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Original Article

The C-Reactive Protein/Albumin Ratio As An Early Diagnostic Marker Of Neonatal Sepsis In Preterm Neonates: A Case-Control Study

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Abstract:

Background: Neonatal sepsis is a serious systemic infection that might be fatal. Early diagnosis is challenging. The c-reactive protein (CRP)/albumin ratio is a promising biomarker that may help with early diagnosis and timely management of sepsis.

Aim of the work: to study the sensitivity and specificity of the CRP/albumin ratio as a diagnostic marker of neonatal sepsis in preterm newborns.

Patients and Methods: in this case-control study CRP/albumin ratio was estimated in 154 preterm newborns admitted to Neonatal Intensive Care Units (NICUs) of Cairo University Children's Hospitals. They were divided into 2 groups. Group (I), the sepsis group "based on positive blood culture" (n=54), and group (II), a control group, with no clinical signs or laboratory evidence of sepsis (n=100).

Results: The mean age of newborns in the sepsis group was 3 ± 2.5 days vs 4.5 ± 2.5 days for the control group. The sepsis group had a mean ± SD CRP/albumin ratio higher than that of the control group (18.5 ± 20 vs 0.6± 0.7, p= 0.00). 30 (55%) of those in the sepsis group died; they had a mean ± SD CRP/albumin ratio of 20± 21, vs 15 ± 17 for those who survived (p value=0.3). Neonatal Sepsis was best diagnosed by the CRP/albumin ratio above the cutoff value of 1.5 with 100 % sensitivity, 95% specificity, 91.5 % positive predictive value (PPV), 100 % negative predictive value (NPV), (area under the curve (AUC)= 0.99, and 95 % confidence interval (CI) 0.983 - 1), which was not different than that of CRP alone (p=0.800). CRP above the cutoff point of 4.3 showed 96.3 % sensitivity, 96% specificity, 92.9 % PPV, 98 % NPV, (AUC= 0.99 , 95 % CI 0.983 - 1). The I/T ratio (shift to the left) above the cutoff point of 0.2 showed 64.8% sensitivity, 100 % specificity, 100% PPV and 84% NPV (AUC= 0.94 , 95% CI 0.891 - 0.973).

Conclusion: CRP/albumin ratio is a highly sensitive and specific 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 above 1.2 and the I/T ratio above 0.2 in predication of true positive cases and exclusion of the true negative cases.

Level of Evidence of Study: IV (*1*)**.**

Keywords: Neonatal sepsis; CRP/albumin ratio; preterm neonates; early-onset sepsis; late-onset sepsis; c-reactive protein

Abbreviations: AUC: area under the curve; CI: confidence interval; CPAP: continuous positive airway pressure; CRP: C-Reactive Protein; CONS Coagulase-negative *Staphylococcus aureus*; CS: cesarean section; EOS: early-onset sepsis; HB: hemoglobin; HT: hematocrit; I/T ratio: immature to mature neutrophil ratio; LOS: late-onset sepsis; MRSA: Methicillin-resistant *Staphylococcus aureus*; MV: Mechanical ventilator; NPV: negative predictive value; NICUs: neonatal intensive care units; NVD: normal vaginal delivery; PLT: platelet count; PPV: positive predictive value; ROC: Receiver operating characteristic; SE: Standard error; TPN: total parenteral nutrition; WBC: white blood cell count

Introduction

Neonatal sepsis is one of the leading causes of morbidity and mortality among neonates, particularly in middle and lower-income countries (*2*, *3*). Early suspicion of sepsis in preterm newborns is crucial to institute timely management as sepsis may progress rapidly to

hemodynamic instability, shock and death. The clinical manifestations of neonatal sepsis are non-specific and can be associated with other neonatal diseases, making the diagnosis based on physical examination alone difficult (*2*). Diagnosing sepsis is challenging as there is no specific biomarker, and it depends mainly on positive culture, which could be delayed or affected by many other factors such as prior use of antibiotics (*4*), hence there is a need for reliable biomarkers of sepsis that are readily available, sensitive, specific, and its processing does not consume much time (*5*). The C-reactive protein (CRP) has been extensively used as a marker for diagnosing bacterial neonatal sepsis; however, it is non-specific and can be elevated in other occasions, such as inflammatory conditions leading to abusive use of antibiotics. Recently, the CRP/albumin ratio has been studied as an independent prognostic marker for systemic inflammation and nutritional status in patients with infection, malignancy, and other diseases (*6*). Its usefulness in justifying the use of antibiotics is still debatable. This role has been well-described in adult literature. However, there are few studies on pediatrics, especially in neonates. We aimed to study the sensitivity and specificity of the CRP/albumin ratio as a diagnostic marker of neonatal sepsis in preterm newborns.

