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**Original Research Article**

# Predictive value of CRP and albumin ratio in neonatal sepsis

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## ABSTRACT

**Background:** The role of hypoalbuminemia and raised C-reactive protein(CRP) levels in predicting critical prognosis has been described extensively in adult literature. However, there are limited studies in pediatrics, particularly neonates. The study was conducted to assess the predictive value of the CRP vs Serum albumin in earlier identification and as a prognostic indicator of neonatal sepsis.
**Methods:** In this research, from July 2021 to February 2022 a total of 150 studies were enrolled at Adichunchanagiri Institue of medical sciences. Complete clinical and laboratory data were collected. To identify the potential independent risk factor for neonatal sepsis, multivariate logistic regression analysis was performed. Receiver operating characteristic curve analysis was used to evaluate the prediction accuracy of CAR in identifying neonatal sepsis.
**Results:** A total of 150 neonates were included in the study out of which 78 neonates were preterm, 32 neonates were late preterm and 40 neonates were term neonates. CAR levels were higher in neonates with sepsis and showed a gradual increase among the control group, mild sepsis group, and severe sepsis group. The prevalence of neonates with overall sepsis,mild sepsis, and severe sepsis increased significantly from CAR tertile 1to tertile 3. Multiple logistic regression analysis showed that CAR was an independent risk factor for the presence of sepsis (OR = 11.123, 95%CI 6.74–14.5, p<0.001) and severe sepsis (OR=1.568, 95% CI 1.3-2.4, p<0.001). ROC curve analysis showed that CAR had a well-discriminatory power in predicting sepsis (area under the curve= 0.74, 95% CI, 0.71-0.77, p<0.001) and severe sepsis (AUC=0.70, 95% CI, 0.67-0.74, p<0.001).
**Conclusions:** CAR was an independent predictor for the presence and severity of neonatal sepsis.

**Keywords:** C-reactive protein-to-albumin ratio, CRP, Albumin, Neonatal sepsis

## INTRODUCTION

Sepsis is a systemic inflammatory response syndrome caused by infection and accompanied by pathological inflammation and organ system dysfunction, which seriously threatens human health.[1] Due to their immature immune system, neonates are more susceptible to infections. Therefore, a delayed diagnosis will increase the risk of morbidity and mortality.[2-4] Neonatal sepsis is a serious and life-threatening disease, which accounts for 15.2% of all deaths in the neonatal period worldwide.[5] Sepsis-related mortality is largely preventable with prevention of sepsis itself, timely recognition, rational antimicrobial therapy, and aggressive supportive care. However, it is sometimes difficult to diagnose neonatal sepsis because of nonspecific signs and symptoms.[4] Blood culture remains the gold standard, although it requires a long waiting time and can be affected by multiple factors.[6] Therefore, it is critical to identify rapid, sensitive, and specific new biomarkers. CRP and ALB, known as positive and negative acute phase reactants, respectively produced by the liver are commonly used to assess inflammatory processes. Research has shown inflammatory response can influence albumin synthesis. The role of reduced serum albumin (ALB) and raised C-

reactive protein (CRP) levels in predicting a critical prognosis has been described extensively in adult literature but is very limited in pediatrics. Fleck et al reported that adult patients with septic shock had a lower serum ALB level.[7-14] The C-reactive protein-to-albumin ratio (CAR), as an emerging inflammation index, has attracted substantial attention. Yu-et al reported that the CAR was an independent predictor for the presence of sepsis and postburn 30-day mortality in adults.[15] The study was conducted to assess the predictive value of the CRP vs. serum albumin in earlier identification and as a prognostic indicator of neonatal sepsis.

## METHODS

### *Study population*

This is a prospective study conducted at Adhichunchangairi institute of medical sciences, Mandya, Karnataka from June 2021 to February 2022. Neonates suspected of sepsis were enrolled in this study. Neonates include term and preterm with a risk factor for sepsis aged -from birth to 28 days postnatally. Subjects with congenital heart disease, major congenital malformation, a suspected inborn error of metabolism, and those missing clinical and laboratory data presented in the study were excluded. The study protocol complied with the Declaration of Helsinki and was approved by the hospital's ethics review board. All procedures included in this study were undertaken as part of routine clinical practice and the data which could identify subjects were removed. The following data were collected: clinical information, including age, gender, weight, temperature, respiratory rate, heart rate, systolic blood pressure, and diastolic blood pressure; laboratory data include CRP and ALB.

### *Statistical analysis*

Data was collated into an electronic spreadsheet and statistical analysis was performed using PASW Statistics 18.0 software application (SPSS Inc., Chicago, USA). Quantitative variables were presented as the mean± standard deviation (SD) or medians (interquartile range) and analyzed using independent Student's *t*-tests, one-way ANOVA, or Mann-Whitney U-test, depending on their distribution. Categorical variables were expressed as percentages (N, %) and were analyzed using Chi-square or Fisher's exact tests, as appropriate.

