

## Serum Albumin and C-reactive protein Ratio as Predictors of Mortality in Critically Ill Children: A Prospective Observational Study at A Tertiary Care Centre

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### ABSTRACT

**Introduction:** Critically ill children admitted to Pediatric Intensive Care Units (PICU) have a high risk of mortality. Various prognostic scoring systems have been devised and validated in PICU. However, their applicability is precluded by the lack of resources, expensive laboratory parameters and unavailability of real time test results. There is a need to identify a simple, rapid, and readily accessible biomarker to predict prognosis of critically ill children at admission to the PICU.

**Methods:** We aimed to predict mortality in critically ill children using ratio of C-reactive protein [CRP] and serum albumin levels.

**Prospective** observational study was conducted in children [aged 1 month to 12 years, of either sex], admitted to PICU. Serum albumin, CRP were measured to calculate the ratio and mortality was predicted using Receiver operating characteristic (ROC) curves.

**Result:** Among 116 study subjects, 41(35.34%) had respiratory system disorders, 23(19.83%) had CNS disorders, followed by 19 (16.38%) of sepsis. We observed a mortality of 18.1% among children studied, while 81.9% of children survived.

**Conclusion:** The CRP/Albumin ratio among non survivors was significantly greater as compared to survivors (15.3 vs 5.3, p=0.000).

**Keyword:** critically ill children, c-reactive protein, albumin, predictors of mortality

### 1. INTRODUCTION

Admitted to pediatric intensive care units (PICUs), critically unwell children face a significant risk of death. Predicting the outcomes of pediatric patients and classifying their risk at the time of PICU admission are essential. In addition to meeting the requirements of the patients' families, this will assist in allocating the limited resources and initiating the proper course of treatment [1-4]. In PICUs, numerous prognostic scoring systems have been developed and proven effective [5]. Unfortunately, the lack of resources prevents many of these scales from being applicable. Certain laboratory measures used for scoring are costly, and their outcomes might not be immediately accessible upon admission [6]. As a result, finding a quick, easy, and accessible biomarker is essential for determining a child's prognosis upon admission to the PICU and confirming a response to treatment. Acute phase protein C reactive protein (CRP) is created in response to inflammation, trauma, ischemia, infection, and other factors that cause inflammation after being stimulated by different cytokines. In the

pediatric population, CRP has also been demonstrated to be a poor predictor of death when compared to other biomarkers [7]. Low serum albumin levels, or hypoalbuminemia, at the time of PICU admission have been linked to increased mortality and prolonged mechanical ventilation [8]. Serum albumin is a significant plasma transporter of numerous hormones, medications, and bioactive components. It is also the primary determinant of colloid osmotic pressure [9]. Recently, across a range of patient age groups, the CRP/Albumin ratio has been identified as a predictor for poor prognosis or mortality. Albumin and CRP are considered good diagnostic markers for sepsis. Overall, a combination of hypoalbuminemia and raised CRP, have better sensitivity (96.83%) and specificity (91.89%) than either of them alone in determining mortality in critically ill children [10]. It has been discovered that the CRP/albumin ratio is a more sensitive measure in a wide range of conditions, including adult infections, autoimmune diseases, and cardiovascular and cancer problems [7]. The purpose of this study was to estimate the accuracy of the CRP/albumin ratio for PICU patient death after 28 days

## 2. MATERIALS & METHODS

The critically ill patients admitted to PICU of either sex and aged between 1 month to 12 years were enrolled during the period of 2 years (January 2020 to December 2021). Patients who were expected to have low albumin level in their usual state of health like immune deficiency, malabsorption syndrome, nephritic syndrome, protein losing enteropathy, celiac diseases, chronic liver disease, chronic renal failure and patient with known congenital anomalies were excluded from the study.

Clinical history, examination findings, investigation reports, and follow-up findings were recorded in a semi-structured, pre-validated case record proforma.

CRP levels were measured using Immunoturbidimetry method, and up to 6 mg/L was considered to be normal. Serum albumin level estimation was done using albumin-bromocresol green (BCG) binding technique. Hypoalbuminemia was defined as serum albumin levels below 2.5g/dl at any time during PICU stay. The CRP/Albumin ratio at the time of PICU admission was noted. The outcome was recorded in the form of death or discharge on the 28th day of PICU admission. The Ethical Committee of the Medical College approved the study.

A written informed valid consent was taken from either or both the parents and/or caretaker of the patient in specially designed consent form and was validated by translation into the local language.

