

Association of Procalcitonin to Albumin Ratio with the Presence and Severity of Sepsis in Neonates

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Purpose: Previous studies have demonstrated that procalcitonin and albumin have a close correlation with sepsis. However, the role of procalcitonin (PCT) to albumin (ALB) ratio (PAR) in sepsis was still unclear, especially in neonates. Thus, this study aimed to investigate the association between PAR and neonatal sepsis.

Patients and Methods: A total of 1,196 neonates with suspected sepsis were included in this study. Neonates were divided into control group and sepsis group, according to whether they were diagnosed with sepsis. Neonates with sepsis were further divided into mild sepsis and severe sepsis group according to the severity of sepsis. PAR was calculated as serum PCT (ng/mL)/ALB (mg/mL). All statistical analyses were performed using the statistical package SPSS 24.0, as appropriate.

Results: Compared with the control group, neonates with sepsis had a higher PAR. PAR also showed a significant gradual increase in the control, mild sepsis, and severe sepsis groups ($P < 0.001$). Correlation analysis showed that there was a strong positive correlation between PAR and hsCRP, neonatal sequential organ failure assessment score (nSOFA), and prolonged length of hospital stay ($P < 0.001$). On multiple logistic regression, higher PAR was independently associated with the presence and severity of neonatal sepsis. According to the receiver operating characteristic curve analysis, a $PAR \geq 0.065$ had 64% sensitivity and 72% specificity in predicting the presence of neonatal sepsis (area under curve (AUC)=0.72, 95% CI=0.69–0.75, $P < 0.001$) and a $PAR \geq 0.070$ had 69% sensitivity and 63% specificity in predicting the presence of severe sepsis (AUC=0.71, 95% CI=0.68–0.74, $P < 0.001$).

Conclusion: PAR is significantly higher in neonates with sepsis and correlated with the severity of the disease. Increased PAR is an independent predictor useful for identifying the presence and severity of neonatal sepsis.

Keywords: procalcitonin-to-albumin ratio, neonatal sepsis, severe sepsis, predictor

Introduction

Neonatal sepsis remains a leading cause of morbidity and mortality in infants worldwide.^{1–3} It is estimated there may be about 3 million cases of neonatal sepsis in the world.⁴ Compared with adults, the immune system of neonates is not yet mature. Therefore, neonates were more prone to be infected by pathogenic microorganisms and can further develop neonatal sepsis. Neonatal sepsis has been a common and fatal disease affecting neonates all over the world. Currently, the gold standard for diagnosis of neonatal sepsis is blood culture.⁵ However, the blood culture faces a low positive detection rate of pathogenic microorganisms, owing to the pre-hospital antimicrobial exposure, inadequate blood volume from neonates, and a low bacteremia.⁶ In addition, blood culture needs a long waiting time for the results. Meanwhile, neonatal

sepsis can present with subtle signs but can rapidly progress to multisystem organ failure and meningitis.⁷ Therefore, the rapid identification of neonatal sepsis is the key to successful treatment in neonatal sepsis.

Procalcitonin (PCT) is a 116-amino acid peptide produced in the thyroid C-cells and adipose tissue in healthy individuals.⁸ Under normal physiological conditions, serum PCT was maintained at a low level (<0.05 ng/mL).⁹ However, in the case of systemic inflammation, especially bacterial infection, PCT is produced in large quantities by many tissues. Currently, multiple studies have demonstrated that PCT was a useful biomarker to assist the clinician in the diagnosis of sepsis in adults and children (including neonates).^{10–13} Albumin (ALB) is a protein synthesized by the liver hepatocytes and makes up 40–60% of the total proteins in the body.¹⁴ ALB is the main protein responsible for maintaining the colloid-osmotic pressure and can act as a transporter of several endogenous and exogenous compounds.¹⁴ In addition to being a nutritional indicator, ALB was closely related with the inflammation and hypoalbuminemia was frequently seen in patients with inflammatory diseases.^{15–18} Qian and Liu¹⁹ also found that the rates of hypoalbuminemia are common among children with sepsis and serum albumin level was negatively correlated with the prognosis.

