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ORIGINAL RESEARCH

Predictive Value of C-Reactive Protein-to-Albumin Ratio for Neonatal Sepsis

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Purpose: Previous studies have reported that C-reactive protein-to-albumin ratio (CAR) was a risk factor for sepsis in adults. However, little is known regarding the role of CAR in neonates with sepsis. The aim of this study was to explore the relationship between CAR and neonatal sepsis.

Patients and Methods: In this research, from January 2016 to February 2020, a total of 1076 neonates were enrolled at Henan Children's Hospital in China. 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 (ROC) curve analysis was used to evaluate the prediction accuracy of CAR in identifying neonatal sepsis.

Results: 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 1 to tertile 3. Multiple logistic regression analysis showed that CAR was an independent risk factor for the presence of sepsis (OR = 10.144, 95% CI 4.151–24.790, $P < 0.001$) and severe sepsis (OR = 1.876, 95% CI 1.562–2.253, $P < 0.001$). ROC curve analysis showed that CAR had a well discriminatory power in predicting sepsis (area under curve (AUC) = 0.74, 95% CI, 0.71–0.77, $P < 0.001$) and severe sepsis (AUC = 0.70, 95% CI, 0.67–0.74, $P < 0.001$).

Conclusion: CAR was an independent predictor for the presence and severity of neonatal sepsis.

Keywords: C-reactive protein-to-albumin ratio, neonatal sepsis, risk factor, severe 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] Sepsis has become the primary cause of death in the non-cardiac intensive care unit, and its incidence rate of sepsis keeps increasing.[2,3] Due to their immature immune system, neonates are more susceptible to infections. Therefore, a late diagnosis and treatment can further lead to neonatal sepsis.[4] Neonatal sepsis is a serious and life-threatening disease, which accounts for 15.2% of all deaths in the neonatal period worldwide.[5] An early diagnosis and treatment of neonatal sepsis can help prevent severe and life-threatening complications, and subsequently, reduce mortality, which can also avert the need for unnecessary antibiotics. However, it is sometimes difficult to diagnose neonatal sepsis due to the unclear diagnostic criteria and un-specificity

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clinical signs.[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.

C-reactive protein (CRP) is an acute-phase protein produced by the liver that increases in case of inflammation or infection in the body. Studies have demonstrated that CRP is a determining predictor and risk factor for sepsis in adults and newborns.[7–9] Albumin (ALB) is another protein produced by the liver, which makes up 40% to 60% of the total proteins in the blood.[10] Serum albumin concentration is frequently used as an indicator of malnutrition.[11] Currently, many studies demonstrated that there also was a close correlation between ALB and inflammation.[11–13] Fleck et al[14] reported that adult patients with septic shock had a lower serum ALB level. The C-reactive protein-to-albumin ratio (CAR), as an emerging inflammation index, has attracted substantial attention. Yu et al[15] reported that the CAR was an independent predictor for the presence of sepsis and postburn 30-day mortality in adult. However, there are few published data on the relationship between the CAR and neonatal sepsis. Thus, this study aims to investigate the role of the CAR in neonatal sepsis.

Materials and Methods

Study Population

This was a retrospective study conducted in Henan Children's Hospital (Zhengzhou, China). From January 2016 to February 2020, consecutive neonates suspected with sepsis were enrolled in this study. The inclusion criteria were described as follows: 1) neonates with suspected sepsis and 2) aged 1–28 days. Neonates with the following conditions were excluded from this study: (1) missing the clinical and laboratory data presented in this study and 2) subjects with other diseases, such as congenital heart disease, hematological system diseases, cancer and major congenital malformation. 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. We confirmed that all the data was anonymized and maintained with confidentiality; therefore, the requirement for informed consent has been waived because of the retrospective nature of the current study.

Definition

According to the published International Pediatric Sepsis Consensus, neonatal sepsis is defined as suspected or confirmed infection accompanied with ≥2 systemic inflammatory response syndromes (SIRS).[16] Severe sepsis was defined as sepsis plus one of the following: cardiovascular organ dysfunction, acute respiratory distress syndrome, two or more other organ dysfunctions.[16] The rest of the population were served as the control group.

