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CRP/albumin ratio: A promising marker of gram-negative bacteremia in late-onset neonatal sepsis

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What is already known on this topic?

Both C-reactive protein and albumin used as inflammation markers in sepsis; however, they are insufficient to identify the possible causative agent.

What this study adds on this topic?

By using these two markers together as the C-reactive protein/albumin ratio in neonatal sepsis, the causative microorganism can be independently predicted as Gram-negative or Gram-positive without waiting for blood culture results.

ABSTRACT

Objective: Neonatal sepsis is a clinical condition that results in serious morbidity and mortality unless urgently diagnosed and treated. Obtaining the results of blood cultures to determine the causative agent in sepsis is a time-consuming process. The CRP/albumin ratio is an inflammatory marker that has started to be used in recent years. The aim of our study was to investigate the relationship between CRP/albumin and Gram-negative bacterial sepsis in neonates.

Material and Methods: This study was conducted on 112 premature neonates with sepsis. The patients were divided into two groups according to culture results as Gram-negative and Gram-positive bacterial sepsis. The laboratory and demographic features of the patients were obtained from the hospital records. A receiver operating characteristic curve was plotted to evaluate the predictive value of the CRP/albumin ratio for Gram-negative sepsis.

Results: CRP/albumin was significantly higher in the Gram-negative group ($p<0.001$). According to the receiver operating characteristic curve, the optimal cut-off value of CRP/albumin for the prediction of Gram-negative sepsis was >35.17, which had a specificity of 97% and sensitivity of 56% (AUC=0.839; 95% CI: 0.743-0.944; $p<0.001$). A multivariate logistic regression analysis revealed that CRP/albumin (OR=1.082, 95% CI: 1.033-1.134, $p=0.001$) and absolute neutrophil count (OR=1.145, 95% CI: 1.000-1.312, $p=0.049$) were still associated with Gram-negative sepsis after adjustment for variables found to be statistically significant in univariate analysis and correlated with Gram-negative sepsis.

Conclusion: The CRP/albumin ratio is independently related to Gram-negative sepsis in neonatal sepsis and may be useful in predicting Gram-negative bacteremia.

Keywords: Albumin, bacteremia, C-reactive protein, Gram-negative bacterial infection, neonatal sepsis

Introduction

Neonatal sepsis leads to significant morbidity and mortality in neonates and ranks third among the causes of neonatal death (1). Early diagnosis and management of sepsis with appropriate combination therapy are important to prevent mortality. Cause-targeted therapy is only possible upon obtaining the results of blood cultures, which is the gold standard for diagnosis; unfortunately, the durationto obtain blood culture results may range from 48 hours to 6 days (2, 3). Considering all these concerns, the causative organism should be determined, and appropriate therapy is initiated as soon. This would also ensure unnecessary antibiotic use. Literature reports have been published to distinguish Gram-positive (GP)

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and Gram-negative (GN) microorganisms in sepsis and other infections (4-6).

C-reactive protein (CRP) is one of the acute-phase proteins released in inflammation. It is used for the diagnosis and follow-up of sepsis and determining treatment efficacy (7-9). The advantage of CRP in infants is its low serum level, which is rapidly elevated within 6-8 hours in cases of sepsis (10). However, CRP levels increase even in non-infectious conditions such as premature rupture of membranes in delivery, and vaccination or maternal fever in neonates (11). Serum albumin is a negative acute-phase reactant. In critical care, hypoalbuminemia grade is correlated to that of infection-triggered inflammation. Similarly, the CRP/albumin ratio (C/A) has also been shown to correlate with infection severity (12). In recent years, this ratio was shown to be correlated with mortality in premature infants and other patient groups in addition to sepsis (13-15).

The combination of these parameters may be more sensitive and useful in predicting bacteremia in neonatal sepsis. We aimed to investigate the relationship between C/A and GN and GP bacteremia, and its possible predictive role in the differential diagnosis of these two sepsis types.