PCT-to-ALB ratio (PAR), based on PCT and ALB levels, indicates not only the infection/inflammation, but also the body nutritional status. Studies have reported that PAR was an early diagnostic predictor in discriminating urosepsis from adult patients with febrile urinary tract infection²⁰ and an independent predictor of the poor prognosis in adult patients with sepsis-induced acute kidney injury.²¹ However, to our knowledge, there are no published studies on the association between PAR and sepsis in neonates. Thus, this study aims to evaluate the relationship between PAR and sepsis in a relatively large neonatal population.

Materials and Methods

Clinical Definition

Neonatal sepsis is defined as systemic inflammatory response syndrome in the presence of or as a result of suspected or proven infection. Severe sepsis was defined as sepsis plus one of the following: cardiovascular organ dysfunction, acute respiratory distress syndrome, or two or more other organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic), according to the published International Pediatric Sepsis Consensus.²² Infection was defined as a suspected or proven infection caused by any pathogen or clinical syndrome associated with a high probability of infection, including clinical exam, imaging, or laboratory tests. The diagnosis of clinical neonatal infection and sepsis was made by two study investigators as per the International Pediatric Sepsis Consensus.²² The severity of neonatal sepsis was assessed by using the neonatal sequential organ failure assessment (nSOFA) score that consisted of respiratory, cardiovascular, and hematological criteria.²³ In this study, neonates with suspected sepsis (not diagnosed with sepsis) were used as the control group.

Study Population

This was a hospital-based observational retrospective study conducted in Henan Children's Hospital (Zhengzhou, China). From January 2016 to December 2020, a total of 1,196 consecutive neonates with suspected sepsis were enrolled in this study. Inclusion criteria include 1) aged 1–28 days, and 2) neonates with symptoms of infection. Exclusion criteria include 1) incomplete clinical and laboratory data at admission, 2) congenital liver defects and previous liver related diseases, and 3) neonates with malignancies, haematological system diseases, or major congenital malformations. The study protocol complied with the Declaration of Helsinki and the approval of the hospital ethics review board was obtained.

Data Collection

The data of the first admission were collected from electronic medical records, including the following aspects: 1) demographic and admission status data, including age, gender, weight, body temperature, respiratory rate, heart rate, systolic blood pressure, and diastolic blood pressure; and 2) laboratory data at admission, including PCT, C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein (TP), and ALB. The detection methods of those laboratory indexes were described in our previous published study.²⁴ For our data, CRP levels <0.8 mg/L were assigned a value of 0.7 mg/L. PCT level >100 ng/mL or <0.02 ng/mL were assigned, 101 ng/mL and 0.01 ng/mL, respectively.

Statistical Analysis

Continuous variables are presented as mean±standard deviation (SD) for normally distributed variables, or medians (interquartile range) for non-normally distributed variables, and analyzed using independent *t*-tests or one-way analysis of variance (ANOVA) test. Categorical variables are expressed as numbers (percentage) and analyzed using Chi-square tests. The correlation between PAR and other clinical and laboratory indexes was analyzed by Spearman correlation coefficients. Multiple logistic regression analysis was used to evaluate whether PAR 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 logistic regression analysis. All data statistical analyses were performed using IBM SPSS version 24.0 (SPSS Inc., Chicago, IL). A two-sided *P*-value of less than 0.05 was considered statistically significant.

Results

Study Population Characteristics

A total of 1,196 neonates suspected with sepsis were enrolled in this study. At present in Table 1, 758 neonates had a diagnosis of sepsis, and the remaining 438 neonates with infection served as controls. According to the severity of sepsis, neonates with sepsis were further divided into mild sepsis and severe sepsis groups.

