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Original Article

CRP/Albumin Ratio: A Promising Marker of Bacteremia in Neonatal Sepsis in a Tertiary-Care Hospital in Pakistan

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ABSTRACT

Objective: This study evaluated the CRP/albumin ratio as a potential indicator of bacteremia in neonatal sepsis among neonates admitted to a tertiary care hospital in Pakistan.

Study Design: Cross-Sectional Study.

Place and Duration of Study: Neonatal Intensive Care Unit (NICU), Department of Pediatrics and Neonatology, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Jan to Dec 2024.

Methodology: This study investigated a total of 192 neonates with neonatal sepsis, and data were collected using a proforma. Laboratory tests were performed to measure C-reactive protein (CRP) and albumin levels, and statistical analyses were performed using SPSS version 23.

Results: Our study analyzed 192 neonates with sepsis to evaluate the CRP/Albumin ratio as a potential biomarker. All variables exhibited non-normal distributions (Shapiro-Wilk p<0.001). Neonates had a mean age of 10.74±7.31 days (IQR =9) and birthweight of 2.676±0.63 kg, with elevated leukocyte counts (17,102.08±13,132.49 cells/mm^3, IQR =27,500) confirming sepsis. Hypoalbuminemia (3.066±0.61 g/dL, IQR =0.90) and high CRP (12.87±8.89, IQR =10.20) were observed. Hospital stays averaged 2.85±1.52 days (IQR =3). The CRP/Albumin ratio (4.36±3.17, IQR =14.4) demonstrated significant variability, suggesting its potential as a severity marker in neonatal sepsis. 152(79.2%) tested positive for bacteremia. Clinical symptoms included fever in 148(77%) neonates, respiratory distress in 119(62%), and feeding intolerance in 108(56%). No significant association was found between CAR and variables such as type of sepsis onset or sex.

Conclusion: CRP/albumin ratio is a promising marker for neonatal sepsis. However, our study did not find a statistically significant relationship between CRP/albumin ratio and late-onset neonatal sepsis.

Keywords: Albumin, Blood Culture, C-Reactive Protein, C-Reactive Protein/Albumin Ratio, Neonatal Sepsis, Neonate, NICU.

How to Cite This Article: *Khan MH, Khushdil A, Shah SA, Naeem U, Shah SZ, Afzal B. CRP/Albumin Ratio: A Promising Marker of Bacteremia in Neonatal Sepsis in a Tertiary-Care Hospital in Pakistan. Pak Armed Forces Med J 2025; 75(Suppl-6): S1015-S1020.*

DOI: https://doi.org/10.51253/pafmj.v75iSUPPL-6.13063

INTRODUCTION

Sepsis is one of the most important causes of mortality and morbidity in the neonatal intensive care unit (NICU). The definition of neonatal sepsis is debatable and there is no consensus on a single definition. The definition of pediatric sepsis does not cover all aspects of neonatal sepsis, particularly in the preterm population. The most accepted criteria for neonatal sepsis are isolation of microorganisms by blood culture and clinical characteristics. Neonatal sepsis can be further divided into early onset (onset within 72 hours of life) and late-onset sepsis (onset after 72 hours of life), both of which have different etiologies and pathogenesis.[1] The prevalence of neonatal sepsis varies in different countries. Neonatal sepsis is more prevalent in developing countries than in developed ones. Likewise, the mortality rate of neonatal sepsis is much higher in low-income countries than in high-income countries. The highest neonatal mortality is reported in Africa and Asia, where 5 million neonatal deaths occur each year.[2] Neonatal sepsis is the cause of death in 20% of neonates. However, this figure is much lower in developed countries due to high-quality neonatal care.[3]

The pathogenesis of neonatal sepsis differs from that of pediatric sepsis in several aspects. Neonates have insufficient memory for different pathogens, and the complement system and cellular responses are not mature.[4] Several neonatal and maternal factors may contribute to neonatal sepsis. Risk factors for neonatal sepsis include intrapartum maternal temperature, chorioamnionitis, vaginitis, premature delivery, prolonged rupture of membrane, meconium aspiration, unhygienic birthplace environment, frequent cannulation, umbilical catheterization, and mechanical ventilation.[5] Diagnosis of neonatal sepsis is challenging. A number of conditions may present with