### *Correlation*

Two continuous variables were examined using Pearson or Spearman correlation test. Multivariate logistic regression analysis usingenter method was performed to evaluate if CAR was an independent riskfactor for the presence and severity of neonatal sepsis. Variables with a $p<0.05$ in the univariate logistic analysis were included in the multiple regression analysis. Prediction accuracy was evaluated using the area under the receiver operating characteristic (ROC) curves. The cut-off point showing the greatest accuracy was determined using Youden's index (sensitivity + specificity –1). The area under the ROC curve (AUC) of the two variables was compared using Delong's test.

## RESULTS

### *Basic characteristics of study subjects*

In this study, a total of 150 neonates were enrolled. There are 85 neonates of female and 65 neonates of males. The subjects were divided into 3 groups based upon the presence of severity of sepsis as a control group, mild sepsis group, and severe sepsis group as shown in (Table 1). The majority of them were diagnosed with mild sepsis (63%) severe sepsis (25%) and a control group (12%). Compared to control, neonates with sepsis were older and had a higher body temperature, respiratory rate, and heart rate ($p<0.05$), Biochemical analyses showed that the levels of CRP and CAR were significantly increased in neonates with sepsis ($p<0.001$). Further analysis showed that neonates with severe sepsis exhibited significantlyhigher levels of CRP and CAR ($p<0.05$), compared to neonates with mild sepsis.

### *Association of CAR with neonatal sepsis*

To further investigate the relationship between the CAR and the severity of neonatal sepsis, the subjects were classified into three groups, accordingto CAR tertiles as shown in (Table 2). Further analysis showed that the prevalence of overall sepsis increased significantly from 34.1% in tertile 1 to 80.2% in tertile 3 ($p<0.001$), moreover, the prevalence of mild sepsis and severe sepsis, also showed a progressive increase from CAR tertile 1 to tertile 3, whilethe control group was more likely to be in tertile 1 and tertile 2 ($p<0.001$).

### *Predictive value of CAR for neonatal sepsis*

As shown in (Table 3), univariate and multivariable binary logistic regression analysis was performed to evaluate the value of CAR in predicting the presence of neonatal sepsis. After adjusting age, temperature, heart rate, respiratory rate, and weight, CAR was proved to be an independent risk factor for the presence of sepsis (OR=11.123, 95%CI 6.74-14.5, $p<0.001$). Meanwhile, CAR tertiles were also independently associated with an increased prevalence of neonatal sepsis. Furthermore, our data also showed that CAR and CAR tertiles were independent risk factors for the presence of severe sepsis.

### *Diagnostic performance of the CAR for neonatal sepsis*

The prediction of neonatal sepsis was assessed using the AUC.

**Table 1: All characteristics variables of the study.**

| Variable | Control (n=18) | Sepsis (n=132) | Sepsis | |
|---|---|---|---|---|
| | | | Mild Sepsis (n=94) | Severe sepsis (n=38) |
| **Age (days)** | 6.0 (2.0- 11.0) | 5.0 (1.0-9.0)[a] | 6.0 (3.0-9.0)[c] | 2.0 (1.0-4.0)[d] |
| **Female (%)** | 14 (9) | 71 (54) | 54 (36) | 17 (12) |
| **Weight (Kg)** | 3.10±0.3 | 2.72±0.25[a] | 2.94±0.3 | 2.26± 0.4[bd] |
| **Temp (degree)** | 37.2±0.2 | 37.8±0.4[a] | 37.4±0.3[c] | 37.9±0.4[d] |
| **Resp (rate/Min)** | 49±5 | 54±3[a] | 52±2[c] | 55±3[d] |
| **HR (B/M)** | 145±10.4 | 156±10.4[a] | 152±7.8[c] | 159±5[d] |
| **SBP (mmHg)** | 75±7.2 | 72±4.6 | 76±5.2[c] | 70±4.5[bd] |
| **DBP (mmHg)** | 44±7.2 | 42±8.2 | 43±6.8[c] | 41±5.6[bd] |
| **CRP (mg/dl)** | 5±0.8 | 14±2.4[a] | 12±2.2[c] | 18±3.2[bd] |
| **Biochemical parameters** | | | | |
| S. albumin (g/d) | 3.2±0.8 | 2.8±0.6[a] | 2.94±0.4[c] | 2.5±0.4[bd] |
| CAR | 1.62±0.4 | 4.6±0.6[a] | 4.0±0.4[c] | 6.8±0.5[bd] |

All the values are presented as the mean±SD or N (%) or as the median (Interquartile range), [a]p<0.05 forsepsis vs control. [b]p<0.05 for severe sepsis vs. mild sepsis. [c]p<0.05 for mild sepsis vs. control, [d]p<0.05 for severe sepsis vs. control.