Table 1 Basic Characteristics of Study Subjects

Variables	Control (n=438)	Sepsis (n=758)	Sepsis	
			Mild sepsis (n=341)	Severe sepsis (n=417)
Age (days)	7.0 (4.0–12.0)	10.0 (5.0–17.0) ^a	11.0 (5.0–18.0) ^b	10.0 (5.0–16.0) ^c
Male, n (%)	248 (56.6%)	461 (60.8%)	206 (60.4%)	255 (61.2%)
Weight (kg)	3.3±0.5	3.2±0.6	3.3±0.6	3.1±0.7 ^{cd}
Temperature (°C)	37.0±0.5	37.4±0.8 ^a	37.4±0.7 ^b	37.2±0.7 ^c
Respiratory (rate/minute)	46.4±7.7	50.0±10.9 ^a	49.7±10.1 ^b	50.2±11.6 ^c
Heart rate (bpm)	141.9±16.5	149.8±19.2 ^a	147.9±18.8 ^b	151.4±19.3 ^c
SBP (mm Hg)	76.3±6.7	76.1±8.4	78.8±6.3 ^b	73.9±9.3 ^{cd}
DBP (mm Hg)	46.4±7.0	46.1±8.0	47.6±7.5	44.8±8.3 ^{cd}
PCT (ng/mL)	0.14 (0.10–0.25)	0.32 (0.14–1.52) ^a	0.23 (0.11–0.80) ^b	0.44 (0.17–2.45) ^{cd}
CRP (mg/L)	0.7 (0.7–0.7)	0.7 (0.7–15.1) ^a	0.7 (0.7–9.6) ^b	0.7 (0.7–17.9) ^{cd}
Biochemical parameters				
AST (U/L)	37.7 (30.0–50.7)	38.3 (28.0–54.9)	36.9 (27.9–49.3)	39.2 (28.1–62.4) ^d
ALT (U/L)	25.6 (20.1–33.3)	28.4 (21.5–37.8) ^a	28.4 (21.5–36.1) ^b	28.4 (21.6–40.0) ^c
TP (g/L)	57.2±6.9	54.0±7.3 ^a	54.8±6.5 ^b	53.4±7.8 ^{cd}
ALB (g/L)	33.8±4.1	30.5±4.9 ^a	31.5±4.8 ^b	29.8±4.9 ^{cd}
PAR (×10 ⁻⁴)	0.040 (0.028–0.075)	0.10 (0.047–0.550) ^a	0.072 (0.036–0.274) ^b	0.145 (0.054–0.880) ^{cd}
nSOFA	0 (0–0)	0 (0–2.0) ^a	0 (0–0)	2.0 (0–2.0) ^{cd}
Length of hospital stay (days)	9.0 (8.0–11.0)	14.0 (10.0–22.0) ^a	12.0 (9.0–18.0) ^b	15.0 (11.0–24.0) ^{cd}

Notes: ^a*P*<0.05 for sepsis vs control. ^b*P*<0.05 for mild sepsis vs control. ^c*P*<0.05 for severe sepsis vs control. ^d*P*<0.05 for severe sepsis vs mild sepsis.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; PCT, procalcitonin; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TP, total protein; ALB, albumin; PAR, procalcitonin-to-albumin ratio; nSOFA, neonatal sequential organ failure assessment.

Characteristics of the study population are shown in Table 1. Compared with the control group, neonates with sepsis were older and had a higher body temperature, respiratory rate, and heart rate. Biochemical analysis revealed that the levels of PCT, CRP, and ALT were higher in neonates with sepsis. Meanwhile, the levels of TP and ALB were lower in neonates with sepsis. Further analysis showed that neonates with sepsis had a higher PAR and nSOFA score and a longer length of hospital stay. Among those variables, only PCT, CRP, TP, ALB, PAR, and the length of hospital stay showed a gradual increase or decrease with the severity of sepsis ($P<0.05$).

Associations Between PAR and the Presence and Severity of Neonatal Sepsis

According to the tertiles of PAR, neonates were divided into three groups: low PAR group ($<0.043\times 10^{-4}$), intermediate PAR group ($(0.043-0.134)\times 10^{-4}$), and high PAR group ($>0.134\times 10^{-4}$). The clinical and laboratory data of the study patients based on tertiles of PAR are presented in Table 2. Neonates in the high PAR group had a higher level of CRP and longer length of hospital stay, compared with other groups. Further analysis showed that the prevalence of overall sepsis and severe sepsis showed a progressive increase from the low PAR group to the high PAR group, while the prevalence of control showed a progressive decrease from the low PAR group to the high PAR group ($P<0.001$).

Correlation Between PAR and Clinical and Laboratory Indexes

As shown in Table 3, PAR was negatively correlated with age ($r=-0.207$, $P<0.001$) and weight ($r=-0.097$, $P=0.001$), and positively correlated with body temperature ($r=0.163$, $P<0.001$), respiratory rate ($r=0.118$, $P<0.001$), and heart rate ($r=0.125$, $P<0.001$). In the correlation analysis between PAR and biochemical indexes, our data showed that PCT was significantly correlated with CRP ($r=0.437$, $P<0.001$), AST ($r=0.174$, $P<0.001$), ALT ($r=0.151$, $P<0.001$), and TP ($r=-0.308$, $P<0.001$). In addition, PAR also showed a strong correlation with the nSOFA score ($r=0.352$, $P<0.001$) and the length of hospital stay ($r=0.322$, $P<0.001$).

