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C-Reactive Protein/Albumin Ratio as an Independent Predictor of Mortality in Critically Ill Pediatric Patients

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Abstract

It is necessary to stratify the risk of pediatric patients at the time of intensive care unit (ICU) admission and to predict their outcomes. This helps to allocate the scarce ICU resources to start the appropriate treatment. The objective of this study was to evaluate the prognostic value of C-reactive protein/albumin ratio on admission to pediatric intensive care unit (PICU) in predicting mortality, PICU length of stay, the need for mechanical ventilation, and the use of inotropic drugs. This cohort study was conducted at Pediatric Cairo University Hospital. The study included 178 critically ill children. Pediatric Risk of Mortality–III (PRISM-III) score was calculated; CRP and serum albumin levels were assessed within 24 hours from admission. The median CRP/albumin ratio was significantly higher in nonsurvivors than survivors (18.60 and 4.65, respectively). The CRP/albumin ratio at a cutoff of $\geq$25.83 had significant discriminatory power in predicting mortality (area under the curve [AUC] = 0.795 and $p < 0.001$) with 85.4% accuracy. Furthermore, CRP/albumin ratio alone showed a comparable discriminatory power to that of PRISM-III score (AUCs = 0.795 and 0.793, respectively). A multivariable logistic regression analysis revealed that each unit of increase in the CRP/albumin ratio increased the risk of mortality by 1.075 (odds ratio [OR] = 1.075). CRP/albumin ratio showed a significantly higher median in ventilated (6.86) compared with non-ventilated (5.22) patients. Patients supported with inotropes showed significantly higher median CRP/albumin ratio (11.70 and 3.68, respectively). CRP/albumin ratio at admission to PICU was a good independent predictor of mortality.

Keywords

- C-reactive protein/albumin ratio
- hypoalbuminemia
- intensive care units
- mortality
- outcomes
- pediatric

Introduction

Critically ill children admitted to pediatric intensive care units (PICU) have a high risk of mortality.[1] The present research is trying to optimize the consistency of care of these children to improve their short- and long-term outcomes.[2]

It seems necessary to stratify the risk of pediatric patients at the time of intensive care unit (ICU) admission and to predict their outcomes.[3] This helps to allocate the scarce ICU resources, to start the appropriate treatment, and to satisfy the needs of the patients' families.[4]

Various prognostic scoring systems have been devised and validated in PICU.[5] However, the applicability of many of these scales is precluded by the unavailability of resources. Some scoring laboratory parameters are expensive, and their results may not be readily available on admission.[6] Therefore, it is necessary to identify a simple, rapid, and readily accessible biomarker to confirm response to treatment and to predict prognosis of critically ill children at admission to the PICU.

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.[7] CRP has also been shown to be a poor predictor of mortality compared with other biomarkers in the pediatric population.[8]

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Serum albumin is the main determining factor of colloid osmotic pressure and is a major plasma carrier of many hormones, drugs, and bioactive elements.[9] Hypoalbuminemia at admission to a PICU has been investigated. It was associated with higher mortality and longer duration of mechanical ventilation.[10]

The prognostic performance of the CRP/albumin ratio has been investigated in critically ill adult patients and revealed favorable findings.[7,11] However, it has not been evaluated in the pediatric population.

Based on this knowledge, the aim of our study was to evaluate the prognostic value of CRP/albumin ratio on admission to PICU in predicting mortality, the duration of PICU stay, and the need for mechanical ventilation, and inotrope use. Additionally, to compare the performance of CRP/albumin ratio with Pediatric Risk of Mortality–III (PRISM-III) score.

Methods

Ethical Considerations

The protocol of this study was approved by the Research Ethics Committee of the Faculty of Medicine, Cairo University. Informed consent was obtained from the patients' guardians. All patients' data were kept confidential after assigning a code number to each patient, known only by the researchers.

Study Design and Setting

This cohort study was conducted at Pediatric Cairo University Hospital, a tertiary educational medical institution. Data were collected from critically ill patients admitted to the PICU between March 2018 and February 2019.

Eligibility Criteria

Inclusion criteria: All patients admitted to the PICU of Pediatric Cairo University Hospital whose age was 1 month to less than 14 years were included.

Exclusion criteria: Patients aged less than 1 month or more than 14 years were excluded. Additionally, patients with severe protein-energy malnutrition; chronic liver disease/cirrhosis; nephrotic syndrome or nephritis; chronic gastrointestinal or kidney disease affecting the growth (malabsorption syndrome, celiac disease, inflammatory bowel disease, chronic renal failure); second or third-degree burns; and receipt of parenteral nutrition, blood products, or albumin before admission were also excluded.

Collection of Data

All patients were subjected to full history taking (including demographic data and reason for admission) and thorough medical assessment (including vital signs, nutritional status and systematic examination). All data were recorded in the data collection sheet. Patients were followed up until discharge or death, and the outcome measures (including mortality after PICU admission, the length of PICU stay, the need for mechanical ventilation, and the need for inotrope support) were recorded in the datasheet.