Subjects and Methods

This case-control study was conducted at the neonatal intensive care units of (NICUs), Children Hospitals, Faculty of Medicine, Cairo University, over a period of 6 months, starting July 2021 till January 2022. The study was approved by the Ethical Committee of the Faculty of Medicine, Cairo University, Egypt (approval number: MS-435-2021), and written consent was obtained from all caregivers of participants.

Participants

The study included 154 preterm newborns with gestational age less than 37 weeks, divided into 2 groups. Group (I), the sepsis group, included newborns confirmed to have neonatal sepsis based on positive blood culture (n=54), and a control group, that included preterm neonates with no clinical signs or laboratory evidence of sepsis (n=100). Full-term neonates, those with major congenital anomalies, congenital cyanotic heart disease, and those with inborn errors of metabolism were excluded.

Methods

Sepsis was suspected according to the third international consensus definitions of sepsis and septic shock (sepsis 3) (7) based on at least 2 clinical and 2 laboratory criteria. The clinical criteria included: 1) vital signs including, hyperthermia (core body temperature ≥38°C) or hypothermia <36°C or temperature instability, 2) Cardiovascular manifestations such as tachycardia (heart rate >160 beats/min) or bradycardia (heart rate <100 beats/min) or rhythm instability, 3) Respiratory manifestations such as tachypnea (respiratory rate >60 breaths/min) or recurrent apnea >20 seconds, increased oxygen requirements or requirement for ventilator support, 4) Gastrointestinal manifestations such as feeding intolerance suspected by the presence of gastric residuals, abdominal distension, gross or occult blood in the stool, 5) The onset of crises of apnea/bradycardia, lethargy, and hypotonia, hypotension <5th percentile for age or systolic blood pressure <2 SD below normal of age, 6) Skin and subcutaneous lesions such as mottling and sclerema, whereas laboratory criteria were as follows: white blood cell (WBC) count <5 or >20 × 109 cells/L, immature to total neutrophil ratio (I/T ratio) >0.2 (*7*), platelet count (PLT) <100 × 109/L, and CRP >10 mg/L. The diagnosis was verified after a positive blood culture, thus they were included in the study.

Clinical data of studied neonates were collected from files of patients and their progress notes, including gestational age, maternal dates, Ballard scores (*8*), mode of delivery, birth weight, and APGR score at 1,5 and 10 minutes.

Thorough clinical examination for assessment of the general condition and neonatal reflexes, assessment of vital signs, and full systemic examination to detect signs of neonatal sepsis were included. Medical interventions (endotracheal tube, mechanical ventilation, TPN, central venous/umbilical catheterization) were also recorded.

As regards laboratory investigations, data was recorded at the time of sepsis evaluation, including complete blood count (CBC) with differential leucocytic count, calculation of the I/T ratio C-reactive protein, serum albumin level, blood culture, and CRP/albumin ratio was calculated by dividing CRP/Albumin levels.

The sepsis group (n=54) was further subdivided into 2 groups; Group (A) included newborns with early-onset sepsis (EOS) that occurred within the first 72 hours of life (n=40), and Group (B) included those with late-onset sepsis (LOS) that occurred after 72 hours of life (n=14).

Statistical Analysis

Data was collected, coded, and imported into IBM SPSS, (USA) version 23 of the Statistical Package for Social Science. The non-parametric data were shown as the median and interquartile range (IQR), whereas the numerical parametric data were shown as the mean and standard deviations. Numbers and percentages were used to represent the qualitative characteristics. The statistical test of significance used was the chi-square test and Mann- Whitney was used for non-parametric data for qualitative variables. Independent t-tests and one-way ANOVA were used for numerical data, ROC curve analysis with the Youden index test to detect the best cutoff point, its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC). The significance level was set as a p-value equal to or less than 0.05.