Predictive Value of PAR for the Presence and Severity of Neonatal Sepsis

As present in Table 4, after adjusting age, temperature, heart rate, respiratory rate, CRP, AST, ALT, and TP, multivariable binary logistic regression analysis revealed that PAR was an independent risk factor for the presence

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

Variables	Tertile 1 ($<0.043\times 10^{-4}$) (n=395)	Tertile 2 ($(0.043-0.134)\times 10^{-4}$) (n=404)	Tertile 3 ($>0.134\times 10^{-4}$) (n=397)	P
Age (days)	10.0 (7.0–17.0)	8.0 (4.0–15.0) ^a	7.0 (3.0–14.0) ^b	<0.001
Male, n (%)	216 (54.7%)	245 (60.6%) ^a	248 (62.5%) ^b	0.066
CRP (mg/L)	0.7 (0.7–0.7)	0.7 (0.7–1.1) ^a	3.0 (0.7–36.4) ^{bc}	<0.001
Clinical data				
Control, n (%)	232 (58.7%)	140 (34.7%) ^a	666 (16.6%) ^{bc}	<0.001
Overall sepsis	163 (41.3%)	264 (65.3%) ^a	331 (83.4%) ^{bc}	<0.001
Mild sepsis, n (%)	99 (25.1%)	124 (30.7%)	118 (29.7%)	>0.05
Severe sepsis, n (%)	64 (16.2%)	140 (34.7%) ^a	213 (53.7%) ^{bc}	<0.001
nSOFA	0 (0–0)	0 (0–1.0)	0 (0–2.0) ^{bc}	<0.001
Length of hospital stay (days)	10.0 (8.0–13.0)	11.0 (8.0–16.8) ^a	15.0 (11.0–22.0) ^{bc}	<0.001

Notes: ^a $P<0.05$ for Tertile 2 vs Tertile 1. ^b $P<0.05$ for Tertile 3 vs Tertile 1. ^c $P<0.05$ for Tertile 3 vs Tertile 2.

Abbreviations: CRP, C-reactive protein; PAR, procalcitonin-to-albumin ratio; nSOFA, neonatal sequential organ failure assessment.

Table 3 Correlations Between PAR and Clinical Parameters

Variables	Overall Population		Neonates with Sepsis	
	r	P	r	P
Age (days)	−0.207	<0.001	−0.245	<0.001
Weight (kg)	−0.097	0.001	−0.073	0.045
Temperature (°C)	0.163	<0.001	0.084	0.021
Respiratory (rate/minute)	0.118	<0.001	0.52	0.150
Heart rate (bpm)	0.125	<0.001	0.088	0.015
CRP (mg/L)	0.437	<0.001	0.420	<0.001
AST (U/L)	0.174	<0.001	0.176	<0.001
ALT (U/L)	0.151	<0.001	0.131	<0.001
TP (g/L)	−0.308	<0.001	−0.158	<0.001
nSOFA	0.352	<0.001	0.312	<0.001
Length of hospital stay (days)	0.322	<0.001	0.200	<0.001

Abbreviations: CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TP, total protein; PAR, procalcitonin-to-albumin ratio; nSOFA, neonatal sequential organ failure assessment.

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

Variables	Univariate		Multivariate*	
	OR (95% CI)	P	OR (95% CI)	P
Presence of overall sepsis				
PAR	1.688 (1.359–2.097)	<0.001	1.211 (1.035–1.416)	<0.001
PAR tertiles				
Tertile 1	I		I	
Tertile 2	2.684 (2.015–3.575)	<0.001	2.236 (1.605–3.116)	<0.001
Tertile 3	7.138 (5.124–9.944)	<0.001	3.966 (2.630–5.982)	<0.001
Presence of severe sepsis				
PAR	1.136 (1.087–1.187)	<0.001	1.080 (1.037–1.125)	0.001
PAR tertiles				
Tertile 1	I		I	
Tertile 2	2.743 (1.958–3.842)	<0.001	2.283 (1.597–3.264)	<0.001
Tertile 3	5.987 (4.294–8.348)	<0.001	3.760 (2.554–5.536)	<0.001

Notes: *Adjusted for age, temperature, heart rate, respiratory rate, CRP, AST, ALT, and TP.