### Statistical analysis

Data was entered in MS Excel, coded and analyzed in statistical software STATA, version 10.1, 2011. Descriptive variables were expressed as frequency and percentages. Central tendency of quantitative variables was expressed as mean for normally distributed and median for not normally distributed variables. ROC curve was plotted to assess prediction of mortality by using serum albumin levels, CRP levels and CRP/Albumin ratio.

## 3. RESULTS

### Age & Gender wise distribution of subjects:

Out of 116 children enrolled, the majority of the study subjects belonged to the 1 to 5 years of age [41.38%], followed by 6 to 10 years [31.9%]. 13.79% of study subjects belonged to the less than 1 year old. The male-to-female ratio in the present study was 1.27:1 [Figure 1].

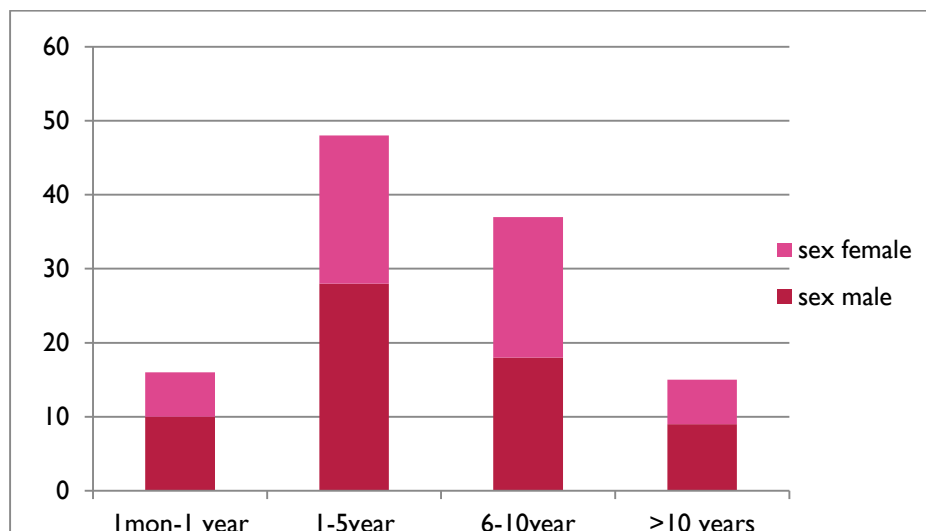


Fig 1: age & gender wise distribution of subjects.

### Distribution of subjects according to Diagnosis at the time of PICU admission

As per the diagnosis of children at the time of admission to the PICU, 35% had Respiratory disorders (Pneumonia, Bronchiolitis, ARDS, Pleural effusion), followed by Central Nervous System (Meningoencephalitis, ADEM, PRES) in 19.83%. Sepsis was observed among 16.3% of children & Surgical conditions (Acute appendicitis, Peritoneal perforation, Tracheo esophageal fistula) in 11.21% of children (Figure 2).