Pediatric Risk of Mortality–III score was calculated for each patient. This is an internationally validated score that assesses the risk of mortality. The score consists of age in addition to 17 physiological and laboratory parameters including systolic blood pressure, heart rate, temperature, pupillary response, mental status, acidosis, pH, arterial partial pressure of carbon dioxide ($PaCO_2$), arterial partial pressure of oxygen (PaO_2), total carbon dioxide, prothrombin time (PT), partial thromboplastin time (PTT), blood glucose, serum concentrations of potassium, blood urea nitrogen (BUN), creatinine, and total white blood cells (WBCs) and platelet count.[12]

C-reactive protein and serum albumin levels were determined for all patients within the first 24 hours of admission. Albumin analysis was done using on automated auto analyzer (dimension clinical chemistry system). Hypoalbuminemia was defined as a serum albumin level of less than 3.5 g/dL.[10] Serum concentration of CRP was determined by nephelometry on a Nephstar protein analyzer (Goldsite Diagnostic Inc., Shenzhen, China). CRP/albumin ratio was calculated using SPSS software program (Statistical Package for Social Science version 24 for windows; SPSS Inc., Chicago, IL, United States) by dividing serum CRP levels by serum albumin levels. Primary outcome was the survival to discharge. Secondary outcome was the Length of PICU stay, need for inotropes, and mechanical ventilation.

Statistics

Data analysis was performed using SPSS version 22. All numerical variables were checked for normality by Shapiro–Wilk test. Normally distributed numerical variables were presented as mean $\pm$ SD, and differences between the two groups were tested using independent *t*-test. Abnormally distributed numerical variables were expressed as a median and interquartile range (25th–75th percentile), and differences between the two groups were tested using Mann–Whitney *U* test. Categorical variables were summarized as frequencies and percentages, and the association between variables was tested using χ^2 tests (Pearson's chi-square for independence or Fisher exact tests as appropriate). Spearman's rank correlation was performed between PICU stay and CRP/albumin ratio. The receiver operating characteristic (ROC) curve analyzed the discriminatory power of CRP/albumin ratio in predicting different outcomes. Cutoff values were identified along with associated sensitivity, specificity, and accuracy. A multivariable logistic regression analysis using forward stepwise (likelihood ratio) method was performed to determine the independent predictors of mortality. All variables showed significant differences between survivors and nonsurvivors (body mass index [BMI], serum CRP level, serum albumin level, CRP/albumin ratio,

PRISM III score, the need for mechanical ventilation, the need for inotropes, BUN, and platelets count) were included. A p-value of ≤ 0.05 was considered statistically significant.

Results

Three hundred fifty critically ill patients were admitted to the PICU between March 2018 and February 2019. This study was undertaken on 178 critically ill children who fulfilled the eligibility criteria and all 178 patients were included. More than half (54.5%) of them were males, and their ages ranged

from 1.0 to 156.0 months with a median age of 11.0 (IQR = 4.0–30.0)

Thirty-six patients died with a mortality rate of 20.2%. The mean BMI was significantly lower in nonsurvivors compared with survivors (14.21 ± 2.66 and 15.49 ± 3.36, respectively, $p = 0.035$). The median CRP/albumin ratio was significantly higher in nonsurvivors than survivors (18.60 and 4.65, respectively). Likewise, there were significant differences between survivors and nonsurvivors with regards to serum albumin and CRP levels. Additionally, the median PRISM-III score was significantly higher among nonsurvivors (7.0 and 2.0, respectively). There was a statistically significant association between the need for mechanical ventilation and inotrope support and mortality ($p = 0.001$ and < 0.001, respectively). Higher percentages of nonsurvivors were mechanically ventilated and received inotropic drugs (77.1% and 82.4%, respectively). On the other hand, there were no significant differences between the two groups with regards to age, sex, serum creatinine, WBCs, or duration of stay in the PICU ($p > 0.05$) as shown in ►**Table 1**.

►**Table 2** shows a statistically significant association of the patient's diagnosis and mortality ($p < 0.05$). Significantly higher percentages of patients diagnosed as sepsis, CNS diseases, and CVS disorders were expired (30.6%, 22.2%, and 13.9%, respectively).

Among the studied patients, 78 (43.8%) needed mechanical ventilation. The CRP/albumin ratio showed a significantly higher median in ventilated (6.86) compared with nonventilated (5.22) patients. Also, the median albumin level was significantly lower in ventilated patients ($p = 0.004$). Otherwise, there was no significant differences between ventilated and nonventilated groups concerning their age, sex, serum CRP, or PRISM-III score ($p > 0.05$) as demonstrated in ►**Table 3**.