Material and Methods

This retrospective observational study was conducted on patients diagnosed as having neonatal sepsis in our neonatal intensive care unit (NICU) between January 2015 and January 2018. Our unit has a capacity of 30 incubators and admits approximately 500 patients annually. We enrolled a total of 112 patients followed with suspected neonatal sepsis in the NICU. Neonatal sepsis was diagnosed according to the recommendations of the European Medicines Agency (EMA) (meeting dated 2010): the presence of at least two clinical symptoms and at least two laboratory signs are required in addition to suspected or proven infection (positive culture, microscopy or polymerase chain reaction (16).

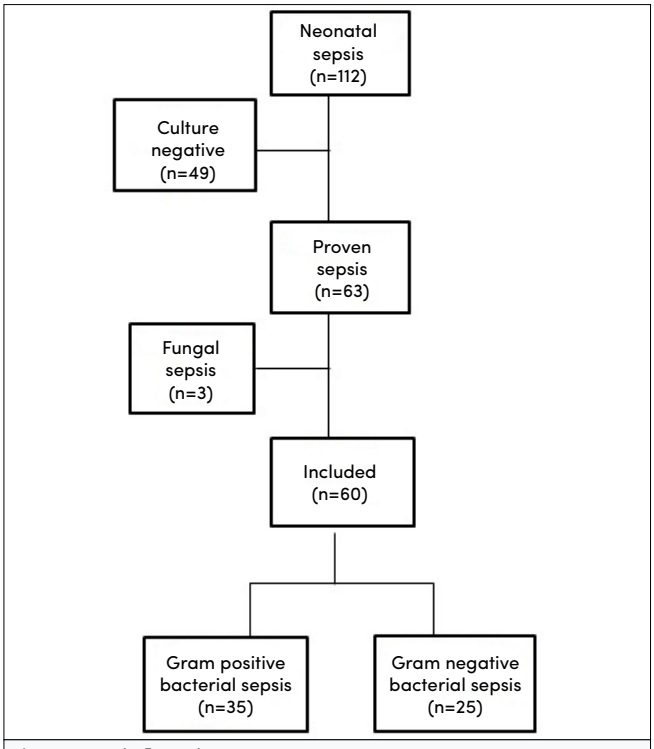

Figure 1. Study flow-chart

Forty-nine patients were excluded due to negative blood culture (Figure 1). The remaining 63 patients had proven sepsis as confirmed through clinical and blood culture data. Proven sepsis was defined as the presence of blood culture proliferation in addition to the above-mentioned criteria (16, 17). The diagnoses of suspected neonatal sepsis and proven sepsis were made by an expert neonatologist. This study only enrolled patients with late-onset neonatal sepsis, which was defined as having sepsis after the 72nd hour of life (16, 18). Three of the patients with confirmed sepsis were excluded because they were noted to have fungal sepsis. Thirty-five patients had GP bacterial proliferation and 25 had GN bacterial proliferation. The patients were grouped into two groups based on Gram staining as GP bacterial sepsis (GPBS) and GN bacterial sepsis (GNBS). Age (days) at the time of diagnosis of suspected sepsis, sex, gestational age, delivery method, maternal age, birth weight, laboratory findings, and CRP/albumin levels were obtained from medical records. Patients with septic shock were not included in the study because they may have low results in albumin levels and affect the study results.