**Table 2: The presence and severity of neonatal sepsis according to CAR tertiles.**

| Variables | Tertile 1 (<0.021*10$^{-3}$) | Tertile 2 (<0.030*10$^{-3}$) | Tertile 3 (<0.034*10$^{-3}$) | P value |
|---|---|---|---|---|
| **Age (days)** | 4.2 | 3.6 | 5.4 | 0.424 |
| **Male, N (%)** | 23 (24.4) | 18 (18.6) | 22 (20.7) | 0.045 |
| **Clinical data (N)** | | | | |
| Control | 34 | 23 | 18 | <0.003 |
| Overall sepsis | 35 | 24 | 21 | <0.002 |
| Mild sepsis | 24 | 16 | 13 | <0.004 |
| Severe sepsis | 11 | 8 | 8 | <0.003 |

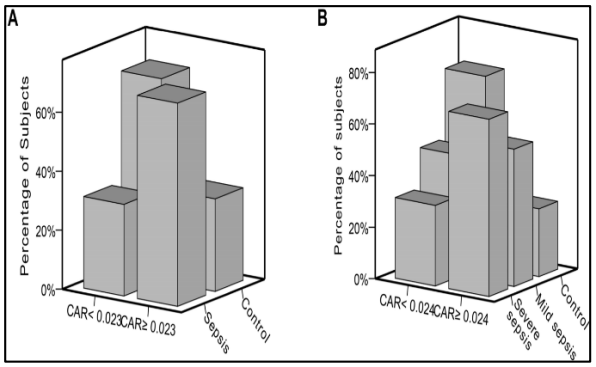


**Figure 1: ROC Curve of CARB, CRP, and ALB in predicting sepsis and severe sepsis in neonates, A) The ROC curve for CAR, CRP, and ALB inpredicting sepsis, B) The ROC curve for CAR, CRP, and ALB in predicting severe sepsis.**

As shown in (Figure 2), the AUC for the CAR was 0.74 (95% CI, 0.71-0.77, p<0.001), which was significantly higher than the AUC for CRP (AUC=0.65, 95% CI, 0.61-0.68, p<0.001) and ALB (AUC=0.71, 95% CI, 0.68-0.74, p<0.001) (p<0.05).

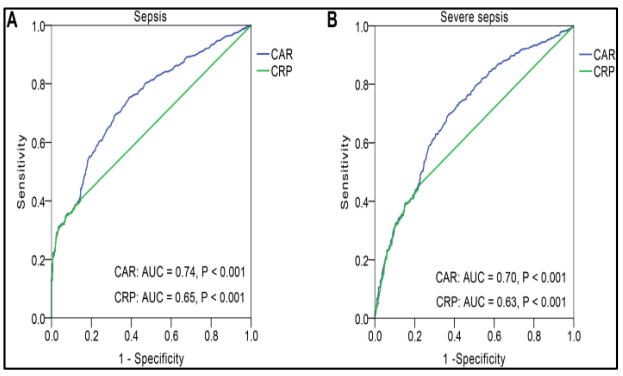


**Figure 2: Distribution of neonates in high or low CAR groups, A) The distribution of neonates with sepsis in high (≥0.023) or low (<0.023) CAR groups, B) The distribution of neonates with severe sepsis in high (≥0.024) or low (<0.024) CAR groups.**

**Table 3: Regression analysis to assess the presence of neonatal sepsis and severe sepsis according to CAR tertile.**

| Variable | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95% CI) | P | OR (95%CI) | P |
| **Presence of sepsis** | | | | |
| CAR | 18.567 (5.76-34.56) | <0.002 | 11.123 (6.74-14.5) | <0.001 |
| **CAR TertilesTertile 1** | I | | I | |
| Tertile 2 | 2.134 (1.86-3.23) | <0.001 | 2.878 (1.789-3.92) | <0.001 |
| Tertile 3 | 6.542 (4.88-13.86) | <0.001 | 5.890 (3.97-7.98) | <0.001 |
| **Presence of severe sepsis** | | | | |
| CAR | 1.568 (1.3-2.4) | <0.001 | 1.23 (1.08-1.56) | 0.001 |
| **CAR TertileTertile 1** | I | | I | |
| Tertile 2 | 2.43 (1.67-3.24) | <0.001 | 2.213 (1.67-3.22) | <0.001 |
| Tertile 3 | 5.356 (3.7-8.28) | <0.002 | 3.98 (2.87-5.93) | <0.001 |

The optimal cut-off value of CAR was 0.023, with 69% sensitivity and 63% specificity. Additionally,the value of CAR in predicting severe sepsis was also evaluated. Compared to that for CRP and ALB, CAR showed good discriminatory power in predicting severe sepsis (AUC=0.70, 95% CI, 0.67-0.74, p<0.001) (Figure 1). The optimal cut-off value of CAR was 0.024, with 69% sensitivity and 64% specificity. According to the cut-off value, subjects were divided into two groups: the high CAR group and the low CAR group. Further analysis showed that the prevalence of neonatal sepsis and severe sepsis was significantly higher in the high CAR group (Figure 2).