Results

The mean age at diagnosis of the sepsis group was 3 ± 2.5; 30 (56%) of them were males, 40 (74%) of them were born by Caesarean section (CS), they had a mean gestational age of 31 ± 2.3 weeks and a mean birth weight of 1.44 ± 0.5 kgs. The mean age of the control group was 4.5 ± 2.5; 53 (53%) of them were males, 79(79%) of them were born by CS, they had a mean gestational age of 33 ± 1.35 weeks and a mean birth weight of 1.4 ± 0.4 kgs. The APGAR scores after 1,5 and 10 minutes were significantly lower in the sepsis group than in the control group (p= 0.000). The sepsis group had slightly higher heart rate (140 ± 25 vs 138 ± 11 beats/min, p= 0.002), higher respiratory rate (62 ± 8 vs 52 ± 11 breath/min, p=0.00), lower systolic blood pressure (63 ± 13 vs 75± 7 mmHg, p=0.00), lower diastolic blood pressure (36 ± 10 vs 40 ± 5 mmHg, p=0.001) in comparison to the control group. The temperature was incomparable between both groups (36.9 ± 0.5 vs 36.7 ± 3.4 Celsius, p= 0.5). (Table 1).

Table 1. Characteristics and vital signs of studied sepsis and control groups

		Sepsis Group No.= 54		Control Group No.= 100		P value
		Number	%	Number	%	
Sex	Female	24	44	47	47	0.570
	Male	30	56	53	53	
Mode of delivery	NVD	14	26	21	21	0.863
	CS	40	74	79	79	
Outcome	Survived	24	45	100	100	0.00
	Died	30	55	0	0	
		Mean ± SD		Mean ± SD		
Gestational age in weeks		31 ± 2.3		33 ± 1.35		0.000
Birth weight in kilograms		1.4 ± 0.4		1.84 ± 0.4		0.000
Age in days		3 ± 2.5		4.5 ± 2.5		0.01
Apgar after 1 minute		2.9 ± 1.4		4.75 ± 1.21		0.000
Apgar after 5 minutes		5.7 ± 2		7.75 ± 0.86		0.000
Apgar after 10 minutes		7.8 ± 1.7		9.60 ± 0.59		0.000
Respiratory rate (breath/min)		62 ± 8		52 ± 11		0.000
Heart rate (beats/min)		140 ± 25		138 ± 11		0.002
Systolic blood pressure (mm/hg)		63 ± 13		76 ± 7		0.000
Diastolic blood pressure(mm/hg)		36 ± 10		41 ± 6		0.001
Temperature (Celsius)		36.9 ± 0.4		36.7 ± 3.4		0.562

NVD: normal vaginal delivery; CS: cesarean section.

The encountered risk factors for neonatal sepsis, mechanical ventilation (MV), umbilical catheter insertion, TPN for a longer duration and received more frequent blood transfusions. (Table 3). Table 3 illustrates the significant differences between the 2 groups. The CRP/albumin ratio ranged from 1.6 to 96 with a mean ± SD of 18.5 ± 20, and this was a statistically significantly higher than that of the control group (range 0.06 to 4.3 with a mean ± SD of 0.6± 0.7) (p= 0.000).

In the sepsis group; Coagulase-negative *Staphylococcus aureus* (CONS) was the most commonly isolated organism in 24 (45%) of cases, followed by *Klebsiella pneumoniae* in 15(27%) of cases. (Figure 1). There were positive correlations between the CRP/albumin ratio, the time of

sampling, and the CRP levels (p=0.034, p= 0.000, respectively). Negative correlations were found between CRP/albumin ratio and APGAR after 1 min, and mean platelets count, and albumin level (p-values= 0.010, 0.036, 0.000 respectively). (Table 4).

Table 2. Risk factors of neonatal sepsis in studied groups

		Sepsis Group Number= 54	Control Group Number= 100	P value
CPAP frequency	number (%)	3 (6%)	30 (30%)	0.000
MV frequency	number (%)	49(90%)	9 (9%)	0.000
CPAP or MV duration in days	Mean ±SD	12 ± 5.7	4 ± 1.7	0.000
Umbilical Cath frequency	number (%)	50 (92%)	34 (34%)	0.000
Umbilical Cath duration in days	Mean ±SD	13.7 ± 7.8	11.8 ± 2.5	0.093
TPN frequency	number (%)	53 (98%)	51 (51%)	0.000
TPN duration in days	Mean ±SD	16 ± 8.4	9.8 ± 3.4	0.000
Blood /plasma transfusion frequency	number (%)	43 (80%)	4 (4%)	0.000
Frequency of blood /plasma transfusion	Mean ±SD	2.8 ± 2	1.2 ± 0.5	0.006