Table 1. Baseline characteristics of study patients

	GPBS (n=35)	GNBS (n=25)	p
Baseline characteristics			
Age, median (IQR) days	12 (7-18)	11 (6-19)	0.748
Male/female, n	21/14	14/11	0.757
Gestational age, week	31±5	32 ±4	0.441
Maternal age, years	27±7	29±6	0.251
Birth weight, median (IQR) grams	1300 (850-2175)	1530 (1153-2930)	0.154
Mode of delivery (C/V) n	31/4	23/2	0.999
Laboratory findings			
CRP/Albumin Ratio, median (IQR)	12.0 (6.3-18.2)	38.7 (17.8-58.5)	<0.001
CRP, median (IQR) mg/L	33 (18.4-54)	105 (50.4-156)	<0.001
Albumin, median (IQR) g/dL	2.9 (2.8-3.1)	2.8 (2.5-3.1)	0.120
WBC X10^3, median (IQR) mm^3	11.8 (7.9-16.9)	15.5 (7.5-24.4)	0.139
ANC X10^3, median (IQR)	4.4 (2.3-7.3)	8.6 (4.9-15.2)	0.021
Hb, median (IQR) g/dL	12.83±3.25	11.63±2.71	0.183
RDW	20.11±7.64	18.35±2.93	0.290
MPV	9.17±2.82	11.43±2.63	0.004
Platelet count x10^3, median (IQR) mm^3	196 (101-364)	119 (56-270)	0.210

Data are presented as mean ± standard deviation (SD) number or median and interquartile range (IQR). p≤0.05 was considered statistically significant.
ANC: Absolute neutrophil count; CRP: C reactive protein; C/V: Cesarean/Vaginal route; Hb: Hemoglobin; GPBS: Gram-positive bacterial sepsis; GNBS: Gram-negative bacterial sepsis; MPV: Mean platelet volume; RDW: Red cell distribution width; WBC: White blood cell count

Table 2. Univariate and multivariate analyses for predicting GNBS						
	Univariate			Multivariate		
Variable	p	OR	(95%CI)	p	OR	(95%CI)
Statistically significant variables						
CRP/Albumin ratio	<0.001	1.093	1.041-1.147	0.001	1.082	1.033-1.134
ANC	0.048	1.103	1.001-1.216	0.049	1.145	1.000-1.312
MPV	0.010	1.497	1.100-2.036			
Variables which correlated with CRP/Albumin						
Platelet	0.215	0.998	0.994-1.001			

All the variables from Table 1 were examined and only those significant at p<0.05 level and correlated with CRP/Albumin are shown in univariate analysis. Multivariate logistic regression analyses including all the variables in univariate analysis with enter method. P≤0.05 was considered statistically significant.
ANC: absolute neutrophil count; CRP: C-reactive protein; CI: Confidence interval; MPV: mean platelet volume; OR: odds ratio

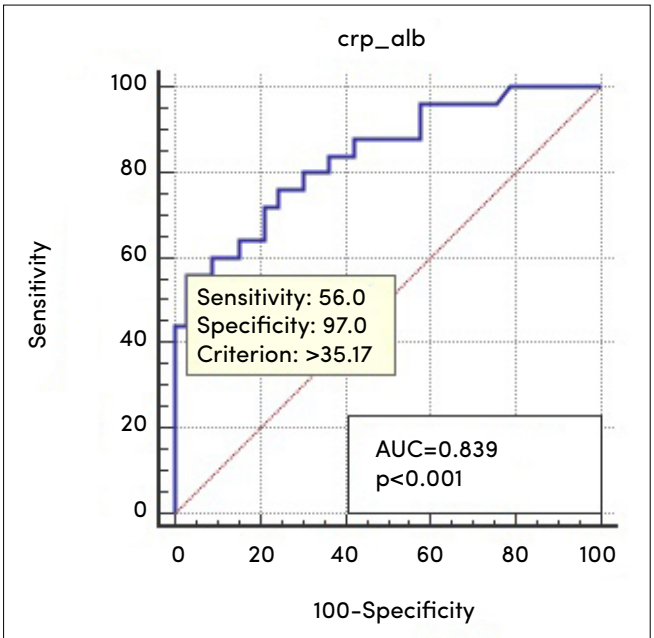

Figure 2. ROC curve analysis of CRP/albumin ratio for predicting Gram-negative bacterial sepsis

