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Microbiology

CRP TO ALBUMIN RATIO: A DIAGNOSTIC MARKER OF GRAM-NEGATIVE BACTEREMIA IN NEONATAL SEPSIS

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ABSTRACT **Background -** Neonatal sepsis ranks third among the causes of neonatal death. Appropriate treatment is only possible after obtaining the results of blood cultures, which is the gold standard for diagnosis, but the blood culture results may range from 48 hours to 6 days. The CRP/albumin ratio is a marker that has started to be used in recent years. The aim of our study was to investigate the relationship between CRP/albumin ratio with Gram positive and Gram-negative bacterial sepsis in neonates. **Methodology Study design-** Retrospective observational Study. **Study Centre**- Bundelkhand Medical College, Sagar, Madhya Pradesh. Study duration- December 2020 to DEC 2022 **Methods and material -** 142 neonates with sepsis were enrolled in this study. The patients were divided into two groups according to culture results as Gram-negative and Gram-positive bacterial sepsis. The blood culture reports and serological reports of the patients were obtained from the hospital records for the comparision of CRP/albumin ratio with gram negative and gram positive sepsis. **Result –** Among 142 patients with neonatal sepsis, 98 patients were culture positive with 58 had Gram Positive bacterial infection, 40 had Gram Negative bacterial infection and 5 had fungal infection. Based on the statistical data obtained CRP/albumin was significantly higher in the Gram-negative group (>39.5) as compared to gram positive group (>12.7). Interpretation & conclusions - CRP/albumin ratio could be used in the early diagnosis of bacterial infection in neonates until the blood culture reports are available. It will also reduce treatment costs and prevent unnecessary antibiotic use.

KEYWORDS : Gram positive bacteria, Gram negative bacteria, CRP/albumin, 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 treatment 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 duration of obtaining blood culture results may range from 48 hours to 6 days [2, 3]. Considering these concerns, the causative organism should be determined, and appropriate therapy should be initiated as soon as possible. Sepsis is the most common cause of mortality among patients admitted to Intensive Care Unit (ICU) [1,2]. Recent evidence suggests the association of higher C-reactive protein (CRP)/Albumin value with the sepsis [3,4]. On admission CRP/Albumin has been reported to have high predictive capability of sepsis. It is important to predict the prognosis of patients who require critical care in the intensive care unit (ICU) to determine the direction of treatment. To date, many studies have evaluated parameters or biomarkers used for the prediction of prognosis in critically ill patients. However, these factors are difficult to determine, and the immediate application of such prognostic information is complicated when dealing with unstable patients. A simple, quick, and accessible parameter is needed to confirm treatment response and predict mortality in ICU patients. C-reactive protein (CRP) is an acute-phase protein that is produced following stimulation by various cytokines in response to infection, ischemia, trauma, and other inflammatory conditions. High CRP levels have been studied in relation to prognosis and mortality in critically ill patients [2–6]. On the other hand, low serum albumin is known to be associated with poor prognosis and mortality [7,8]. The advantage of CRP in infants is its low serum level, which is rapidly elevated within 6-8 hours in the 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 the 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. Based on this, we speculated that the ratio of CRP to albumin could be used as a predictive marker for mortality. Recently, the CRP/albumin ratio, a combination of markers for systemic inflammation and nutritional status, has been extensively studied as an independent prognostic marker in patients with infection, malignancy, and other diseases [9–15]. However, there are relatively few studies conducted focusing on critical care patients in the ICU. Appropriate treatment is only possible after obtaining the results of the blood cultures, which is the gold standard for diagnosis, but the blood culture results may range from 48 hours to 6 days. The CRP/albumin ratio is a marker that has started to be used in recent years. The aim of our study was to investigate the relationship between CRP/albumin ratio with Gram positive and Gram-negative bacterial sepsis in neonates.