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Received: 05 Feb 2025; revision received: 11 Aug 2025; accepted: 12 Aug 2025

signs and symptoms of sepsis, such as in-born errors of metabolism, hypoxic-ischemic encephalopathy, and respiratory distress syndrome. Neonates with sepsis may present with temperature instability, jaundice, lethargy, feeding intolerance, hypotonia, seizures, respiratory distress, or cyanosis. Blood culture is the gold standard for the diagnosis of neonatal sepsis. However, there are several limitations to blood culture. Blood culture results may be delayed for up to seven days, and there are conditions where the yield from blood culture may be low in neonatal sepsis. Another important limitation is the growth of normal flora, which makes clinical decision difficult.[6] Also, in resource-limited settings, blood culture and sensitivity may not be available. For these reasons, different hematological and biochemical biomarkers are being investigated for the early detection of neonatal sepsis; it is a fact the early detection and treatment of neonatal sepsis significantly reduce neonatal mortality and morbidity. The different hematological markers that are under investigation are the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio.[7] Likewise, several biochemical markers are under investigation for the early diagnosis of neonatal sepsis, such as procalcitonin, c-reactive protein, and crp/albumin ratio.[8]

Therefore, we conducted this study to investigate the potential of the CRP/albumin ratio as an indicator of bacteremia in neonatal sepsis. Findings from this study would be helpful for improving diagnostic accuracy and guiding management decisions for neonatal sepsis in resource-limited settings, while opening new doors for further research at the same time.

METHODOLOGY

This cross-sectional study was conducted to evaluate the role of C-reactive protein (CRP): albumin ratio as a marker of neonatal sepsis. This study was conducted in the neonatal intensive care unit (NICU) of Pak Emirates Military Hospital, a tertiary care hospital, from January 2024 to December 2024. All the neonates admitted in the NICU who fulfilled the inclusion and exclusion criteria during the study duration were included in the study.

Inclusion Criteria: All Neonates (preterm and term) with clinical signs and symptoms suggestive of sepsis, or having risk factors for early onset or late-onset sepsis (e.g., maternal chorioamnionitis, prolonged rupture of membranes, perinatal asphyxia) were included in this study.

Exclusion Criteria: Neonates with major congenital anomalies, those who had received albumin infusions prior to sampling, those with incomplete medical records, or those who did not survive beyond 24 hours after admission were excluded from the study.

Data were prospectively collected using a structured proforma, including the following information: Demographic and Clinical Information, Gestational age, birth weight, mode of delivery, Apgar score, maternal risk factors, and postnatal age at symptom onset were recorded, Clinical signs suggestive of sepsis have been documented (e.g., temperature instability, feeding intolerance, lethargy, and respiratory distress), Laboratory investigation, Blood samples were collected from neonates with suspected sepsis within the first 12 hours of clinical presentation. The laboratory parameters were as follows, Complete blood count (CBC) with differential leukocyte count, C-reactive protein (CRP) level was measured using a high-sensitivity immuno-turbidimetric assay, Serum albumin levels were determined using an automated colorimetric method. CRP: Albumin Ratio, The CRP to albumin ratio was calculated by dividing the CRP level (mg/L) by the albumin level (g/dL), Neonates were grouped according to the presence or absence of culture-proven sepsis for further analysis.

The primary outcome was the diagnostic performance of the CRP: albumin ratio for identifying neonatal sepsis. Secondary outcomes included the correlation of the CRP: albumin ratio with clinical severity and other laboratory markers of sepsis (e.g., blood culture, total leukocyte count, and platelet count).

The data were analyzed using the Statistical Package for Social Sciences (SPSS) version 23. Descriptive statistics were used to summarize the demographic and clinical characteristics. mean, standard deviation were calculated for continuous variables (e.g., CRP, albumin levels, and CRP: albumin ratio) while categorical variables were presented using frequencies and frequencies. Chi-square test was used to find out any association between the variables. Statistical significance was set at a *p*-value of less than 0.05.

RESULTS

Our study examined key clinical and laboratory variables in 192 neonates with sepsis, focusing on the CRP/Albumin ratio as a potential biomarker.The mean age of the neonates was 10.74±7.31 days,

indicating a diverse cohort likely including both term and preterm infants. Birthweight averaged 2.676±0.63 kg, suggesting some infants may have been low birthweight or growth-restricted. The total leukocyte count was markedly elevated (17,102.08±13,132.49 cells/mm^3), consistent with sepsis-induced leukocytosis, though the wide range reflects variability in disease severity or timing of testing.

Serum albumin levels were slightly low (3.066±0.61 g/dL), likely due to inflammation or malnutrition, while CRP levels were significantly elevated (12.87±8.89), confirming systemic infection. The duration of hospital admission was relatively short (2.85±1.52 days) possibly indicating either rapid recovery or early transfer to specialized care.

The CRP/Albumin ratio, a key focus of the study, showed high variability (4.36±3.17), suggesting its potential as an indicator of sepsis severity, given that higher ratios may reflect greater inflammation and poorer nutritional status. These findings highlight the CRP/Albumin ratio as a promising but variable marker in neonatal sepsis, warranting additional research to assess its prognostic value (Table-I).