CPAP: continuous positive airway pressure; MV: Mechanical ventilator; TPN: Total Parenteral Nutrition

Table 3. Lab results among studied groups

		Sepsis Group No.= 54		Control Group No.= 100		P value
HB (g/dl)	Mean ±SD	11.9 ± 2		15.5 ± 2		0.000
HT	Mean ±SD	34.5± 8		46.7 ± 7.7		0.000
PLTs (x10^{3})	Mean ±SD	214 ± 190		283 ± 110		0.005
TLC ((x10^{3})	Mean ±SD	13 ± 11		9.5 ± 4		0.002
Shift to the left (I/T)	Mean ±SD	0.24 ± 0.12		0.08± 0.04		0.000
CRP (mg/dl)	Mean ±SD	42 ± 40		2 ± 2		0.000
	Range	4 – 188		0.2 – 12		
CRP/Albumin ratio	Mean ±SD	18.5 ± 20		0.6± 0.7		0.000
	Range	1.6-94		0.06-4.3		
Albumin (g/dl)	Mean ±SD	2.5 ±0.5		3.25 ±0.46		0.000
	Range	1.6 –3.6		2 –4.6		
		Number	%	Number	%	
CRP (normal <5mg/dl)	Negative	8	15	98	98	0.000
	Positive	46	85	2	2	
Albumin (normal >3g/dL)	Low	31	57	97	97	0.000
	Normal	23	43	3	3	

ALB: albumin; CRP: C Reactive Protein; HT: hematocrit; HB: hemoglobin; PLTs: platelets; TLC: Total Leucocytic Count.

In our study group, early-onset sepsis (EOS) was more frequent that late-onset sepsis (74% vs 26%), the mean ± SD CRP was not statistically different between both groups (p= 0.4). (Table 5). 30 (55%) of the patients in the sepsis group died, while there were no mortalities in the control group. Patients who died had a mean ± SD CRP/albumin ratio of 20± 21, vs 15 ± 17 for those who survived with insignificant difference (p value=0.3). Sepsis among newborns with confirmed sepsis was best diagnosed by the CRP/albumin ratio above the cutoff value of 1.5 with 100 % sensitivity, 95% specificity, 91.5 % positive predictive value (PPV), 100 % negative predictive value (NPV), the area under the curve (AUC) was 0.992 and 95 % confidence interval (CI) 0.983 to 1 to 0.998, which marginally superior to the CRP alone above the cutoff point of 4.3 which showed 96 % sensitivity, 96% specificity,92.9 % PPV, 98 % NPV, AUC was 0.992 and 95 % CI 0.983 to 1. The albumin level below the cutoff point of 2.8 showed 66 % sensitivity, 94% specificity, 85 % PPV, 83 % NPV, the AUC was 0.84 and 95 % CI 0.78 to 0.91 for sepsis diagnosis. CRP/ albumin ratio for both diagnosis and prognosis were not much better than the CRP alone. (Table 6). (Figure 2). The sepsis group had a significantly higher I/T ratio than the control group (0.24 ± 0.12 vs 0.08± 0.04, p= 0.00) as shown in Table 3.

Table 4. Correlation between CRP/Albumin ratio and the other studied parameters in the sepsis group

	CRP/Albumin ratio			CRP/Albumin ratio	
	R	P value		R	P value
Gestational age (in weeks)	0.107	0.290	MV duration (in days)	0.014	0.890
birth weight (in grams)	0.073	0.471	Umbilical Cath duration (days)	-0.012	0.908
Diagnosis of sepsis age (in days)	0.180	0.074	TPN duration (in days)	0.028	0.787
Time of sample (age in days)	0.214	0.034	Blood/plasma transfusion rate	-0.151	0.203
Apgar after 1 minute	-0.255	0.010	HB	-0.083	0.409
Apgar after 5 minutes	0.163	0.105	HT	-0.105	0.300
Apgar after 10 minutes	0.134	0.183	PLT	-0.210	0.036
Respiratory rate (breath/min)	-0.027	0.786	TLC	-0.047	0.643
Heart rate (beats/min)	0.107	0.290	Staff	0.122	0.228
Systolic blood pressure (mm/hg)	-0.026	0.795	Segmented	0.078	0.439
Diastolic blood pressure(mm/hg)	-0.036	0.725	Shift to the left(I/T)	0.083	0.414
Temperature (Celsius)	0.013	0.897	CRP level mg/L	0.985	0.000
Jaundice duration (in days)	0.051	0.706	Albumin level (g/dl)	-0.47	0.000

CRP: C Reactive Protein; HT: hematocrit; HB: hemoglobin; PLTs: platelets; MV: Mechanical ventilator; TPN: Total Parenteral Nutrition.