Abbreviations: CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TP, total protein; PAR, procalcitonin-to-albumin ratio.

of sepsis (OR=1.211, 95% CI=1.035–1.416, $P<0.001$) and severe sepsis (OR=1.080, 95% CI=1.037–1.125, $P=0.001$). Further analysis showed that PAR tertiles were also independently associated with an increased prevalence of neonatal sepsis.

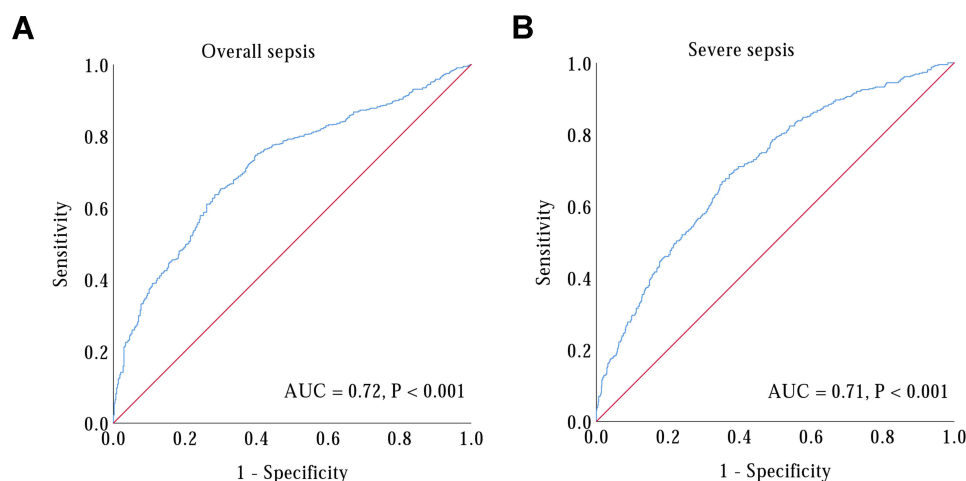


Figure 1 ROC curve of PAR in predicting the presence and severity of neonatal sepsis. **(A)** The ROC curve for PAR in predicting the presence of sepsis; **(B)** the ROC curve for PAR in predicting severe sepsis.

Diagnostic Value of PAR in Neonatal Sepsis

The ROC curve analysis was performed to evaluate the diagnostic value of the PAR in neonatal sepsis. As shown in [Figure 1A](#), the AUC for the PAR in predicting overall neonatal sepsis was 0.72 (95% CI=0.69–0.75, $P<0.001$). The optimal cut-off value of PAR was 0.065×10^{-4} , with 64% sensitivity and 72% specificity. Additionally, we further evaluated the ability of the PAR to predict severe sepsis. The AUC was 0.71 (95% CI=0.68–0.74, $P<0.001$), with a sensitivity and specificity of 69% and 62%, respectively, at a cut-off value of 0.076×10^{-4} ([Figure 1B](#)).

Discussion

Neonatal sepsis, characterized by systemic inflammatory response syndrome caused by infection, is a serious and life-threatening disease in newborns.²⁵ Compared with adult, neonates were more susceptible to infection, and then develop into sepsis, severe sepsis, septic shock, and death.²⁶ Based on a systematic review and meta-analysis of studies reporting population-based sepsis incidence in neonates, Fleischmann-Struzek et al⁴ reported that neonates had a high risk of sepsis and a higher mortality, between 11% and 19%. Early and accurate diagnosis of neonatal sepsis can reduce the development of sepsis and the occurrence of death events and decrease the overuse of antibiotics. Currently, blood culture, the gold diagnosis of neonatal sepsis, faces some challenges, such as pre-hospital antimicrobial therapy, inadequate volume of blood, and a long waiting time,^{5,6} which lead to the low positive rate of blood culture and the inability to give early clinical result feedback. Circulating blood biomarkers have advantages in terms of convenience, being economical, and rapid, which can provide important information in the early diagnosis of neonatal sepsis.

