



Evaluation of Hypoalbuminemia as a Predictor of Clinical Outcome in Critically Ill Children in Alexandria University Children's Hospital

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Abstract

Outcome prediction is an important target in intensive care unit for providing information on patient outcomes for clinicians and family of critically ill patients. Hypoalbuminemia on admission is common in critical illness in all populations and proved to be a strong predictor of clinical outcome in adults. Because it is a simple, cheap and sensitive marker, it has been used for several purposes in adult Intensive Care Units (ICU) including outcome prediction. Although hypoalbuminemia is a common finding in critically ill children, there is a lack of data that evaluate its usefulness in predicting clinical outcome. In this retrospective study, we aimed to evaluate hypoalbuminemia as a predictor of clinical outcome in 487 critically ill children admitted to a tertiary hospital. Results showed that hypoalbuminemia was present at admission in 40.66% patients that increased to 53.8% during rest of the PICU stay. Hypoalbuminemia at admission was an independent predictor of mortality. Also, we found that patients with hypoalbuminemia at admission had a significantly higher Pediatric Logistic Organ Dysfunction score (PELOD), prolonged Pediatric Intensive Care Unit (PICU) stay and higher mortality. Patients with hypoalbuminemia during admission had significantly longer length of PICU stay, more need for mechanical ventilation, worse PELOD score, higher Pediatric Index of Mortality 2 (PIM2) score and higher mortality. Thus hypoalbuminemia at admission can be helpful for risk assessment and can be used as an outcome predictor in critically ill children.

Keywords: hypoalbuminemia; serum albumin; clinical outcome; predictor; critically ill children; pediatric intensive care unit (PICU).

Introduction

Albumin is a water-soluble protein; it is distributed in the intravascular space and two-thirds in the extravascular space. It constitutes more than 50% of total plasma proteins, contributing about 80% of the plasma colloid osmotic pressure and is responsible for the transport and binding of many molecules.¹This multifunctional protein is also an important

extracellular non-enzymatic antioxidant, thereby protecting against oxidative stress-induced injury.² Abnormally low serum albumin levels are frequent and early biochemical derangements in critically ill adults with a reported incidence of 30–40%; the etiology of which is complex.³ Normally, albumin has a long half-life (15–19 days), but the plasma albumin can rapidly fall by 10–15 g/l in 3 to 5 days in critically ill patients.⁴

The inflammatory process can decrease the synthesis increase of albumin and increase its breakdown. Diversion of synthetic capacity to other acute phase reactant proteins is another cause of hypoalbuminemia in critical illnesses. During critical illness, capillary permeability increases dramatically and alters albumin exchange between intravascular and extravascular compartments.^{1,5,6}

In a comprehensive meta-analysis of 90 studies in adult patients with acute or chronic diseases, a strong dose-response relationship was found between serum albumin level and outcome. Each 1g/dL decrease in serum albumin level significantly raised the odds of mortality by 137%, prolonged ICU and hospital stay by 28% and 71%, respectively, and increased resource utilization by 66%.⁷

Because it is a simple, sensitive, specific, and low-cost assay, it has been routinely used for various clinical and research purposes, including ICU outcome prediction, diagnosis, therapeutic guidance, and as a marker of severity. Large number of the studies on this issue have focused on ICU adult patients generally and specific groups of patients with a variety of pathologic conditions.⁸

However, there is a paucity of data on the incidence and significance of hypoalbuminemia in critically ill children admitted to intensive care unit. This study aimed to evaluate hypoalbuminemia as a predictor of clinical outcome in critically ill children in Alexandria university children's hospital, Egypt.

Subjects and Methods

This retrospective study was conducted on the medical records of all patients admitted to the PICU which is located in a tertiary teaching hospital (Alexandria University Children's Hospital at El-Shatby) from the 1st of January 2014 to the 31st of December 2016.