Collection and Biochemical Analyses

The following data were collected: 1) clinical information, including age, gender, weight, temperature, respiratory rate, heart rate, systolic blood pressure and diastolic blood pressure; 2) laboratory data at admission, including procalcitonin (PCT), CRP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein (TP), ALB, blood urea nitrogen (BUN), creatinine (CREA) and uric acid (UA). The methods for detecting those laboratory index have been described in our previous published study.[17] CRP values of <0.8 mg/L (measurement limits) were considered as 0.7 mg/L. PCT levels >100 ng/mL or <0.02 ng/mL were considered as 101 ng/mL and 0.01 ng/mL, respectively. CAR was calculated using the formula CRP/ALB.

Statistical Analysis

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. The correlation between two continuous variables were examined using Pearson or Spearman correlation test. Multivariate logistic regression analysis using enter method was performed to evaluate if CAR was an independent risk factor for the presence and severity of neonatal sepsis. Variables with a P value <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 ROC curve (AUC) of the two variables were compared using Delong's test. All data analysis was performed

using SPSS 22.0 software (SPSS Inc., Chicago, Illinois, USA). A two-sided P value of <0.05 was considered statistically significant.

Results

Basic Characteristics of Study Subjects

In this study, a total of 1076 neonates were enrolled. There are 652 males and 424 females, with a mean age of 9.0 (5.0, 16.0) days. According to whether they have been diagnosed with sepsis and the severity of sepsis, the subjects were divided into three groups: control group, mild sepsis group and severe sepsis group (Figure 1). The majority of them (n = 624, 58.0%) were diagnosed with sepsis, of which 263 neonates were diagnosed with mild sepsis, and 361 neonates were diagnosed with severe sepsis. The remaining 452 neonates without sepsis were served as control. Basic clinical and laboratory data are presented in Table 1. 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 PCT, CRP, BUN, UA, and CAR were significantly increased in neonates with sepsis ($P < 0.001$). On the contrary, the concentration of TP, ALB, and CREA was decreased ($P < 0.05$). Further analysis showed that neonates with severe sepsis exhibited significantly higher levels of PCT, CRP, BUN, CREA, UA, and CAR ($P < 0.05$), compared to neonates with mild sepsis. In those biochemical indicators, we found that only PCT, CRP, and CAR showed a significant progressive rise among the three groups ($P < 0.05$).

Association of CAR with Neonatal Sepsis

To further investigate the relationship between the CAR and severity of neonatal sepsis, the subjects were classified into three groups, according to CAR tertiles. As shown in Table 2, neonates in tertile 3 had higher level of PCT ($P < 0.001$). 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, while the control group were more likely to be in tertile 1 and tertile 2 ($P < 0.001$).

Relationship Between CAR and Clinical Parameters

In the general population, CAR was positively correlated with temperature ($r = 0.117$, $P < 0.001$), respiratory rate ($r = 0.130$, $P < 0.001$), heart rate ($r = 0.127$, $P < 0.001$), PCT ($r = 0.473$, $P < 0.001$), ALT ($r = 0.067$, $P = 0.027$) and BUN ($r = 0.118$, $P < 0.001$), and negatively correlated with DBP ($r = -0.077$, $P = 0.011$) and TP ($r = -0.553$, $P < 0.001$) (Table 3). There was no significant correlations were identified between CAR and weight, SBP, DBP, and ALB. However, in the neonates with sepsis group, CAR was only positively correlated respiratory rate ($r = 0.089$, $P = 0.026$), PCT ($r = 0.448$, $P < 0.001$) and BUN ($r = 0.087$, $P < 0.001$).

Predictive Value of CAR for Neonatal Sepsis

As shown in Table 4, 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, weight, PCT, AST, ALT, TP, UREA and UA, CAR was proved to be an independent risk factor for the presence of

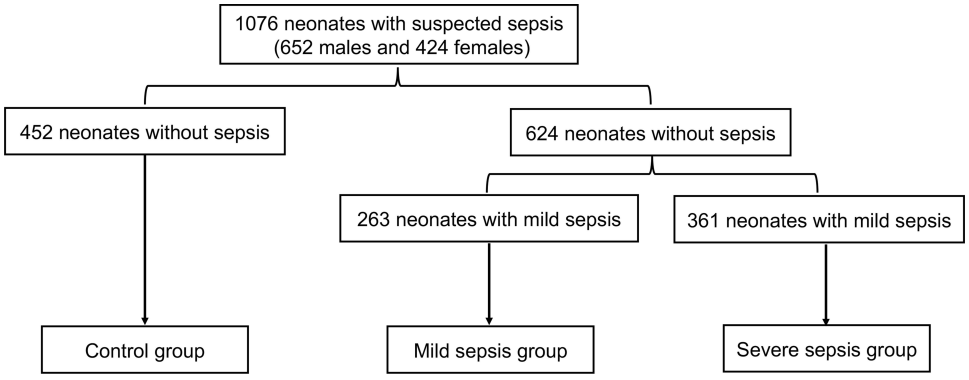

Figure 1 Study participant analysis of suspected sepsis neonates.