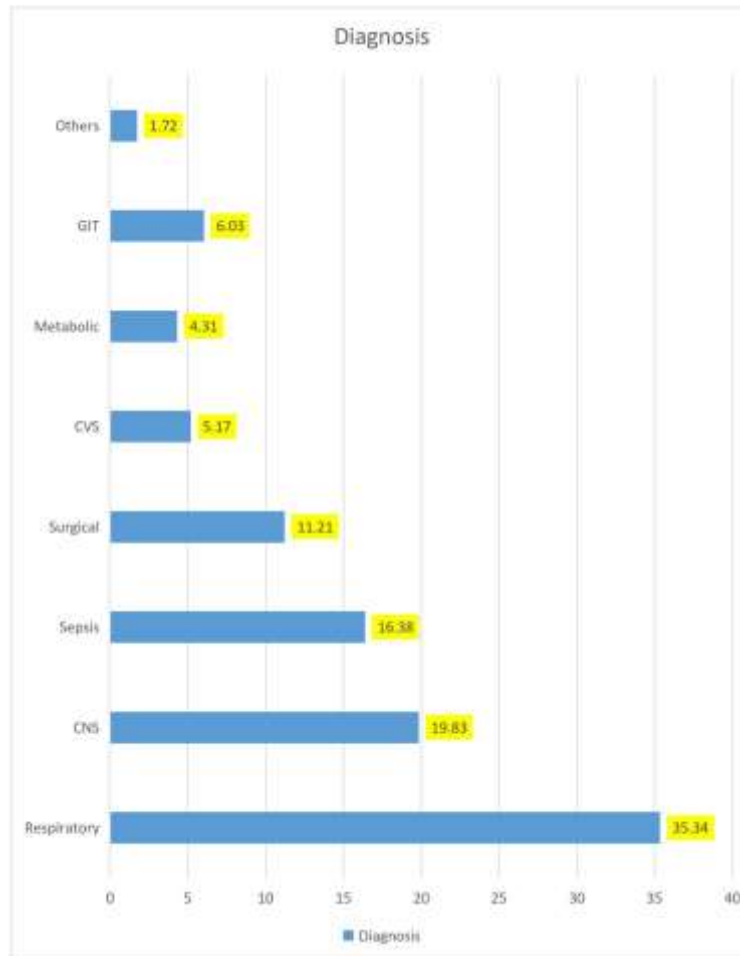


Figure 2: summary of diagnoses of study subjects.

### CRP & Albumin levels

The CRP levels in non-survivors were found to be substantially higher than those in survivors (33.81 vs. 20.81 mg/dl,  $p < 0.05$ ). On the other hand, compared to survivors, non-survivors blood albumin levels were considerably lower (2.48 vs. 4.16 g/dl,  $p < 0.05$ ) (Table 1).

Table 1: CRP & Albumin levels among study subjects.

	CRP levels[mg/dl]			Albumin[g/dl]		
	Survivors	Non survivors	Significance	Survivors	Non survivors	Significance
Mean	20.81 mg/dl	33.81 mg/dl	The t-value is 8.63817. The pvalue is	4.16 g/dl	2.48 g/dl	The t-value is -7.04656. The pvalue is < .00001.
SD	5.96 mg/dl	7.40mg/dl		1.04g/dl	0.71 g/dl	

<b>Median</b>	18.00mg/dl	35.00mg/dl	< .00001. The result is significant at p < .05.	4.50g/dl	2.20g/dl	The result is significant at p < .05.
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#### CRP/Albumin ratio [CAR]

**Table 2: CRP/Albumin ratio**

CAR	Survivors	Non survivors	Significance
Mean	5.39	15.36	The t-value is 15.13293. The p value is < .00001. The result is significant at p < 0.05.
SD	2.28	6.98	
Median	5.00	15.91	

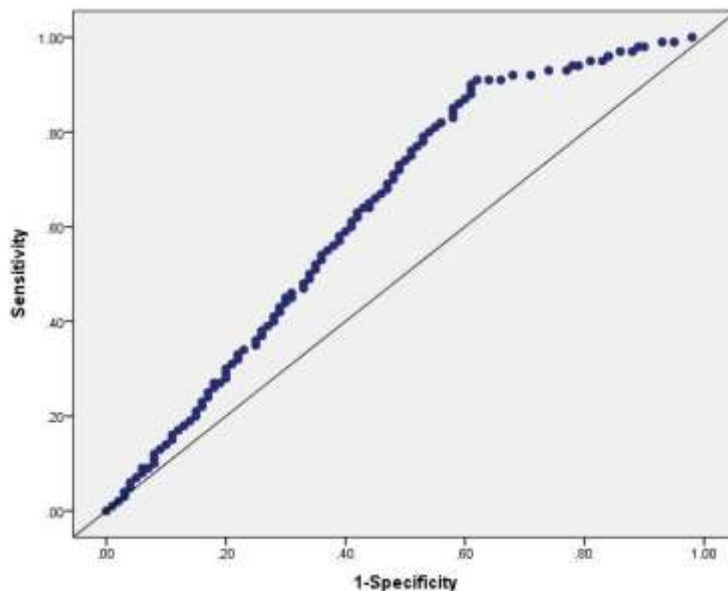
In the current study, we observed that mean CRP/Albumin ratio among non survivors was 15.36, which is significantly greater as compared to survivors (5.39). (15.3 vs 5.3, p < .05.) (Table 2).

#### Prediction of mortality by using CRP/Albumin ratio (AUC: 0.61)

**Table 3: Outcomes among the study subjects.**

Outcome	No. of subjects	Percentage
Survivors	95	81.90
Non-survivors	21	18.10
Total	116	100

Mortality was noted among 18.1% children while 81.9% survived (Table 3).