In 68 (38.2%) of the admitted children, inotropic drugs were administered. Patients supported with inotropes showed significantly higher median CRP/albumin ratio

Table 1 Baseline characteristics of survivors and nonsurvivors

			Survivors N = 142 (79.8%)	Nonsurvivors N = 36 (20.2%)	Total $N = 178$	Test statistic	*p*-Value
Sex	Female	N (%)	62 (43.7%)	19(52.8%)	81(45.5%)	0.962	0.327
	Male	N (%)	80 (56.3%	17 (47.2%)	97 (54.5%)		
Age (month)	Range		1.0–156.0	1.5–144.0	1.0–156.0	0.350	0.726
	Median		11.5	10.5	11.0		
	IQR		4.0–30.0	3.0–30.0	4.0–30.0		
	Mean rank		90.18	86.82			
BMI	Range		8.62–28.84	7.88–20.66	7.88–28.84	2.12	0.035[a]
	Mean ± SD		15.49 ± 3.36	14.21 ± 2.66	15.23 ± 3.27		
Serum CRP	Range		1.2–96.0	9.9–150.0	1.2	5.09	<0.001[a]
	Median		18.0	48.0	24.0		
	IQR		12.0–48.0	24.0–96.0	12.0–48.0		
	Mean rank		79.68	128.25			
Serum albumin	Range		1.5–6.1	1.7–5.3	1.5–6.1	3.79	<0.001[a]
	Median		3.7	3.1	3.7		
	IQR		3.4–4.1	2.6–3.7	3.3–4.0		
	Mean rank		96.87	60.44			
CRP/albumin	Range		.30–30.97	3.0–62.0	.30–62.0	5.45	<0.001[a]
	Median		4.65	18.60	6.23		
	IQR		2.73–11.81	6.67–32.0	3.16–14.61		
	Mean rank		78.90	131.32			
	Range		0–19	0–16	0–19	5.712	<0.001[a]
PRISM-III score	Median		2	7	3		
	IQR		0–3	3–10	0–5		
	Mean rank		78.24	131.14			
Serum creatinine	Range		0.1–2.5	0.1–4.2	0.1–4.2	1.95	0.055
	Median		0.5	0.6	0.5		
	IQR		0.3–0.6	0.3–0.9	0.3–0.7		

(*Continued*)

Table 1 (*Continued*)

		Survivors N = 142 (79.8%)	Nonsurvivors N = 36 (20.2%)	Total *N* = 178	Test statistic	*p*-Value
	Mean rank	84.36	102.57			
BUN	Range	0.3–78.6	3.0–130.6	0.3–130.6	2.68	0.007[a]
	Median	17.0	30.5	20.0		
	IQR	12.0–30.0	14.3–52.0	12.0–33.4		
	Mean rank	83.28	108.82			
WBCs	Range	1.8–72.0	.2–30.0	0.2–72.0	0.05	0.959
	Median	11.5	11.8	11.6		
	IQR	8.3–16.9	9.0–15.5	8.3–16.7		
	Mean rank	88.40	88.89			
Platelets	Range	20.0–1007.0	6.0–794.0	6.0–1007.0	3.75	<0.001[a]
	Median	331.5	203.5	310.0		
	IQR	216.0–436.0	62.5–295.0	184.0–423.0		
	Mean rank	94.83	59.40			
Duration of PICU stay (days)	Range	2–77	1–55	1–77	0.122	0.903
	Median	10	8	8		
	IQR	4–15	5–15	4–15		
	Mean rank	81.76	82.85			
Mechanical ventilation	No	62 (54.9%)	8 (22.9%)	70 (47.3%)	10.98	0.001[a]
	Yes	51 (45.1%)	27 (77.1%)	78 (52.7%)		
Inotrope use	No	74 (64.9%)	6 (17.6%)	80 (54.1%)	23.55	<0.001[a]
	Yes	40 (35.1%)	28 (82.4%)	68 (45.9%)		

Abbreviations: IQR, interquartile range; BMI, body mass index; SD, standard deviation; CRP, C-reactive protein; PRISM-III, Pediatric Risk of Mortality–III score; BUN, blood urea nitrogen; WBC, white blood cell; PICU, pediatric intensive care unit.
[a]Significant at $p \leq 0.05$.

(11.70 and 3.68, respectively). In addition, the median CRP was significantly higher, while serum albumin was significantly lower in patients needed inotropes ($p < 0.001$ and 0.003) (►**Table 4**).

Analysis of ROC curve for prediction of mortality using CRP/albumin ratio revealed that at a cutoff of ≥ 25.83 had significant good discriminatory power in predicting mortality (AUC = 0.795 and $p < 0.001$) with 85.4% accuracy (►**Fig. 1**).