## DISCUSSION

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life. Due to their immature immune system, neonates are more prone to infections. The clinical signs of neonatal sepsis are multiple and nonspecific that include tachycardia or bradycardia, temperature instability, diminished spontaneous activity, apnea, respiratory distress, vomiting, feed intolerance, lethargy, irritability and jaundice.[4] Blood culture remains the gold standard for diagnosis of sepsis because it requires long waiting time and can be affected by multiple factors it is crucial to identify rapid, sensitive, and specific biomarkers. We processed the circulating blood biomarkers that may be useful in the early diagnosis of neonatal sepsis.[16-19] Sepsis is a systemic inflammatory response syndrome, and biomarkers of infection and inflammation play an important role in predicting the presence of neonatal sepsis. CRP is a traditional inflammatory marker and associated with systemic inflammatory status.[20] Many studies demonstrated that CRP was a determining risk factor for infection and inflammation-related diseases such as influenza, pneumonia, sepsis, and trauma.[9,21,22] For neonatal sepsis, CRP was one of the most studied and used laboratory tests, while it suffered from low specificity due to the physiologic rise after birth or non-infectious related conditions.[23,24] In this study, our data showed that the AUC of CRP in the diagnosis of neonatal sepsis was 0.65, with 35% sensitivity. ALB is an acute-phase protein produced by the liver that acts as a modulator of plasma oncotic pressure and transports a variety of ligands, such as bilirubin, fatty acids and drugs.[10] Traditionally, ALB reflects malnutrition. However, some studies have shown that ALB was not a nutrition marker and ALB was not recommended as a nutrition marker by bodies that assess nutrition. Besides, many studies demonstrated that there exists a close correlation between ALB and inflammation.[11,12] Hypoalbuminemia develops in sepsis due to decreased hepatic synthesis, increased leakage in to the interstitial compartment and catabolism. Yang et al reported that hypoalbuminemia was frequent among neonates with sepsis and that lower albumin levels might be associated with a poorer prognosis.[20] Lower serum albumin levels were also associated with more sever inflammation. Godinez-Vidal et al further reported that ALB was apredictor of severity in adult patients with abdominal sepsis.[21]

In recent years, a wide number of studies have found that the CAR, as an emerging risk factor, was closely related to multiple diseases, such as cancer, cardiovascular diseases, and sepsis.[15] Two studies reported that a higher CAR was associated with poor overall survival rates in lung cancer and colorectal cancer adult patients. In addition, it could also be a reliable pro-inflammation marker for increased coronary thrombus burden, acute kidney injury development, coronary artery lesions formation, and intravenous immunoglobulin resistance in adults. In the case of sepsis, Kim et al reported that the CAR was an independent predictor of mortality in adult patients with severe sepsis or septic shock.[24] In the present study, we firstly explored the relationship between CAR and neonatal sepsis and found that the CAR levels were higher in neonates with sepsis and showed a gradual increase within control, mild sepsis, and severe sepsis groups. According to the CAR tertiles, we divided the neonates into three groups. Data showed that the prevalence of overall, mild, and severe sepsis significantly increased from the CAR tertile 1 to tertile 3 (p<0.001), especially for the prevalence of overall sepsis (which

raised to 80.2%). The multivariate analysis showed that the CAR was an independent predictor for neonatal sepsis and severe sepsis. The ROC curve analysis showed that the CAR had a well-discriminatory power in predicting sepsis and severe sepsis.

### *Limitations*

However, the present study encounters several limitations. First, it is a prospective single-center study and we did not track the future clinical outcomes in the present study. Prospective studies involving multiple centers are necessary to evaluate the CAR as a predictor for neonatal sepsis. Secondly, we only measured the CAR at admission and believed that serial CAR measurements may be more useful in monitoring neonatal sepsis.

## CONCLUSION

Current study demonstrated that CAR was an independent predictor for the presence and severity of neonatal sepsis. Higher CAR was positively associated with an increased prevalence of sepsis and the sequence of serum albumin level was found to have a good sensitivity in identifying the prognosis.

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