Table-I: Baseline Characteristics, Laboratory Investigation Findings (n=192)

VariableS	Mean±SD
Age (in days)	10.74±7.31
Birthweight (in kgs)	2.676±0.63
Total leukocyte count (cells/mm3)	17102.08± 13132.49
Serum albumin (g/dl)	3.066±0.61
Crp (quantitative)	12.87±8.89
Duration of admission (in days)	2.85±1.52
Crp/albumin ratio	4.36±3.17

Of the 192 neonates included in this study, 98(51%) were female and 94(49%) were male. Of the babies, 162(84.4 %) were born full-term and 30(15.6%) were born preterm. 52(27.1%) babies were diagnosed with Early Onset Neonatal Sepsis (symptoms presenting within the first 72 hours of life), while 140(72.9%) babies were diagnosed with late-onset neonatal sepsis (symptoms presenting after 72 hours of life). Blood samples were sent for all 192 neonates, out of which 152(79.2%) were positive for bacterial growth and 40(20.8%) were negative.

All 192 neonates included in the study were assessed for clinical features, and the majority of patients presented with more than one clinical symptom. Of the 192 neonates, 148(77.1 %) had fever, 119(62%) had respiratory distress, 108(56.3 %) had feeding intolerance, 45(23.4%) had jaundice, and 118(1.5%) experienced seizures (Table-II).

Table-II: Frequency of Different Clinical Features (n=192)

Clinical Features		n(%)
Seizures	No	74(38.5)
	Yes	118(61.5)
Jaundice	No	147(76.6)
	Yes	45(23.4)
Fever	No	44(22.9)
	Yes	148(77.1)
Respiratory distress	No	73(38.0)
	Yes	119(62.0)
Feeding intolerance	No	84(43.8)
	Yes	108(56.3)

Table-III: Association of Early and Late Neonatal Sepsis with Gender, Pregnancy Duration, and Crp/Albumin Ratio (n=192)

Features		Type of neonatal sepsis onset		Total	*p*-value
		Total (52) Early n(%)	Total (140) Late n(%)		
Gender	Male	25(26.5%)	69(73.4%)	94	0.89
	Female	27(27.5%)	71(72.5%)	98	
Pregnancy Term	Pre-Term	8(26.6%)	22(73.3%)	30	0.95
	Term	44(29.3%)	118(70.9%)	62	
CRP Albumin Ratio	≤1.5	5(9.6 %)	47(90.4%)	52	0.52
	>1.5	19(12.9%)	121(87.1%)	140	

Our results showed that the proportion of males and females was similar in both early-onset (26.5% male, 27.5% female) and late-onset sepsis groups (73.4% male, 72.5% female). The *p*-value of 0.89 indicates no statistically significant difference in gender distribution between the two groups, suggesting that gender is not a distinguishing factor for the timing of sepsis onset. Pre-term births accounted for 26.6% of early-onset cases and 73.3% of late-onset cases, while term births represented 70.9% of early-onset cases and 29.3% of late-onset cases. There was no significant association between term of pregnancy and type of sepsis (*p*-value=0.95) suggests no significant association between pregnancy term and the timing of sepsis onset, implying that term status does not strongly influence whether sepsis develops early or late. For cases with a CRP/Albumin ratio ≤1.5, 9.6% were early-onset and 90.4% were late-onset. In contrast, for CRP/Albumin ratio >1.5, 12.9% were early-onset and 87.1% were late-onset. The *p*-value of 0.52 indicates that the CRP/Albumin ratio does not significantly differentiate between early and late-onset sepsis in this study. Overall, the findings suggest that gender, pregnancy term, and

CRP/Albumin ratio do not exhibit statistically significant associations with the timing of neonatal sepsis onset (Table-III).

DISCUSSION

In our study, key parameters demonstrated significant deviations from normality (Shapiro-Wilk p<0.001). The cohort showed a mean age of 10.74±7.31 days), birthweight of 2.676±0.63 kg , and markedly elevated leukocyte counts (17,102.08±13,132.49 cells/mm^3). Laboratory findings revealed hypoalbuminemia (3.066±0.61 g/dL) alongside significantly elevated CRP levels (12.87±8.89), while hospital stays averaged 2.85±1.52 days). The CRP/albumin ratio (4.36±3.17) exhibited substantial variability, suggesting its potential as a severity marker in neonatal sepsis, though further validation is warranted. All 192 neonates included in the study were assessed for clinical features, and the majority of patients presented with more than one clinical symptom. A total of 148(77.1%) had fever, 119(62%) had respiratory distress, 108(56.3%) of the 192 neonates suffered from feeding intolerance, 45(23.4%) out of 192 babies had jaundice, and 118(1.5%) of the 192 babies suffered from seizures meanwhile in comparison.