Table 2 Association of the patient's diagnosis and mortality

		Mortality						Fisher's exact test	
		Survivors *N* = 142 (79.8%)		Nonsurvivors *N* = 36 (20.2%)		Total *N* = 178			
		N	%	N	%	N	%	χ^2	*p*-Value
Diagnosis	Respiratory	53	37.6%	7	19.4%	60	33.9%	13.012	0.049[a]
	CNS	25	17.7%	8	22.2%	33	18.6%		
	Sepsis	14	9.9%	11	30.6%	25	14.1%		
	Surgical	20	14.2%	3	8.3%	23	13.0%		
	CVS	14	9.9%	5	13.9%	19	10.7%		
	Metabolic	7	5.0%	1	2.8%	8	4.5%		
	GIT	5	3.5%	0	0.0%	5	2.8%		
	Others	3	2.1%	1	2.8%	4	2.3%		

Abbreviations: CNS, central nervous system; CVS, cardiovascular system; GIT, gastrointestinal tract.
[a]Significant at $p \leq 0.05$.

Table 3 Comparison of demographic data, serum CRP, serum albumin, CRP/albumin ratio, and PRISM-III score in relation to the need of mechanical ventilation

			Mechanical ventilation				
			No N = 70 (39.3%)	**Yes N = 78 (43.8%)**	**Total N = 178**	**Test statistic**	***p*-Value**
Sex	Female	N (%)	28 (40.0%)	40 (51.3%)	68 (45.9%)	1.89	0.169
	Male	N (%)	42 (60.0%)	38 (48.7%)	80 (54.1%)		
Age (month)	Range		1.5–156.0	1.0–156.0	1.0–156.0	1.797	0.072
	Median		12.5	7.0	10.5		
	IQR		5.0–36.0	3.0–30.0	4.0–33.0		
	Mean rank		81.17	68.51			
CRP/Albumin	Range		0.33–30.96	0.30–62.0	0.30–62.0	1.93	0.05[a]
	Median		5.22	6.86	6.40		
	IQR		1.22–14.62	3.53–18.0	3.12–15.52		
	Mean rank		67.30	80.96			
Serum CRP	Range		2.0–96.0	1.2–150.0	1.2–150.0	1.96	0.091
	Median		21.0	24.0	24.0		
	IQR		6.0–48.0	12.0–48.0	12.0–48.0		
	Mean rank		68.25	80.11			
Serum albumin	Range		1.5–6.1	1.7–5.3	1.5–6.1	2.90	0.004[a]
	Median		3.9	3.5	3.7		
	IQR		3.5–4.3	3.1–3.9	3.3–4.1		
	Mean rank		85.29	64.81			
PRISM-III score	Range		0–19	0–16	0–19	1.27	0.203
	Median		3	3	3		
	IQR		0–6	0–5	0–6		
	Mean rank		78.75	69.84			

Abbreviations: IQR, interquartile range; PRISM-III, Pediatric Risk of Mortality–III score.
[a]Significant at $p \leq 0.05$.

Furthermore, CRP/albumin ratio showed a comparable discriminatory power to that of PRISM-III score (AUC = 0.793), serum CRP (AUC = 0.773), and serum albumin (AUC = 0.705) with no significant difference ($p > 0.05$) as illustrated in ►**Table 5**.

►**Table 6** demonstrates that the CRP/albumin ratio at a cutoff ≥ 6.95 had poor discriminatory power in predicting the need for mechanical ventilation (AUC = 0.592, $p = 0.05$), with no significant difference from AUC (0.639) of serum albumin alone ($p = 0.35$) (►**Table 6**) (►**Fig. 2**). Whereas, CRP/albumin ratio at a cutoff ≥ 11.07 showed significantly fair power in predicting the need for inotropic support (AUC = 0.742, $p < 0.001$), with no significant difference from AUCs of serum CRP and albumin ($p > 0.05$) (►**Table 7**) (►**Fig. 3**).

Concerning length of PICU stay, we found a significant positive poor correlation between the length of stay in ICU and CRP/albumin ratio (r = 0.28, p value < 0.0001*). Additionally, we found nonsignificant differences between median CRP/albumin ratio of patients with short stay (≤ 3 days) in comparison with patients who were stayed longer than 3 days as illustrated in ►**Table 8**.

A multivariable binomial logistic regression analysis was performed to determine independent predictors of mortality from variables that showed significant association with mortality. Among the studied variables, CRP/albumin ratio, PRISM-III score, the need of mechanical ventilation, and the need for inotropes were contributed significantly to the model. The logistic regression model was statistically significant ($\chi^2 = 64.38$, $p < 0.001$). The model explained 57.4% (Nagelkerke R^2) of the variance and correctly classified 90.7% of cases. Each unit of increase in CRP/albumin ratio increased the risk of mortality by 1.079 (adjusted OR = 1.079).

Each unit of increase in PRISM-III was associated with a significant increase of the risk of mortality by more than one-fold (adjusted OR = 1.27). Moreover, mechanical ventilation and the need for inotropes increased the likelihood of mortality by 20.4% and 25.5.0% (adjusted OR = 0.204 and 0.255, respectively) (►**Table 9**).