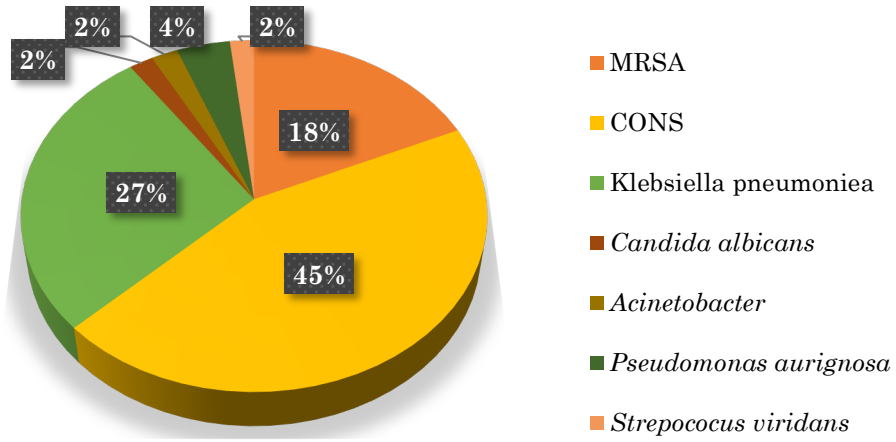


Figure1. Blood culture in the sepsis group
CONS: Coagulase-negative *Staphylococcus Aureus*;
MRSA: Methicillin-resistant *Staphylococcus aureus*

Table 5. Comparison between early-onset and late-onset sepsis groups

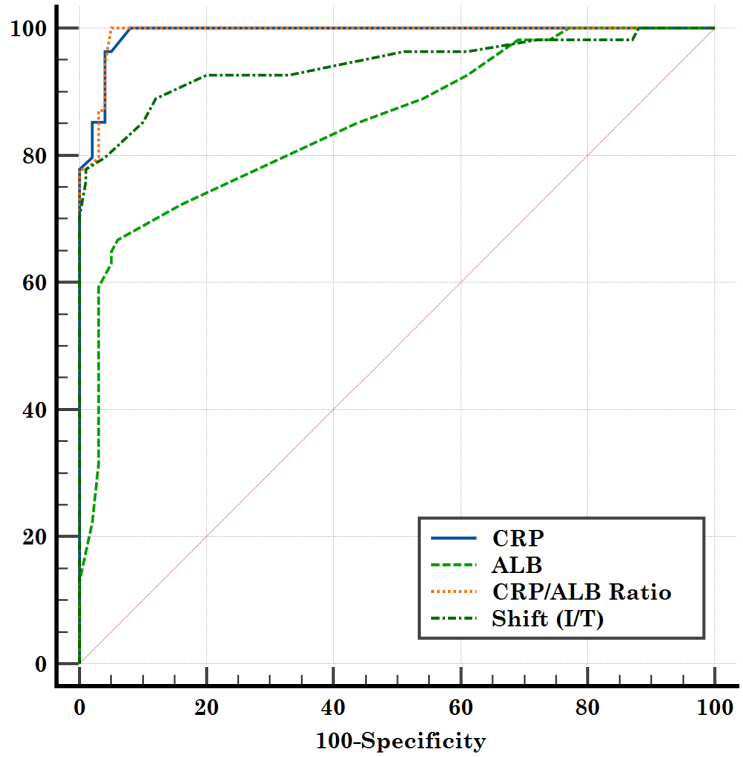
		Early-onset sepsis Number = 40	**Late-onset sepsis** Number = 14	**P value**
CRP	Mean ±SD	34±36	38±51	0.65
	Range	4 – 160	5 – 188	
CRP reference	Negative	5 (12.5%)	3 (21%)	0.49
	Positive	35(87.5%)	11 (78.5%)	
Albumin	Mean ±SD	2.3 ± 0.45	2.8 ± 0.49	0.000
	Range	1.7 – 3.3	1.6 – 3.6	
Alb (normal >3g/dL)	Normal	29 (72.3%)	12 (86%)	0.673
	Low	11 (27.5%)	2 (14%)	
CRP/Albumin Ratio	Mean ±SD	19 ± 19	14 ±22	0.4
	Range	1.6 – 94	1.6– 85.5	

