 (68.7%) were born to multigravida mothers. The 14 (66.7%) of the babies who developed EONS were born to multigravida mothers. Our results were similar to a study done by Agnche et al where 70% of neonates with EONS were born to multigravida mothers. In contrast to our study Jabiri et al reported higher incidence of EONS in primi mothers.[5,6]

Of the total neonates included in the study majority of the newborns were born at term (86.5%), 11 babies were late preterm (11.5%), and 2 babies were early preterm 2 (2.1%). Our study included 13 preterm babies (13.6%) and 83 (86.5%) term babies, of which 4(30.7%) of preterm neonates and 17 (20.4%) of term babies developed early onset neonatal sepsis. Hence, preterm birth had higher chances of developing Early onset neonatal sepsis compared to term neonates, which is similar to the study done by Jabiri et al and Mate Siakwa studies in Switzerland.[6,7]

From our results it has been observed that 21 babies had early onset neonatal sepsis out of which 18 (85.7%) had birth weight more than 2.5 kg. In a study done by Ghana

et al, low birth weight accounted for 55.84% respectively, of the study sample.[8] Of the 96 neonates, male to female ratio was observed to be 1:1. Out of 21 babies with EONS 12 (54.5%) were males and 9 (42%) were females, 7 (33%) of the babies were born to primi mothers and 14 (66%) were born to multigravida. Our results therefore matched majority of the studies which documented male gender preponderance. The percentage of the male sex as a risk factor for early neonatal sepsis was compared to 52% and 59% in the Giannoni and Agnche studies in Ethiopia, respectively.[6,8]

Although the male sex is linked to a 3.7-fold higher risk of early neonatal sepsis than the feminine sex, the mechanism underlying this association is not fully understood. With affects from genetic, immunological, and hormonal factors, it is probably complex. The female immune system contains similar elements, such as genes connected to the X chromosome.[9,10]

Association between maternal CRP and cord blood CRP with neonatal sepsis was done using Chi-square test/Fisher's exact test. It was found that there is an association between CRP 24 hour and CRP 48 Hour with neonatal sepsis ($p<0.05$) and no association was found between maternal CRP and cord blood CRP with neonatal sepsis ($p>0.05$).

The specificity and NPV of maternal CRP in relation to EONS can be compared to a retrospective study done by Lee et al to determine the role of maternal CRP in predicting early onset neonatal sepsis. The sensitivity, specificity, PPV, and NPV of an elevated serum CRP level were 67.7%, 63.3%, 17.2%, and 94.6% for EONS, respectively.[11]

Mithal et al, showed that positive maternal CRP is not only a good predictor of maternal infection but also of early neonatal sepsis.[12] However, in our present study, maternal CRP has low PPV for EONS compared to the above studies. In our study maternal CRP has a high NPV in excluding early onset neonatal sepsis.

Study done by Mehmet et al showed no significant relation among CRP levels measured within 72 h before delivery, and postnatal infectious and non-infectious complications.[13]

Lee et al demonstrated that normal maternal CRP level actually eliminated the risk of EONS.[14] Fisk et al followed a temporal trend of CRP, instead of a normal laboratory cut-off value and showed that a 20 mg/l or higher level of CRP was predictive of postnatal infection.[15] In our study the laboratory cut off value for positive maternal CRP was 0.5 mg/l, however values more than 1 mg/L were considered as significantly elevated maternal CRP values in our study as all mothers had positive CRP.

Maternal CRP demonstrated high sensitivity and NPV, suggesting utility in identifying low-risk neonates when negative. In contrast, cord CRP had excellent specificity and PPV, indicating that a positive cord CRP may signify true infection, although sensitivity remained low due to delayed neonatal CRP response kinetics.

The findings reinforce that CRP, while useful as an adjunct, should not replace blood culture and clinical assessment. Serial CRP testing remains a valuable tool in guiding antibiotic stewardship by supporting early discontinuation of therapy in low-risk neonates.

Limitations include the single-centre design and small sample size, which may limit generalizability. Future multicentric studies integrating CRP with other biomarkers such as procalcitonin and interleukins could improve predictive accuracy.

CONCLUSION

There is no direct relationship between maternal or cord blood CRP and EONS. However, serial monitoring of neonatal CRP at 24 and 48 hours significantly aids in diagnosis. Maternal CRP provides good sensitivity and NPV, whereas cord CRP demonstrates high specificity and PPV, supporting their combined use in risk stratification of neonates born to high-risk mothers.

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