Table 1 Basic Characteristics of Study Subjects

Variables	Control (n = 452)	Sepsis (n = 624)	Sepsis	
			Mild Sepsis (n = 263)	Severe Sepsis (n = 361)
Age (days)	7.0 (4.0, 12.0)	11.0 (6.0, 17.0)[a]	11.0 (6.0, 19.0)[c]	11.0 (6.0, 16.0)[d]
Male, n (%)	264 (58.4)	388 (62.2)	170 (64.6)	218 (60.4)
Weight (kg)	3.3 ± 0.5	3.2 ± 0.6[a]	3.3 ± 0.6	3.1 ± 0.7[bd]
Temperature (°C)	37.0 ± 0.5	37.4 ± 0.8[a]	37.4 ± 0.7[c]	37.3 ± 0.8[d]
Respiratory (rate/minute)	46.6 ± 7.7	49.8 ± 10.1[a]	49.4 ± 9.6[c]	50.1 ± 10.4[d]
Heart rate (bpm)	142.8 ± 16.1	150.7 ± 18.1[a]	149.7 ± 17.6[c]	151.4 ± 18.4[d]
SBP (mm Hg)	76.4 ± 7.1	76.3 ± 8.1	79.3 ± 5.6[c]	74.1 ± 9.0[bd]
DBP (mm Hg)	46.7 ± 7.4	46.3 ± 7.8	47.8 ± 7.5[c]	45.1 ± 7.9[bd]
PCT (ng/mL)	0.14 (0.09, 0.23)	0.30 (0.14, 1.52)[a]	0.22 (0.11, 0.76)[c]	0.37 (0.16, 2.19)[bd]
CRP (mg/L)	0.7 (0.7, 0.7)	0.7 (0.7, 14.1)[a]	0.7 (0.7, 9.2)[c]	0.7 (0.7, 17.3)[bd]
Biochemical parameters				
AST (U/L)	37.6 (30.0, 50.0)	38.4 (27.9, 53.7)	36.1 (27.8, 48.0)	39.6 (27.9, 61.7)[b]
ALT (U/L)	15.1 (20.0, 33.4)	28.5 (22.0, 38.0)[a]	28.6 (22.3, 36.2)[c]	28.5 (21.9, 39.6)[d]
TP (g/L)	57.1 ± 6.1	53.7 ± 7.0[a]	54.4 ± 6.1[c]	53.3 ± 7.6[d]
ALB (g/L)	33.7 ± 4.0	30.3± 4.6[a]	31.2 ± 4.3[c]	29.7 ± 4.7[bd]
BUN (mM)	2.2 (1.4, 3.3)	3.1 (1.9, 4.3)[a]	2.8 (1.9, 3.9)[c]	3.2 (1.9, 4.8)[bd]
CREA (μM)	50.1 (41.3, 57.6)	45.5 (36.0, 60.3)[a]	43.4 (34.7, 53.1)[c]	47.7 (37.2, 64.8)[b]
UA (μM)	137.4 (103.0, 179.1)	144.2 (106.6, 198.5)[a]	143.5 (106.9, 185.4)	145.5 (106.5, 208.4)[d]
CAR (10^{-3})	0.021 (0.019, 0.024)	0.026 (0.022, 0.438)[a]	0.024 (0.021, 0.277)[c]	0.029 (0.022, 0.606)[bd]

Notes: All values are presented as the mean ± SD or n (%) or as the median (interquartile range). [a]P < 0.05 for sepsis 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.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; PCT, procalcitonin; hsCRP, high sensitivity C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TP, total protein; ALB, albumin; BUN, blood urea nitrogen; CREA, creatinine; UA, uric acid; CAR, C-reactive protein-to-albumin ratio.