This study was approved by the Ethics Committee Kahramanmaraş Sütçü İmam University (Protocol No.: 124, Date: March 21st, 2018), and was performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

Statistical analyses

The Statistical Package for the Social Sciences version 17 (SPSS Inc., Chicago, IL, USA) statistical software was used for all analyses. A two-sided P-value ≤0.05 was considered statistically significant. Continuous data are expressed as mean ± standard deviation or median (minimum-maximum), and categorical data as number and percentage. The independent sample t-test was used to compare normally distributed quantitative data and the Mann-Whitney U test was used for non-normally distributed variables. Categorical data were compared using the Chi-square test. Spearman's correlation test was used to assess correlation. An optimal cut-off point for the CRP/albumin ratio, as indicated by the sum of the highest sensitivity and specificity-1, as well as the area under the curve (AUC) with 95% confidence interval (CI) were calculated for the prediction of GNBS using a receiver operator characteristic (ROC) curve with the MedCalc (v12.7.8) software package. Univariate analysis was used to determine variables correlated with GNBS. Those that were statistically significant in the univariate analysis were entered into a multivariate logistic regression model with the backward stepwise method for the prediction of GNBS.

Results

This study assessed a total of 112 patients with a diagnosis of suspected neonatal sepsis, 60 of whom had blood culture proliferation as proven sepsis and were enrolled. The patients were grouped into two groups based on blood culture results: GPBS and GNBS groups. Thirty-five patients had GP bacterial proliferation and 25 had GN bacterial proliferation. The demographic and laboratory variables of the study population are shown in Table 1. There was no significant difference between the groups with respect to age, sex, gestational age, and birth weight (p=0.748, p=0.757, p=0.441, and p=0.154, respectively). CRP/albumin was significantly higher in the GNBS group than in the GPBS group (p<0.001) (Table 1).

C-reactive protein/albumin was negatively correlated to platelet count (r=-0.374, p=0.001).

The ROC curve indicated that the optimal cut-off value of C/A to predict GNBS was >35.17, which had a specificity of 97% and sensitivity of 56% (AUC = 0.839; 95% confidence interval (CI): 0.743-0.944; p<0.001) (Figure 2). Also, the positive predictive value of CRP/Albumin over 35.17was 56% and the negative predictive value was 94%.

In the multiple logistic regression model, using a backward stepwise method revealed that C/A (odds ratio, OR=1.082, 95% CI: 1.033=1.134, p=0.001) and absolute neutrophil count (OR=1.145, 95% CI: 1.000-1.312, p=0.049) remained significant predictors of GNBS after adjusting for the other confounding variables, which were either found to be statistically significant in the univariate analysis (Table 2).

Discussion

In this study, we investigated the relationship between C/A and blood culture results in neonatal sepsis. To the best of our knowledge, this is the first study in which C/A was used to predict the responsible microorganism in neonatal sepsis. We demonstrated that C/A was an independent predictor of GN bacteremia in neonatal sepsis. We also determined an optimal cut-off value for C/A to predict GNBS. We found that a C/A ratio of more than 35.17 predicted GNBS with a sensitivity of 97% and a specificity of 56%.

Cause-specific, rational antibiotherapy reduces mortality and morbidity in neonatal sepsis; therefore, determination of the etiologic pathogen as soon as possible is one of the problems that physicians work on. Some studies investigated procalcitonin, interleukin-1 (IL) receptor 2 and some cytokines such as interleukin (IL)-6, IL-8, tumor necrosis factor-alpha (TNF-α), and granulocyte colony-stimulating factor (G-CSF) to determine the differential diagnosis between GN and GP bacteremia (2, 19-23). However, routine use of these cytokines in clinical practice does not appear feasible. In our study, the C/A ratio was predictive of GNBS with a sensitivity of 56% and a specificity of 97%. Moreover, it is advantageous in that it is easily available in almost every clinic and inexpensive.