The I/T ratio (shift to the left) above the cutoff point of 0.2 showed 64.8% sensitivity, 100 % specificity, 100% PPV, and 84% NPV, (AUC) was 0.941 and 95 % confidence interval (CI) 0.891 to 1 to 0.973. Both the CRP/ albumin ratio above 1.2 and the I/T ratio above 0.2 best identified the true positive cases and excludeed the true negative cases in our study (Table 6) and (Figure 2).

Table 6 . The accuracy of CRP, Albumin and CRP/albumin ratio in diagnosis of neonatal sepsis

	Cut-off	Sensitivity	95% CI	Specificity	95% CI	PPV	95% CI	NPV	95% CI
I/T ratio	>0.2	64.8%	50.6 – 77.3	100%	96.4 - 100	100%		84%	78.6 – 88.3
CRP	>4.3	96.3%	87.3 - 99.5	96%	90.1 - 98.9	92.9%	83.2 - 97.1	98%	92.5 - 99.5
Albumin	≤2.8	66.67%	52.5 - 78.9	94%	87.4 - 97.8	85.7%	73.0 - 93.0	83.9%	78.1 - 88.4
CRP/Albumin	>1.5	100%	93.4 - 100.0	95%	88.7 - 98.4	91.5%	82.1 - 96.2	100%	

CRP: C Reactive Protein; I/T: Immature-to-total neutrophil ratio; PPV positive predictive value; NPV: Negative predictive value.



	AUC	SE	95% CI			P value
I/T ratio	0.941	0.0233	0.891	-	0.973	<0.0001
CRP	0.992	0.004	0.983	-	1.000	0.000
ALB	0.850	0.034	0.785	-	0.916	0.000
CRP/ALB Ratio	0.992	0.005	0.983	-	1.000	0.000

Figure 2. Receiver operating characteristic (ROC) curve for CRP, albumin and CRP/Albumin ratio for the diagnosis of sepsis. AUC: area under the ROC curve; SE: Standard error; CI: Confidence interval

Discussion

C-reactive protein (CRP) is known to be one of the acute-phase proteins generated in inflammation. It is a very sensitive a 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 favorable results (*13*).

Therefore, assessment of both CRP and albumin instead of analyzing every factor independently enables the merging of inflammatory and nutritional variables, both of which have a strong impact on prognosis (*14*, *15*). 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 to have an exceptional 100 % sensitivity, 95% specificity in diagnosis of bacterial sepsis in neonates (*17*). While the ratio was sensitive and specific in diagnosis of bacterial neonatal sepsis, it had modest predictive ability of mortality. In our study, the CRP/Albumin ratio was not different in cases that died or survived (p= 0.3). The predictive ability of CPR/ albumin ratio of severity was confirmed by other researchers but not the work at hand (*15*).

CRP as a biomarker of bacterial sepsis had marginally lower sensitivity and specificity. CRP is a sensitive biomarker of neonatal bacterial sepsis.

The CRP/albumin ratio not different between EOS group and LOS group (p= 0.4). In our study group, EOS was more frequent (74%) than LOS (26%). LOS is more frequently encountered in premature babies due to prolonged hospital admission, the need for mechanical ventilation, and improper use of infection control measures.

The I/T ratio has long been a recognized index of sepsis, but has poor sensitivity and specificity among preterm neonates(*18*, *19*). Among our studied cohort I/T ratio >0.2 had modest sensitivity, but excellent specificity. The value of I/T ratio remains to be studied within a scoring system to identify bacterial sepsis among 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 a highly sensitive and specific 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 above 1.2 and the I/T ratio above 0.2 in predication of true positive cases and exclusion of the true negative cases.

Author Contributions

All authors shared in design, data curation analysis and drafting of the work. All approved the final manuscript. All authors contributed to the study conception and design. All authors shared in literature review. SN and AA collected and analyzed data. DK and SL wrote the first draft of the manuscript, and all authors critically appraised the work. All authors read and approved the final manuscript

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Authors declare there was no extramural funding provided for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

Availability of data and materials

All data generated or analyzed during this study are available with the corresponding author upon request.

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