Table 2 The Presence and Severity of Neonatal Sepsis According to CAR Tertiles

Variables	Tertile 1 (< 0.021*10^{-3}) (n = 361)	Tertile 2 (0.021*10^{-3} – 0.028*10^{-3}) (n = 356)	Tertile 3 (> 0.028*10^{-3}) (n = 359)	*P*
Age (days)	9.0 (6.0, 14.0)	8.0 (5.0, 15.0)	10.0 (5.0, 16.0)	0.524
Male, n (%)	204 (56.5)	213 (59.8)	235 (65.5)	0.046
PCT (ng/mL)	0.13 (0.09, 0.21)	0.17 (0.11, 0.35)	0.52 (0.19, 3.15)	<0.001
Clinical data				
Control, n (%)	238 (65.9)	143 (40.2)	71 (19.8)	<0.001
Overall sepsis	123 (34.1)	213 (59.8)	288 (80.2)	<0.001
Mild sepsis, n (%)	66 (18.3)	94 (26.4)	103 (28.7)	<0.001
Severe sepsis, n (%)	57 (15.8)	119 (33.4)	185 (51.5)	<0.001

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; PCT, procalcitonin; hsCRP, high sensitivity C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TP, total protein; ALB, albumin; BUN, blood urea nitrogen; CREA, creatinine; UA, uric acid; CAR, C-reactive protein-to-albumin ratio.

sepsis (OR = 10.144, 95% CI 4.151–24.790, 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.

Table 3 Correlations Between CAR and Clinical Parameters

Variables	Overall Population		Neonates with Sepsis	
	r	P	*r*	P
Age (day)	0.011	0.717	−0.038	0.343
Weight (kg)	−0.057	0.060	−0.027	0.504
Temperature (°C)	0.117	<0.001	0.015	0.717
Respiratory (rate/minute)	0.130	<0.001	0.089	0.026
Heart rate (bpm)	0.127	<0.001	0.076	0.061
SBP (mm Hg)	−0.057	0.062	−0.057	0.153
DBP (mm Hg)	−0.077	0.011	−0.033	0.416
PCT (ng/mL)	0.473	<0.001	0.448	<0.001
AST (U/L)	−0.044	0.148	−0.028	0.486
ALT (U/L)	0.067	0.027	0.025	0.538
TP (g/L)	−0.553	<0.001	−0.431	<0.001
CREA (μM)	−0.006	0.844	0.006	0.872
UA (μM)	0.038	0.208	0.014	0.727
BUN	0.118	<0.001	0.087	0.029

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; PCT, procalcitonin; hsCRP, high sensitivity C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TP, total protein; ALB, albumin; BUN, blood urea nitrogen; CREA, creatinine; UA, uric acid; CAR, C-reactive protein-to-albumin ratio.

Diagnostic Performance of the CAR for Neonatal Sepsis

The prediction of neonatal sepsis was assessed using the AUC. As shown in Figure 2A, 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). 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 2B). 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: high CAR group and low CAR group. Further analysis showed that the prevalence of neonatal sepsis and severe sepsis was significantly higher in the high CAR group (Figure 3A and B).

Discussion

Sepsis still remains a serious and life-threatening disease, especially in newborns. Indeed, neonates are more prone to infections caused by both bacteria and viruses due to their immature immune systems, and are, therefore, more prone to develop neonatal sepsis. According to the report by Global Sepsis Alliance (GSA), infections leading to sepsis accounted for about one-fifth of the world's neonatal deaths, and raised up to 25% in South Asia and sub-Saharan Africa.[18] However, the clinical signs of neonatal sepsis are multiple, nonspecific and include bradycardia, temperature instability, diminished spontaneous activity, less vigorous sucking, apnea, respiratory distress,

Table 4 Regression Analysis to Assess the Presence of Neonatal Sepsis and Severe Sepsis According to CAR Tertiles

Variables	Univariate		Multivariate*	
	OR (95% CI)	p	OR (95% CI)	p
Presence of sepsis				
CAR	20.596 (8.304–51.085)	<0.001	10.144 (4.151–24.790)	<0.001
CAR tertiles				
Tertile 1	1		1	
Tertile 2	2.882 (2.127–3.905)	<0.001	2.599 (1.767–3.824)	<0.001
Tertile 3	7.849 (5.593–11.014)	<0.001	5.166 (3.406–7.837)	<0.001
Presence of severe sepsis				
CAR	1.876 (1.562–2.253)	<0.001	1.391 (1.141–1.696)	0.001
CAR tertiles				
Tertile 1	1		1	
Tertile 2	2.678 (1.871–3.833)	<0.001	2.416 (1.587–3.677)	<0.001
Tertile 3	5.670 (3.994–8.051)	<0.001	3.767 (2.476–5.732)	<0.001