Table 4 Comparison of demographic data, serum CRP, serum albumin, CRP/albumin ratio, and PRISM-III score and inotrope use

			Inotrope use				
			No N = 80 (44.9%)	Yes N = 68 (38.2%)	Total *N* = 178	Test statistic	*p-Value*
Sex	Female	N (%)	34 (42.5%)	35 (51.5%)	69 (46.6%)	1.189	0.276
	Male	N (%)	46 (57.5%)	33 (48.5%)	79 (53.4%)		
Age (month)	Range		1.0–156.0	1.5–156.0	1.0–156.0	1.27	0.202
	Median (IQR)		11.5 (4.0–36.0)	7.5 (3.0–19.0)	8.0 (3.9–24.0)		
	Mean rank		78.63	69.94			
CRP/albumin	Range		0.30–30.97	0.49–62.0	0.30–62.0	5.70	<0.001[a]
	Median (IQR)		3.68 (0.67–8.76)	11.70 (4.07–23.37)	6.15 (0.30–14.87)		
	Mean rank		58.03	93.88			
Serum CRP	Range		1.2–96.0	2.0–150.0	1.2–150.0	4.91	<0.001[a]
	Median		12.0	47.0	24.0		
	IQR		2.0–33.8	12.0–80.0	12.0–48.0		
	Mean rank		58.58	93.24			
Serum albumin	Range		1.5–6.1	1.7–5.5	1.5–6.1	3.41	0.001[a]
	Median		3.8	3.4	3.7		
	IQR		3.5–4.2	3.0–3.9	3.3–4.1		
	Mean rank		85.59	61.46			
PRISM-III score	Range		0–19	0–16	0–19	0.178	0.858
	Median (IQR)		3 (0–5)	3 (0–7)	3 (0–5)		
	Mean rank		74.56	73.35			

Abbreviations: CRP, C-reactive protein; PRISM-III, PRISM-III, Pediatric Risk of Mortality–III score; IQR, interquartile range.
[a]Significant at $p \leq 0.05$.

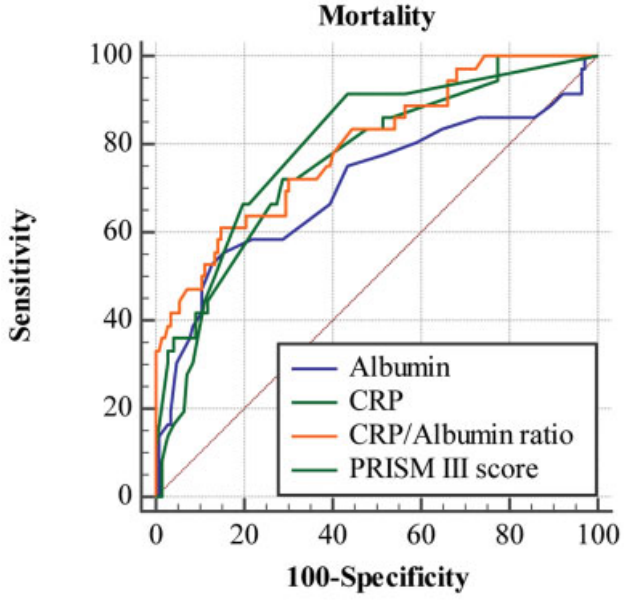

Fig. 1 Receiver operating curves of C-reactive protein (CRP)/albumin ratio, serum albumin, serum CRP, and Pediatric Risk of Mortality–III (PRISM-III) score in predicting mortality.

►**Table 10** shows that 16 (11.2%) patients had CRP/albumin ratio ≥25.83. There was significant association between high cutoff and the need for inotropes and mortality ($p < 0.001$).

Discussion

The C-reactive protein/albumin ratio has recently emerged as a prognostic marker of mortality in critically ill adult patients.[7] To the best of our knowledge, this was the first study to assess the prognostic value of CRP/albumin ratio in critically ill children admitted to PICU.

In the present study, the CRP/albumin ratio determined within the first 24 hours of admission was significantly higher in non-survivors than survivors. ROC curve analysis with CRP/albumin ratio at a cutoff of ≥ 25.83 was significantly predictive of mortality with 85.4% accuracy. Moreover, CRP/albumin ratio showed a comparable discriminatory power to that of serum CRP, serum albumin, and PRISM-III score. Multivariable regression analysis revealed that CRP/albumin ratio, PRISM-III score, and the need for mechanical ventilation and inotropes were significant independent predictors of mortality. CRP/albumin ratio also showed poor to fair predictive power of the need for mechanical ventilation and inotropic support.