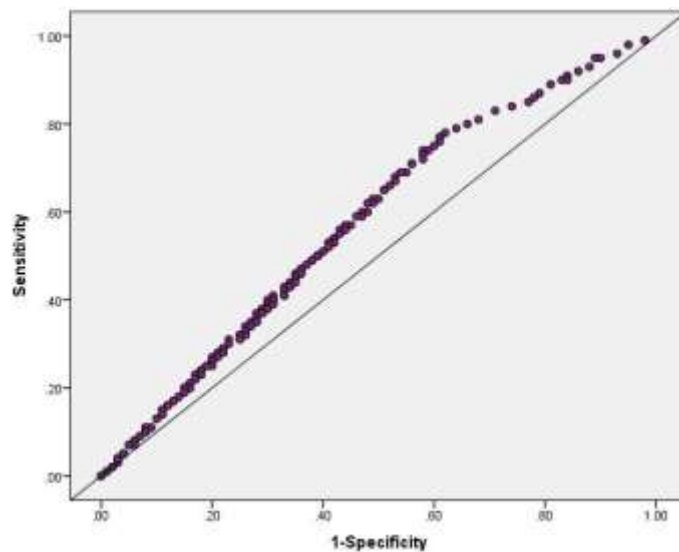


**Figure 3: Prediction of mortality by using CRP/Albumin ratio**

The Prediction model of mortality by using CAR among the children reported the area under curve was 0.61.(Figure 3)

#### Prediction of need of mechanical ventilation by using CRP/Albumin ratio(AUC: 0.56)

Additionally, we also assessed the Prediction of need for mechanical ventilation by using CAR among the study subjects at the time of admission. We observed that the area under curve was 0.56. (Figure 4)



**Figure 4: Prediction of need for mechanical ventilation by using CRP/Albumin ratio.**

#### 4. DISCUSSION

The prediction of outcome in critically ill children admitted to PICU at the time of admission is an important aspect in the current scenario as it helps to counsel the family regarding the prognosis & to allocate the limited available resources in an appropriate manner. The applicability of various validated prognostic scoring systems at present are precluded by various factors like unavailability of resources, long waiting time for the results and the high cost. Here is the emergence of CRP/Albumin ratio (CAR) as a predictor of mortality, which can be readily available, as well as comparatively inexpensive.

Due to its potency as an antioxidant and the fact that albumin is a negative acute phase reactant, which means that its leakage into extravascular spaces is correlated with the degree of systemic inflammation, hypoalbuminemia has been recommended as a straightforward, affordable, and reliable indicator of outcome in critically ill patients admitted to intensive care units (ICUs) under a variety of pathologic conditions. In the current study, we observed that mean albumin levels among non survivors (2.48 g/dl) was significantly lesser as compared to the survivors (4.16 g/dl) (p-value is < .00001) [11].

The **Fairclough's study** in 2009 has mentioned Low albumin levels have been linked to malnutrition and chronic illnesses the most frequently. Based on Fairclough's 2009 study, which found that albumin levels were greatly influenced by nutritional status, Moustafa et al. [12] published supplementary evidence, showing that hypoalbuminemia was a common condition among critically ill children hospitalized to the pediatric intensive care unit (PICU) at Alexandria University Children's Hospital. The albumin levels measured at admission showed statistically significant correlations with various clinical outcomes, such as increased mortality and prolonged PICU stays [13] **Agustin Iskandar et al** in their study assessed the Prediction of mortality by using Albumin levels among the study subjects. They observed AUC of 0.616.

There are many studies available on hypoalbuminemia that shows that hypoalbuminemia is a risk factor for cardiac surgery and graft failure, but studies on the same in children are restricted to certain specific circumstances, such as post-cardiac surgery and pediatric renal transplant recipients reflect the severity and prognosis of the disease in critically ill adult patients. Previous investigations have shown that 33–57% of critically unwell children have hypoalbuminemia. Thus far, there is conflicting evidence about the predictive power of serum albumin concentration for the clinical outcomes of critically ill children in general [14, 15].

##### CRP levels

In a variety of clinical settings, C-reactive protein, a serum acute phase reactant, is a useful inflammatory biomarker. CRP levels are easily determined, and the tests for it are easy and reasonably priced. Furthermore, CRP is a stable protein that functions similarly whether it is kept or used fresh. Furthermore, neither the patient's gender nor genetic makeup will cause it to differ from person to person. We can infer that CRP is a useful marker of inflammation and that it can be utilized as an inflammatory screen. Assessments have been conducted to ascertain its diagnostic potency in this particular scenario [16].