Notes: *Adjusted for age, temperature, heart rate, respiratory rate, weight, PCT, AST, ALT, TP, UREA and UA.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; PCT, procalcitonin; hsCRP, high sensitivity C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TP, total protein; ALB, albumin; BUN, blood urea nitrogen; CREA, creatinine; UA, uric acid; CAR, C-reactive protein-to-albumin ratio.

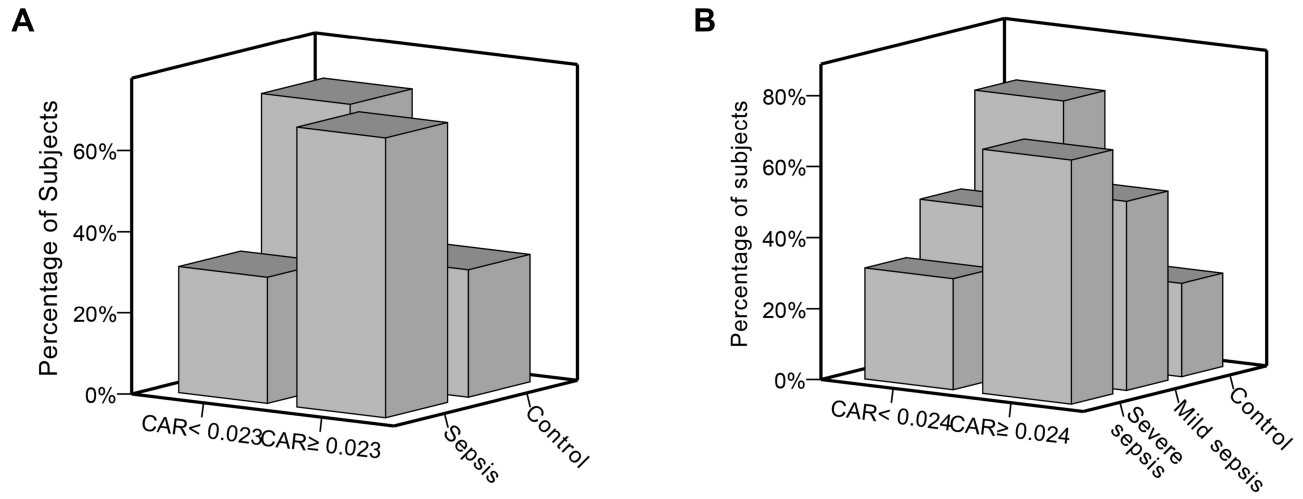

Figure 2 ROC curve of CAR, CRP, and ALB in predicting sepsis and severe sepsis in neonates. (**A**) The ROC curve for CAR, CRP, and ALB in predicting sepsis. (**B**) The ROC curve for CAR, CRP, and ALB in predicting severe sepsis.

