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Original Research Article

An Observational Study to Assess the Predictive Value of CRP and Albumin Ratio in Neonatal Sepsis

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Abstract

Aim: The aim of the present study was to assess the predictive value of the CRP vs Serum albumin in earlier identification and as a prognostic indicator of neonatal sepsis.

Methods: This was a prospective study conducted in the Department of Neonatology. In this study, a total of 200 neonates were enrolled. Neonates include term and preterm with a risk factor for sepsis aged-from birth to 28 days postnatally.

Results: There were 120 neonates of female and 80 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. The majority of them were diagnosed with mild sepsis severe sepsis and a control group. 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 significantly higher levels of CRP and CAR ($p<0.05$), compared to neonates with mild sepsis. The prevalence of overall sepsis increased significantly from tertile 1 to 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 was more likely to be in tertile 1 and tertile 2 ($p<0.001$). After adjusting age, temperature, heart rate, respiratory rate, and weight, CAR was proved to be an independent risk factor for the presence of sepsis. 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.

Conclusion: The present 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.

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] 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 clinical signs. 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 a sensitive indicator of the body, reflecting damage and infection. [7] Albumin (ALB) is a crucial indicator reflecting the body's nutritional status. [8] In infection-related diseases, ALB is a significant prognostic indicator. A study has found that ALB levels drop significantly in the acute stage of infection. [9] Inflammation-related factors cause CRP increase and ALB decrease in acute phase reaction. A study demonstrated that the CRP/ALB ratio (CAR) could be a marker to predict mortality in patients with acute renal injury based on the biological characteristics of CRP and ALB. [10]

Blood culture remains the gold standard, although it requires a long waiting time and can be affected by multiple factors. [11] 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. [12-15]

The aim of the present study was to assess the predictive value of the CRP vs Serum albumin in earlier identification and as a prognostic indicator of neonatal sepsis.

Materials and Methods

This was a prospective study conducted in the Department of Neonatology, Yashvi Children Hospital, Patna, Bihar, India for two years. In this study, a total of 200 neonates were enrolled. 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 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 $p<0.05$ 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

Table 1: Characteristics variables

Variable	Control (n=50)	Sepsis (n=150)	Sepsis	
			Mild Sepsis (n=140)	Severe sepsis (n=60)
Age (days)	6.2 (2.0- 11.0)	5.1 (1.0-9.0)	6.3 (3.0-9.0)	2.2 (1.0-4.0)
Female (%)	10	110	85	25
Weight (Kg)	3.12±0.4	2.74±0.26	2.95±0.4	2.25± 0.5
Temp (degree)	37.4±0.3	37.7±0.5	37.6±0.3	37.6±0.5
Resp (rate/Min)	48±6	53±4	51±2	55±5
HR (B/M)	144±10.6	152±10.5	154±7.6	158±6
SBP (mmHg)	76±7.3	72±4.6	76±5.3	70±4.6
DBP (mmHg)	45±7.5	42±8.2	43±6.7	41±5.5
CRP (mg/dl)	5±0.8	14±2.5	12±2.3	18±3.4
Biochemical parameters				
S. albumin (g/d)	3.2±0.6	2.8±0.4	2.96±0.6	2.5±0.4
CAR	1.64±0.6	4.6±0.6	4.0±0.4	6.7±0.6

There were 120 neonates of female and 80 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. The majority of them were diagnosed with mild sepsis severe sepsis and a control group. 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 significantly higher levels of CRP and CAR ($p<0.05$), compared to neonates with mild sepsis.

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	0.432
Male, N (%)	38	22	20	0.048
Clinical data (N)				
Control	68	45	32	<0.007
Overall sepsis	70	48	42	<0.003
Mild sepsis	48	32	26	<0.005
Severe sepsis	22	16	16	<0.004

The prevalence of overall sepsis increased significantly from tertile 1 to 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 was more likely to be in tertile 1 and tertile 2 ($p<0.001$).

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	19.543 (5.76-34.56)	<0.002	12.130 (6.74-14.5)	<0.001
CAR TertilesTertile 1	I		I	
Tertile 2	2.138 (1.86-3.23)	<0.001	2.868 (1.789-3.92)	<0.001
Tertile 3	6.554 (4.88-13.86)	<0.001	5.884 (3.97-7.98)	<0.001
Presence of severe sepsis				
CAR	1.564 (1.3-2.4)	<0.001	1.26 (1.08-1.56)	0.001
CAR TertilesTertile 1	I		I	
Tertile 2	2.46 (1.67-3.24)	<0.001	2.216 (1.67-3.22)	<0.001
Tertile 3	5.354 (3.7-8.28)	<0.002	3.96 (2.87-5.93)	<0.001

After adjusting age, temperature, heart rate, respiratory rate, and weight, CAR was proved to be an independent risk factor for the presence of sepsis. 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.

Discussion

Sepsis is a potentially life-threatening complication of an infection with high short-term mortality. [16,17] In the past 10 years, the annual incidence of sepsis was 437/100,000, and the mortality rate was 17% in adults in developed countries. The annual incidence of severe sepsis is 270/100,000, and the mortality rate is 26%. [18] The incidence and mortality of sepsis are higher in developing and less developed countries. [19] In addition, treatment challenges and high costs pose a heavy burden on both society and the economy. Therefore, it is crucial to identify and predict the risk of death early in sepsis patients in order to evaluate the severity of the disease and make appropriate treatment decisions.

There were 120 neonates of female and 80 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. The majority of them were diagnosed with mild sepsis severe sepsis and a control group. 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 significantly higher levels of CRP and CAR ($p<0.05$), compared to neonates with mild sepsis. 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. [21,22]

The prevalence of overall sepsis increased significantly from tertile 1 to 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 was more likely to be in tertile 1 and tertile 2 ($p<0.001$). After adjusting age, temperature, heart rate, respiratory rate, and weight, CAR was proved to be an independent risk factor for the presence of sepsis. 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. 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. [23] 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. [24,25] 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 a predictor of severity in adult patients with abdominal sepsis. [21]

Conclusion

The present 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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