In the study of Yang et al. (15) on 214 premature infants, they showed that the high-sensitivity CRP/albumin ratio (hsCRP/A) could be used in the early diagnosis of intrauterine bacterial infection, and especially that the increase in the 48th hour had a better diagnostic sensitivity. They divided preterm infants as infectious and non-infectious groups and demonstrated that the hsCRP/A ratio was significantly higher in the infectious group after admission to the intensive care unit. They also revealed that this ratio was also significantly increased in the survivor group. In our study, we found that, in the GNBS group, the C/A was significantly higher than that in the GPBS group. Another retrospective study conducted by Sun et al. (24) on adult patients with sepsis showed that C/A indicated poor prognosis of patients .Similarly, Kim et al. (14) and Ranzani et al. (25) reported that on admission to hospital, the C/A ratio might be used as an independent predictor of mortality among patients with severe sepsis or septic shock. However, most of these studies focused on mortality or length of hospital stay. We found no study in the literature on C/A showing possible microorganisms in sepsis. In this aspect, our work is original.

C-reactive protein levels increase in response to infection and this increase is proportional to infection severity (14). However, CRP levels in neonates may also increase due to non-infectious causes such as premature rupture of membranes, vaccination, fetal distress, maternal fever, and meconium aspiration (11). In contrast, albumin is a negative acute-phase reactant released in inflammation (12). This may be explained by increased catabolism rates in sepsis and redistribution secondary to increased vascular permeability, which causes capillary leakage (26). The degree of hypoalbuminemia in critically ill patients correlates with the intensity of the inflammatory response triggered by infection (25). Therefore, the difference between CRP and albumin in sepsis is gradually widening. Given that the use of the ratio between CRP and albumin will include minor reductions in albumin values, it will also change without significant difference in albumin values and provide a value that positively correlates with infection, i.e. a high rate indicates a high inflammatory status (25).

Gram-negative bacteremia causes a more profound inflammatory response than GP bacteremia (27). Gram-negative infections probably increase TNF-α and IL-1, IL-6, IL-10, and IL-8 production to a higher degree than GP infections (28). This may be explained by a complex immune response to different pathogens in sepsis. In vitro studies have shown that GN, GP, and fungal agents initiate inflammatory cascades by different mechanisms (28, 29). The lipopolysaccharide patterns of GN bacteria activate neutrophils through Toll-like receptor-4 (TLR-4), whereas lipoteichoic acid in GP bacteria initiates the inflammatory cascade via TLR-2 (29). Studies have shown that other inflammatory marker levels such as procalcitonin and CRP were higher in GN infections compared than in GP infections (19, 30). Similarly, we found both CRP, ANC, MPV, and C/A levels were higher in the GNBS group.

In the present study, the ratio of GP bacteria was higher among patients with blood culture proliferation (GP 58.33%, GN 41.66%). In agreement with previous studies, Staphylococcus was the most common pathogen followed by Klebsiella and Enterobacter (19, 27).

Our study has some limitations. First, it only enrolled patients with late-onset neonatal sepsis because the expected CRP response does not occur early in early neonatal sepsis. Secondly, the C/A ratio having low specificity for predicting GNBS may be explained by the low number of subjects; there is a clear need for further studies on this subject. As the capillary leakage will gradually increase in the later stages of sepsis, albumin levels will also decrease gradually. However, because our patients were diagnosed in the early period, the fact that this decrease has not yet developed may have caused no albumin difference between the two groups. The retrospective nature of the study is another limitation.

In conclusion, determining the offending pathogen of neonatal sepsis as soon as possible until blood culture results are available will ease the choice of empiric antibiotic therapy, it will also reduce treatment costs and prevent unnecessary antibiotic use. On the other hand, we believe that the C/A ratio may offer an advantage in clinical practice by virtue of its low cost and being readily available. There is, however, a need for further studies on this subject.

Ethical Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kahramanmaraş Sütçü İmam University (Protocol No.: 124, Date: March 21st, 2018).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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