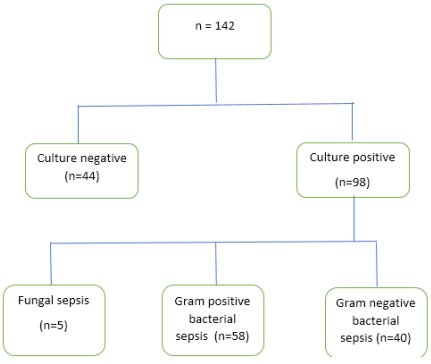
MATERIAL AND METHODS

This was a single centre, hospital (in-patient) based, retrospective observational study was conducted on patients diagnosed as having neonatal sepsis in Bundelkhand Medical College, Sagar neonatal intensive care unit (NICU) between December 2020 and December 2022. Our unit has a capacity of 20 incubators and admits approximately 600 patients annually. We enrolled a total of 142 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]. 44 patients were excluded due to negative blood culture. The remaining 98 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]. 5 of the patients with confirmed sepsis were excluded because they were noted to have fungal sepsis. 58 patients had Gram Positive bacterial proliferation and 40 had Gram Negative bacterial proliferation. The patients were grouped into two groups based on Gram staining as Gram Positive bacterial sepsis (GPBS) and Gram Negative 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.

RESULTS AND OBSERVATIONS

Among 142 patients with neonatal sepsis, 98 patients were culture positive with 58 had Gram Positive bacterial infection, 40 had Gram Negative bacterial infection and 5 had fungal infection. Based on the statistical data obtained CRP/albumin was significantly higher in the Gram-negative group (>39.5) as compared to gram positive group (>12.7).



Baseline characteristics of study patients			
	GPBS (n=58)	GNBS (n=40)	P value
Age (median)	11	9	0.647
Gender (Male/Female)	32/26	22/18	0.685
Gestational age (week)	32±4	33±5	0.547
Maternal age (years)	28±6.5	29±5.7	0.352
Laboratory findings			
CPR/Albumin Ratio	12.7	39.5	0.04
CPR, median (IQR) mg/l	34.8	103.6	0.002
Albumin, median (IQR) mg/l	2.7	2.8	0.124

DISCUSSION

C-reactive protein (CRP) is known to be one of the acute-phase proteins generated in inflammation. It is a very sensitive biomarker in diagnosis neonatal sepsis and follow up on the response to treatment [9]. Infants are reported to have low serum CRP levels, which quickly rise within 6–8 hours in cases of infection and sepsis [6, 10]. However, it is non-specific and may increase in non-infectious situations such as maternal fever or premature rupture of the membranes during birth [11]. Serum albumin is considered a negative acute-phase reactant [12]. Sepsis in neonates is associated with hypoalbuminemia. It has been reported that lower albumin levels are linked to less favourable results [13]. Therefore, assessment of both CRP and albumin instead of analysing every factor independently enables the merging of inflammatory and nutritional variables, both of which have a strong impact on the prognosis [14, 15]. In the present study, the ratio of Gram Positive bacteria was higher among patients with blood culture proliferation in agreement with previous studies [19, 27]. Adult research have shown that in critically unwell or patients with sepsis, the CRP/albumin ratio is linked to increased mortality, organ failure, and longer hospital stays. More recently, it has been shown that in critically unwell children in the pediatric intensive care unit, a high CRP/albumin ratio was predictive of worse outcomes (i.e., organ failure and death) [16]. In our study, the CRP/albumin ratio was found significantly higher in the Gram-negative group (>39.5) as compared to gram positive group (>12.7) in diagnosis of bacterial sepsis in neonates. The complexity of the sepsis response makes it unlikely that a single biomarker will ever be ideal and used solely in clinical practice. A combination of several sepsis biomarkers may be more effective; therefore, further investigations, including other markers such as procalcitonin, should be done for early diagnosis of neonatal sepsis. We recommend that the CRP as a sepsis biomarker is still optimum to be used and that the CRP/albumin ratio could add a little benefit for diagnosis of sepsis. The main limitation of the study was the lack of long-term outcome of the studied neonates as this was out of the scope of this study.

CONCLUSION

CRP/albumin ratio is an early diagnostic biomarker for neonatal sepsis in premature newborns that has marginal superiority to the CRP in the diagnosis of neonatal bacterial sepsis. More studies are needed to validate the sensitivity and specificity of a score that combines both the CRP/ albumin ratio. 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.

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