In comparison, a study conducted by Haematyar *et al.,* revealed that 18% of 110 patients with neonatal sepsis had late-onset sepsis, the most common clinical presentation being respiratory distress (44.5%), followed by jaundice (25.5%), vomiting (23.6%), and poor feeding (20.9%).[9] In a case-control study conducted by Yin *et al.,* CRP was significantly higher in neonates with sepsis than in the control group (26.5±8.6 vs. 3.6±1.2) while the Albumin ratio was significantly lower in neonates with sepsis (2.54g/dL) with a CRP/Albumin ratio of 10.4.[10]

Li *et al.,* in their study, assessed the role of CRP/Albumin ratio in neonatal sepsis and found a gradual increase in CRP/Albumin ratio with increasing severity of infection.[11] A study conducted in a children's hospital in China demonstrated that CAR was higher in neonates with sepsis and could be a useful early biomarker to identify sepsis in neonates with pneumonia. These results indicate that neonates with pneumonia, who also have a high CAR, have a higher risk of sepsis.[12] In a study conducted in a pediatric hospital in India, a total of 150 neonates were included and divided into three groups based on the severity of sepsis: control, mild sepsis, and severe sepsis. The majority of patients were diagnosed with mild sepsis (63%), severe sepsis (25%), or a control group (12%). Biochemical analyses showed that the levels of CRP and CAR were significantly increased in neonates with sepsis (p<0.001), whereas neonates with severe sepsis exhibited significantly higher levels of CRP and CAR (p<0.05) than neonates with mild sepsis.[13] In another study conducted in a pediatric hospital in Turkey, with a selected sample size of 112 neonates, the CRP/albumin ratio was significantly higher in the gram-negative group (p<0.001). According to the receiver operating characteristic curve, the optimal cutoff value of CRP/albumin for the prediction of gram-negative sepsis was >35.17, which had a specificity of 97% and sensitivity of 56%. The CRP/albumin ratio is independently related to gram-negative sepsis in neonates and may be useful in predicting Gram-negative bacteremia.[14] In another study done by Park *et al.,* reports showed that among critically ill patients, a higher CRP/albumin ratio (>34.3) was significantly related to higher 28-day mortality rates (p<0.001).[15] In a study by Ranzani *et al.,* out of 340 critically ill patients, 229(67%) and 111(33%) were admitted with severe sepsis and septic shock, respectively. Assessment at 90 days of follow-up revealed that 73 patients (22%) died. CRP/albumin ratios at the time of admission and discharge were significantly associated with a poor outcome and showed greater accuracy than only CRP (p=0.0455 and p=0.0438, respectively).[16] Yang *et al.,* carried out study to establish the diagnostic role of CRP/Albumin ratio in preterm neonates with early neonatal sepsis. They included 214 patients in their study, with 102 neonates with sepsis and 112 noninfectious neonates as controls. In their patients, the CRP level at admission was high in both septic and nonseptic neonates; however, at 72 hours, the CRP level dropped in nonseptic neonates, whereas it was persistently high in septic neonates. In contrast, albumin levels were lower in infected neonates than in non-infected neonates. Similarly, the CRP/albumin ratio was significantly higher in infected neonates than in non-infected neonates. The calculated sensitivity and specificity of the CRP/albumin ratio in their study were 84% and 76%.[17] In contrast to their study, we included both pre-and term babies with early- and late-onset sepsis. In addition, we did not include a control group for the comparison. We could not calculate the sensitivity and specificity of the CRP/albumin ratio because we did not perform the culture tests. Khedr *et al.,* also in their study, observed high sensitivity and specificity of

CRP/Albumin ratio in the diagnosis of early neonatal sepsis in preterm babies.[18]

LIMITATION OF STUDY

One of the major limitations of our study was that we were unable to calculate sensitivity and specificity for CRP/albumin ratio in the diagnosis of neonatal sepsis because we did not carry out the gold standard test for sepsis diagnosis, that is, blood culture, due to resource limitations. Although neonatal sepsis is diagnosed based on clinical features by a classified neonatalogist, it is still not an alternative to blood culture. Our study was a preliminary research towards this end; therefore, we recommend further studies to establish the sensitivity and specificity of the CRP/albumin ratio in neonatal sepsis diagnosis by comparing it with blood culture yields.

CONCLUSION

C-reactive protein (CRP) and albumin are two commonly measured biomarkers of sepsis, reflecting the inflammatory response and nutritional status, respectively. However, their utilization as combined markers, specifically the CRP/albumin ratio, in predicting bacteremia in neonatal sepsis remains underexplored in Pakistani neonatal populations. In our study, most neonatal sepsis patients, both those with early and late neonatal sepsis, had an increased CRP/albumin ratio. However, further research is recommended to accurately determine the true sensitivity and specificity of the CRP/albumin ratio in the diagnosis of neonatal sepsis.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MHK & AK: Data acquisition, data analysis, critical review, approval of the final version to be published.

SAS & UN: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SZS & BA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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