However, in contrast to other biomarkers, it has been demonstrated that CRP has a poor predictive value of mortality in the

pediatric population [8]. Elevated CRP levels at ICU discharge may not be sufficient for individual clinical decision making, as they only represented a very minor risk factor for readmission and in-hospital mortality.

The current study assessed the CRP levels among the study subjects, & observed that mean CRP levels among non survivors (33.81 55mg/dl) was significantly greater as compared to the survivors (20.81 mg/dl) (p-value is <.00001).

#### CRP/Albumin ratio (CAR)

In critically ill adult patients, the C-reactive protein/albumin ratio has recently been identified as a predictive marker of mortality. Evaluation of CRP with albumin may increase its power to be an indicator of inflammation. CRP level increases in response to infection and this increase is proportional to infection severity [17]. In contrast, albumin is a negative acute phase reactant released in inflammation. This may be explained by increased catabolism rate in sepsis and redistribution secondary to increased vascular permeability which causes a capillary leak. The severity of the infection-induced inflammatory response is correlated with the degree of hypoalbuminemia in critically ill individuals [18]. As a result, the distinction between albumin and CRP in infections is progressively growing. In persons with severe sepsis or septic shock, CAR was an independent predictor of 180-day death [19]. In addition, CAR was a helpful predictive tool for adult surgical oncology patients' overall survival [20, 21]. Research on the CAR's prognostic efficacy in critically ill adult patients has produced encouraging results [7]. However, very few studies are available in the pediatric population. The current study was conducted at a tertiary healthcare center PICU at the time of admission using CAR to predict the need for mechanical ventilation, as well as mortality. In the current study, we compared the CAR according to different diagnoses & observed maximum CAR among subjects presented with sepsis (13.31), followed by surgical cases (8.17), metabolic causes (6.86), GI tract etiology (6.19), respiratory causes (5.99). We observed that mean CAR among non survivors was 15.36, which is significantly greater as compared to survivors (5.39) (p-value is <.00001). Also, the area under curve for the Prediction of need for mechanical ventilation by using CAR among the study subjects at the time of PICU admission was 0.56, which is statistically significant.

#### Mechanical ventilation

When we assessed the need for mechanical ventilation among the study subjects, 80.95% subjects were on mechanical ventilation among non survivors, which was significantly higher as compared to use of mechanical ventilation among survivors [p-value 0.000]. In the current study, 2 patients had severe pulmonary hemorrhage so intubation was not possible and succumbed and remaining 2 suddenly went into cardio-respiratory arrest and could not be revived. In the current study we also assessed the Prediction of need for mechanical ventilation at the time of admission to PICU by using CAR & it was observed that the area under curve was 0.56, which is statistically significant. In study by **Shereen A. Mohamed et al** [22] The CAR revealed a substantially higher median in ventilated patients (6.86) compared to non-ventilated patients (5.22), with 43.8% of the subjects requiring mechanical ventilation. [23]

#### Prediction of mortality by using various indices

In the current study we observed that the area under curve for Prediction of mortality by using Serum albumin levels was 0.51, by using CRP was 0.569 & by using CAR was 0.61. **Agustin Iskandar et al** in their study observed area under curve for Prediction of mortality by using CRP/Albumin ratio (AUC) of 0.203, and it was statistically significant (p-value: 0.002) [24].

### 5. CONCLUSION

To summarize, the Survivors had a mean CRP level of 20.81mg/dl & serum albumin levels of 4.16g/dl with a CAR of 5.39 while Non Survivors had a mean CRP levels of 33.81mg/dl & serum albumin levels of 2.48g/dl with a CAR of 15.36. Maximum CAR was observed among subjects presented with sepsis (13.31), followed by surgical cases (8.17), metabolic causes (6.86), GI tract etiology (6.19) & respiratory causes (5.99).

Also, we observed better Prediction of mortality by using CAR (0.61), as compared to isolated CRP levels (0.569) or serum albumin levels (0.51) (Table 4).

**Table 4: comparison of prediction of mortality in different studies using various indices.**

Various indices	Prediction of mortality [AUC] compared to other study	
	Current study	Mohamed, El Hawary et al [22]
Serum Albumin	0.51	0.705



Serum CRP	0.569	0.773
CRP/Albumin Ratio	0.61	0.795

**CONSENT FOR PUBLICATION:** All authors unanimously agreed to publish this article.

**CONFLICT OF INTEREST:** None

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