Table 5 The best cutoff values, sensitivity, specificity, and AUC of PRISM III score and CRP/albumin ratio, serum CRP, and serum albumin in predicting mortality

Mortality	Cutoff	Sensitivity (%)	Specificity (%)	AUC	95% CI	Accuracy%	*p-Value*
PRISM III score	≥10.5	19.4	94.3	0.793	0.726–0.850	79.1	<0.001[a]
CRP/albumin ratio	≥25.83	41.7	96.5	0.795	0.727–0.851	85.4	<0.001[a]
Serum CRP	>38	72.22	71.13	0.773	0.704 To 0.832	83.1	<0.001[a]
Serum albumin	≤3.1	52.78	87.32	0.705	0.632 to 0.771	82.0	0.003*

Abbreviations: AUC, area under the curve; CRP, C-reactive protein; PRISM-III, PRISM-III, Pediatric Risk of Mortality–III score.
Note: Pairwise comparison of ROC curves (based on difference between areas under the curve) revealed nonsignificant difference between them ($p > 0.05$).
[a]Significant at $p \leq 0.05$.

Table 6 The best cutoff values, sensitivity, specificity, and AUC of CRP/albumin ratio, and serum albumin in predicting the need of mechanical ventilation

MV	Cutoff	Sensitivity (%)	Specificity (%)	AUC	95% CI	Accuracy %	*p*-Value
CRP/albumin ratio	≥6.95	48.7	58.6	0.592	0.509- 0.672	53.4	0.050[a]
Serum albumin	≤3.8	73.08	51.43	0.638	0.555 to 0.716	62.8	0.003[a]

Abbreviations: AUC, area under the curve; CRP, C-reactive protein; MV, mechanical ventilation.
Note: Pairwise comparison of ROC curves (based on difference between areas under the curve) revealed nonsignificant difference between them ($p = 0.35$).
[a]Significant at $p \leq 0.05$.

C-reactive protein is a serum acute phase reactant and a valuable inflammatory biomarker in various clinical conditions. C-reactive protein levels can be easily measured, and its assays are inexpensive and convenient. Additionally, CRP is a stable protein that provides similar results in fresh or stored state. Moreover, it does not vary from person to person or influenced by genetic makeup or gender of the patient.[13]

C-reactive protein has been used as a prognostic marker in critical care settings.[13] It has been reported that CRP level was associated with an increased risk of mortality in chronic obstructive pulmonary disease.[14] In pediatric noncardiovascular critically ill patients CRP was found to be an independent predictor of PICU mortality.[15] On the other hand, CRP has been shown to have a poor prognostic value of mortality compared with other biomarkers in the pediatric population.[8] Elevated CRP levels at ICU discharge represented only a very moderate risk factor for readmission and in-hospital mortality and they might not be enough for individual clinical decision-making.[16]

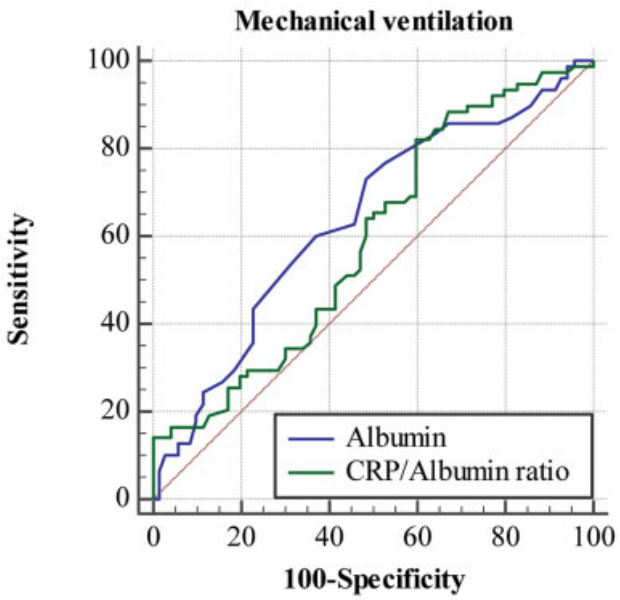

Fig. 2 Receiver operating curves of C-reactive protein (CRP)/albumin ratio and albumin in predicting the need of mechanical ventilation.

Hypoalbuminemia has been advocated as a simple, cheap, and consistent indicator of outcome in critically ill adults and children admitted to ICU in different pathologic conditions.[17]

In a prospective observational study conducted at the PICU of a tertiary care hospital, hypoalbuminemia has been found to be a significant predictor of mortality and morbidity in critically ill children.[18] In addition, the outcome of critically ill children with hypoalbuminemia admitted to a tertiary care center was assessed. A very important role of albumin levels in determining the treatment options and the outcome of the treatment was detected. Besides, albumin levels were associated with the rate of morbidity and mortality.[19] Subsidiary evidence was reported by Moustafa et al,[20] where hypoalbuminemia was a frequent feature in critically Ill children admitted to PICU in Alexandria University Children's Hospital. Albumin levels obtained at admission demonstrated statistically significant associations with clinical outcomes including longer length of PICU stay and higher mortality.[20]

As a potential outcome predictor, serum albumin level has been added as a component parameter in the Acute Physiology And Chronic Health Evaluation (APACHE)-III score.[21] However, hypoalbuminemia can be caused by previous

Table 7 The best cutoff values, sensitivity, specificity, and AUC of CRP/albumin ratio, serum CRP, and serum albumin in predicting inotrope use