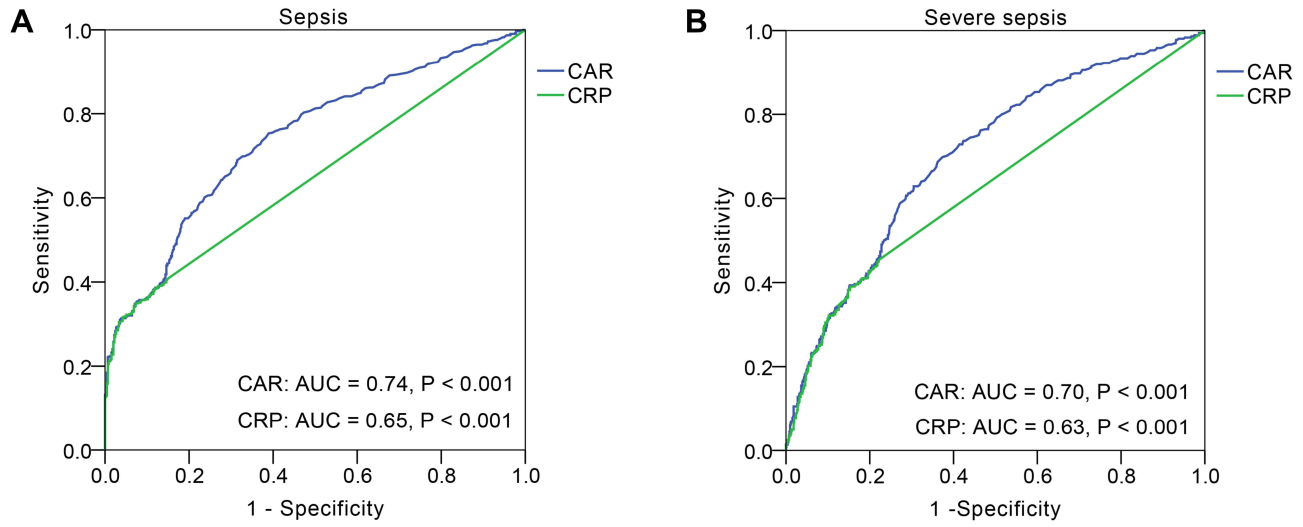

Figure 3 Distribution of neonates in high or low CAR groups. (**A**) The distribution of neonates with sepsis in high (≥0.023) or low (<0.023) CAR groups. (**B**) The distribution of neonates with severe sepsis in high (≥0.024) or low (<0.024) CAR groups.

vomiting, diarrhea and jaundice.[4] In addition, blood culture, the gold standard for sepsis diagnosis, also has shortcomings in the diagnosis of neonatal sepsis, such as a long waiting time, inadequate volume of blood, and prehospital antimicrobial therapy.[6] Therefore, we need rapid and sensitive predictors to diagnose neonatal sepsis. We processed the circulating blood biomarkers that may be useful in the early diagnosis of neonatal sepsis.[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 closely associated with systemic inflammatory status.[20] Many studies have 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 diagnosis of neonatal sepsis was 0.65, with 35% sensitivity (data not shown).

ALB is another protein produced by the liver. It can maintain the colloid-osmotic pressure, keep fluid from leaking out of blood vessels, nourishes tissues, and transports hormones, vitamins, drugs, and calcium throughout

the body.[10] Traditionally, ALB is regarded as an indicator of malnutrition. However, some studies have shown that ALB was not be a nutrition marker and ALB was not recommended as a nutrition marker by bodies that assess nutrition.[25–27] Besides, many studies demonstrated that there exists a close correlation between ALB and inflammation.[11,12,28] Low ALB levels could widely be seen in patients with inflammatory diseases and were associated with more severe inflammation.[29,30] Sepsis is often complicated with organ dysfunctions.[31] Sepsis could damage the liver through hemodynamic alterations, assault on the hepatocytes, or both, which further reduced the liver's ability to synthesize with ALB.[32] Yang et al[33] reported that hypoalbuminemia was frequent among neonates with sepsis, and that lower albumin levels might be associated with a poorer prognosis. Lower serum albumin levels were also associated with more severe inflammation. Godinez-Vidal et al[34] further reported that ALB was a predictor of severity in adult patients with abdominal sepsis.

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.[15,35–38] Two studies reported that a higher CAR was associated with poor overall survival rates in lung cancer and colorectal cancer adult patients.[39,40] In addition, it could also be a reliable pro-inflammation marker for increased coronary thrombus burden,[35] acute kidney injury development,[41] coronary artery lesions formation and intravenous immunoglobulin resistance in adults.[42] In the case of sepsis, Kim et al[43] reported that the CAR was an independent predictor of mortality in adult patients with severe sepsis or septic shock. In addition, the CAR can also predict sepsis and prognoses in adult patients with severe burn injuries.[15]

In the present study, we firstly explored the relationship between the CAR and neonatal sepsis in a relatively large population 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 up 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.

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

Conclusion

Our 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.

Ethics Approval and Consent to Participate

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved the Hospital Ethics Review Board of Henan Children's Hospital. We confirmed that all the data were anonymized and maintained with confidentiality; therefore, the requirement for informed consent has been waived because of the retrospective nature of the current study.

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Disclosure

Tiewei Li and Xiaojuan Li should be considered co-first authors. The authors report no conflicts of interest in this work.

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