Procalcitonin (PCT), a marker of bacterial infection, exhibits greater specificity than other proinflammatory markers.^{27–29} Studies have demonstrated that PCT is a specific inflammatory marker of sepsis, and the efficiency of PCT in identifying early bacterial infection is better than CRP.^{30–32} A meta-analysis of 3,244 patients showed that the AUC of PCT in the diagnosis of sepsis was up to 0.85.¹³ In addition, PCT can also be used to guide the monitoring of the therapeutic effect of antibiotics, which can result in improved survival and lower antibiotic treatment duration.^{33,34} In terms of neonates, PCT level physiologically after birth and reaches a peak level at 24 hours, and then decreases gradually to normal at 48–72 hours, suggesting that PCT may not be a better early marker of neonatal sepsis.^{35,36} However, according to the physiological characteristics of serum PCT in early newborns, setting the PCT cut-off values of sepsis can improve the accuracy of neonatal sepsis diagnosis.³⁷

ALB was the most abundant protein in blood produced by the liver. Traditionally, ALB is considered as a nutritional index, which can reflect the nutritional status of the body.¹⁷ However, some studies reported that ALB is a marker related to inflammation.^{15–17,38,39} In sepsis, pathogens, toxins, or inflammatory mediators can impair the ability of liver function to synthesize ALB, resulting in a significant decrease in ALB content.⁴⁰ Godinez-Vidal et al⁴¹ reported that ALB could

be a predictor of severity of abdominal sepsis in adult patients, while it was not a predictor of mortality. In neonates, Yang et al⁴² reported that a lower level of ALB was frequent among neonates with sepsis and associated with a poorer prognosis.

In recent years, to further improve the potential predictive value of each single marker, PCT and ALB were combined to generate a new index: PAR. PAR can both indicate the infection/inflammation and the nutritional status, which may enhance the predictive value. Studies have reported that PAR or ALB/PCT was an independent predictor of 28-day mortality in acute respiratory distress syndrome (ARDS) patients⁴³ and could be used as a sensitive early diagnostic marker for nosocomial blood stream infection in patients with intra-cerebral hemorrhage.⁴⁴ A low ALB/PCT ratio was associated with a high risk to experience shock in patients with intra-cerebral hemorrhage.⁴⁴ Luo et al²⁰ reported that PAR was an early diagnostic predictor that can discriminate between urosepsis and febrile urinary tract infection, and urosepsis patients with high PAR were more likely to experience uroseptic shock. However, in terms of the association between PAR and neonatal sepsis, there is no relevant research report at present.

In this study, we firstly explore the association between PAR and sepsis in a relatively large neonatal population and found that PAR was higher in neonates with sepsis and showed a gradual increase among control group, mild sepsis group, and severe sepsis group. According to PAR tertiles, neonates were divided into three groups, and our data showed that the prevalence of overall sepsis increased significantly from 41.3% in PAR tertile 1 to 83.4% in PAR tertile 3 ($P<0.001$). Additionally, the prevalence of severe sepsis also showed a gradual increase from 16.2% in PAR tertile 1 to 53.7% in PAR tertile 3. Multivariate analysis showed that PAR was an independent predictor for the presence of neonatal sepsis and severe sepsis. ROC curve analysis revealed that PAR had a well discriminatory power in predicting sepsis and severe sepsis. In addition, compared with PCT, ALB, and CRP, our data showed that CAR had a higher discriminatory power in predicting sepsis and severe sepsis (data not shown).

This study also has several limitations. First, neonatal sepsis was diagnosed by two independent doctors based on their clinical features and was not confirmed by positive blood culture. Therefore, the accurate incidence rate of neonatal sepsis may have bias. Second, this is a retrospective single center study, and the results may also differ from other centers. Third, owing to the measurement limits, CRP levels <0.8 mg/L were assigned a value of 0.7 mg/L, and PCT levels >100 ng/mL or <0.02 ng/mL were assigned, 101 ng/mL and 0.01 ng/mL. This definition may lead to bias. At last, PAR was only measured at admission and serial PAR measurement may be more useful in monitoring the association between PAR and neonatal sepsis.

Conclusions

In conclusion, our study demonstrated that PAR was an independent predictor for neonatal sepsis. Additionally, in neonates with sepsis, those with low PAR were more likely to have severe sepsis.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by 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

The authors report no conflicts of interest.

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