Inotrope use	Cutoff	Sensitivity (%)	Specificity (%)	AUC	95% CI	Accuracy %	*p*-Value
CRP/albumin ratio	≥11.07	50	77.5	0.742	0.664–0.810	64.9	<0.001[a]
Serum CRP	>38	55.88	77.50	0.734	0.655–0.803	67.6	<0.0001
Serum albumin	≤3.4	52.94	81.25	0.663	0.581–0.739	64.9	0.0005[a]

Abbreviations: AUC, area under the curve; CRP, C-reactive protein; CI, confidence interval.
Note: Pairwise comparison of ROC curves (based on difference between areas under the curve) revealed nonsignificant difference between them ($p > 0.05$).
[a]Significant at $p \leq 0.05$.

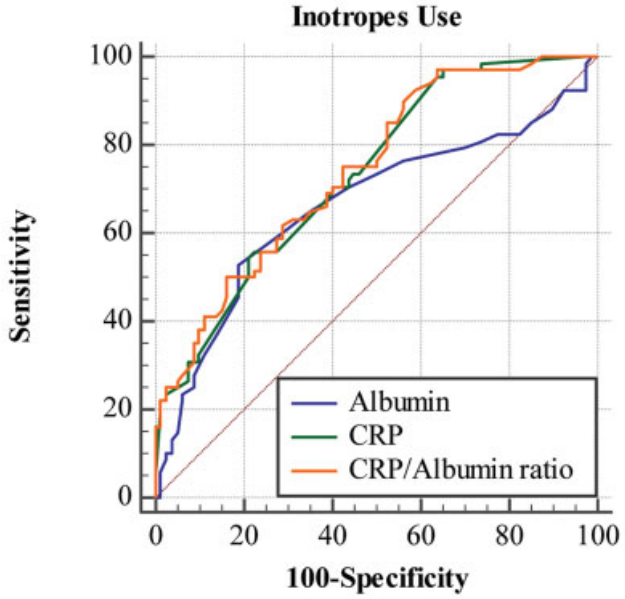

Fig. 3 Receiver operating curves of C-reactive protein (CRP)/albumin ratio, serum albumin, and serum CRP in predicting the need of inotrope support.

illness or general conditions, such as liver disease, kidney damage, and malnutrition.[22] To avoid these weaknesses, a combination of CRP and albumin may be more valuable prognostic markers for outcomes across various diseases, providing both inflammatory and nutritional information.[11] Since the combination of albumin and CRP into a single index has been suggested, subsequent studies have shown that the CRP/albumin ratio is more reliable for prognosis than CRP or albumin alone.[23]

In the current study, the CRP/albumin ratio determined within the first 24 hours of admission was significantly higher in non-survivors than survivors. Comparable findings were reported by Park et al,[7] who reported a greater accuracy of CRP/albumin ratio compared with CRP alone for predicting mortality. Furthermore, the CRP/albumin ratio was an independent risk factor for mortality at 28 days in critically ill adult patients admitted to the ICU. Further study in older adults concluded that the CRP/albumin ratio at admission to the ED was associated with all-cause in-hospital mortality.[11] As well, CRP/albumin ratio was an independent predictor of 180-day mortality in adults with severe sepsis or septic shock.[24] Moreover, CRP/albumin ratio was useful prognostic tool for overall survival in adult surgical oncology patients.[25,26] CRP/albumin ratio was also found to be a potentially useful prognostic marker for predicting a poor prognosis in ST elevation myocardial infarction patients.[27]

Based on the ROC curve results, cutoff values of ≥ 25.83 for the CRP/albumin ratio were found to be significantly predictive of mortality with 85.4% accuracy. Comparison of CRP/albumin ratio discriminatory power with that of PRISM-III, which is a validated scoring system for assessing the risk of mortality among children was assessed. The present study revealed that CRP/albumin ratio alone showed a comparable discriminatory power to that of PRISM-III score. This is a valuable finding because the CRP/albumin ratio is relatively simple and easy to use in all settings when compared with the extensive variables of PRISM-III score.[7]

Mortality is the most frequently assessed outcome, but the morbidity outcomes as the need for mechanical ventilation and inotropic drugs, besides the length of stay in PICU are also important.[17]

Table 8 Correlation between the length of PICU stay and CRP/albumin ratio

		Duration of PICU stay		Mann–Whitney *U* test	
		≤3 days	>3 days	Z mw	*p*-Value
CRP/albumin ratio	Range	0.30–56.47	0.36–62.0	1.86	0.062
	Median	3.43	6.49		
	IQR	0.85–12.97	3.43–15.36		
	Mean rank	67.16	85.21		

Abbreviations: PICU, pediatric intensive care unit; CRP, C-reactive protein; IQR, interquartile range.

Table 9 Multivariable binary logistic regression for determining independent predictors of mortality

Chi-square test		Nagelkerke R^2	Percentage accuracy in classification	Variables	Adjusted odds ratio	*p*-Value
χ^2	*p*-Value					
64.38	<0.001[a]	57.4%	90.7%	Mechanical ventilation	0.204	0.020[a]
				Inotropes use	0.255	0.045[a]
				CRP/albumin ratio	1.079	0.008[a]
				PRISM III score	1.27	<0.001[a]
				Constant	0.161	0.002[a]

Abbreviations: CRP, C-reactive protein; PRISM-III, PRISM-III, Pediatric Risk of Mortality–III score.
[a]Significant at $p \leq 0.05$.

In this study, CRP/albumin ratio showed a significantly higher median in ventilated (6.86) compared with nonventilated (5.22) patients. However, the CRP/albumin ratio at a cutoff ≥ 6.95 showed a poor discriminatory power in predicting the need for mechanical ventilation (AUC = 0.592). Parallel to this finding, it has been stated that hypoalbuminemia at admission to a PICU was associated with a higher likelihood of the need for,[20] as well as the duration of mechanical ventilation.[10]

In the present study, patients supported with inotropes showed significantly higher median CRP/albumin ratio (11.70 and 3.68, respectively). ROC curve results demonstrated that CRP/albumin ratio at a cutoff ≥ 11.07 had significantly moderate power in predicting the need for inotropic support.

The current study revealed poor association between CRP/albumin ratio and PICU stay. Compared with our finding in pediatric patients, Li et al[28] have demonstrated significantly increased total length of hospital stay in adult patients admitted to medical ICU with CRP/prealbumin more than 0.24. Another study has reported a significantly

Table 10 Comparison of patient's groups based on CRP/albumin ratio cutoff

			CRP/albumin ratio		Tests of significance	
			<25.83 N = 160 (88.8%)	**≥25.83 N = 20 (11.2%)**	**Test statistic**	***p*-Value**
Sex	Female	N	71	10	2.047	0.152
		%	43.8%	62.5%		
	Male	N	91	6		
		%	56.2%	37.5%		
Age (month)	Median		10.5	15.0	0.120	0.905
	IQR		4.0–30.0	4.0–22.0		
BMI	Mean ± SD		15.28 ± 3.39	14.74 ± 1.58	1.135	0.265
Mechanical ventilation	No	N	66	4	2.175	0.140
		%	49.3%	28.6%		
	Yes	N	68	10		
		%	50.7%	71.4%		
Inotropes use	No	N	79	1	15.09	<0.001[a]
		%	59.4%	6.7%		
	Yes	N	54	14		
		%	40.6%	93.3%		
Mortality	No	N	137	5	38.162	<0.001[a]
		%	86.7%	25.0%		
	Yes	N	21	15		
		%	13.3%	75.0%		

Abbreviations: CRP, C-reactive protein, BMI, body mass index, SD, standard deviation.
[a]Significant at $p \leq 0.05$.

higher CRP/prealbumin in ICU adult patients with severe pancreatitis who had a longer period of ICU stay.[29]

For accurate estimation of the magnitude of risk of CRP/albumin ratio on mortality and for determining other risk factors of mortality a multivariable analysis binomial logistic regression analysis was applied. It revealed that CRP/albumin ratio, PRISM-III score, and the need for mechanical ventilation and inotropes were significant independent predictors of mortality. Each unit of increase in CRP/albumin ratio increased the risk of mortality by 1.075 (adjusted OR = 1.075). Each unit of increase in PRISM-III was associated with a significant increase of the risk of mortality by more than one-fold (adjusted OR = 1.285). Moreover, mechanical ventilation and inotropic support increased the likelihood of mortality by 20.3% and 24.0% (adjusted OR = 0.203 and 0.240, respectively).

Integration of CRP/albumin ratio with PRISM-III score showed higher accuracy (90.9%) in predicting mortality than either predictor alone (85.4% and 79.1%, respectively). Similarly, the addition of serum albumin to other scoring systems as APACHE-III and IV scores was beneficial.[30] However, the CRP/albumin ratio alone may provide some advantages in time and cost.

Conclusion

CRP/albumin ratio within 24 hours of admission to a PICU was a good independent predictor of mortality. CRP/albumin ratio alone showed a comparable predictive power of PRISM-III score. So, the use of the CRP/albumin ratio alone helps to identify patients at greater risk of mortality to make prompt therapeutic decisions. Integration of CRP/albumin ratio with PRISM-III score showed higher accuracy in predicting mortality than either predictor alone. Furthermore, CRP/albumin ratio was a poor predictor of the need for mechanical ventilation, and a moderate predictor of the need for inotropic drugs.

Small-sized cohort was the limitation of this study, so we recommend further multicenter studies including higher numbers of patients.

Authors' Contributions

S.A.M. did the study design, collected the data, and wrote the manuscript. R.H. did the laboratory work and shared in the study design. All authors have revised and approved the manuscript.

Note

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflict of Interest

None declared.

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