We included all patients aged more than one month and less than fourteen years admitted to the PICU whose albumin level was measured within

the first 24-hours of admission. Hypoalbuminemia was defined as a serum albumin level of less than 2.5 g/dL in infants aged less than one year and a level less than 3.4 g/dL in older children.⁹

Patients who were not expected to have a normal albumin level in their usual state of health were excluded. These included:

- Patients who had severe protein-energy malnutrition (PEM) (weight for height -3 standard deviations). The Anthroplus software was used for the calculations.¹⁰
- Chronic liver disease and liver cirrhosis.
- Nephrotic syndrome and nephritis.
- Presence of a chronic gastrointestinal or kidney disease affecting the growth (malabsorption syndrome, celiac disease, inflammatory bowel disease, chronic renal failure).
- Receipt of parenteral nutrition before admission.
- Second or third-degree burns.
- Patients who received blood products or albumin before measuring the albumin level.

Baseline data collected were age, sex, weight, height, length of PICU stay, Pediatric Index of Mortality 2 (PIM2), Pediatric Logistic Organ Dysfunction (PELOD) score, diagnosis categorized by primary system affected and receipt and duration of mechanical ventilation. Our primary outcomes were the fate of patients in PICU (discharged or deceased) and length of PICU stay.

Collected data analyzed using SPSS (Statistical Package for Social Science) program for statistical analysis (version 21). Comparisons were carried out between two studied independent non-normally distributed subgroups using Mann-Whitney U test.¹¹ We used Chi-square test to test the association between qualitative variables. The area under the curve (AUC) of the receiver operating characteristic (ROC) was carried out using MedCalc Software version 14. The multivariate logistic model was used to estimate the probability of a binary response based on one or more predictor. The calibration was assessed by

directly comparing the observed and customized predicted mortality across subcategories of risk¹² A p-value< 0.05 was considered statistically significant.

Results

Eight hundred twenty-five patients were the final number of patients included. Four hundred eighty-seven patients were the final number of included patients eligible for the study and analysis as shown in figure 1. Table- I shows demographic data of the studied patients. Table- II shows disease categories. Respiratory causes were the most common cause of admission to the PICU followed by sepsis.

As regards hypoalbuminemia at admission; the patients with were significantly older than those without (15 vs. 7, p=0.000). Patients with had a significantly longer length of PICU stay (6 vs. 4)and worse PELOD score (11 vs. 2) than those without (p=0.002, p=0.000) respectively. There were no statistically significant differences in the need and duration of mechanical ventilation and PIM2 between the two groups (p=0.953, p=0.182, p=0.458) respectively. The number of deceased patients with was significantly more than those without (72 vs. 53, p=0.000) (Table- III).

As regards hypoalbuminemia during admission; the patients with were significantly older than those without (15 vs. 6, p=0.000). Patients with had longer length of PICU stay (6 vs. 4), more need for mechanical ventilation (63.74% vs. 53.55%), worse PELOD score (11 vs. 2) and higher PIM2 (38.75% vs. 30%) than those without (p=0.000, p=0.020, p=0.000, p=0.001) respectively. There was no significant difference in duration of mechanical ventilation between the two groups (p=0.106). The number of deceased patients with was significantly more than those without (91 vs. 34, p=0.000) (Table- IV).

Figure 2 and 3 shows Kaplan-Meier survival analysis of patients with and without hypoalbuminemia at and during admission. Patients with hypoalbuminemia had significantly worse survival than patients without

hypoalbuminemia. (Log rank = 6.003, p=0.014) (Log rank = 4.888, p=0.027) respectively.

Figure 4 shows the diagnostic test of the accuracy of serum albumin level at admission and the fate. The cut-off value of serum albumin at admission to predict the fate was found to be 3g/dL (sensitivity 72%, specificity 60.5%).

Hypoalbuminemia at admission was proved to be statistically significant independent predictors of mortality (p= 0.025) (Table- V).

Figure 1: Flow diagram of the studied cases.

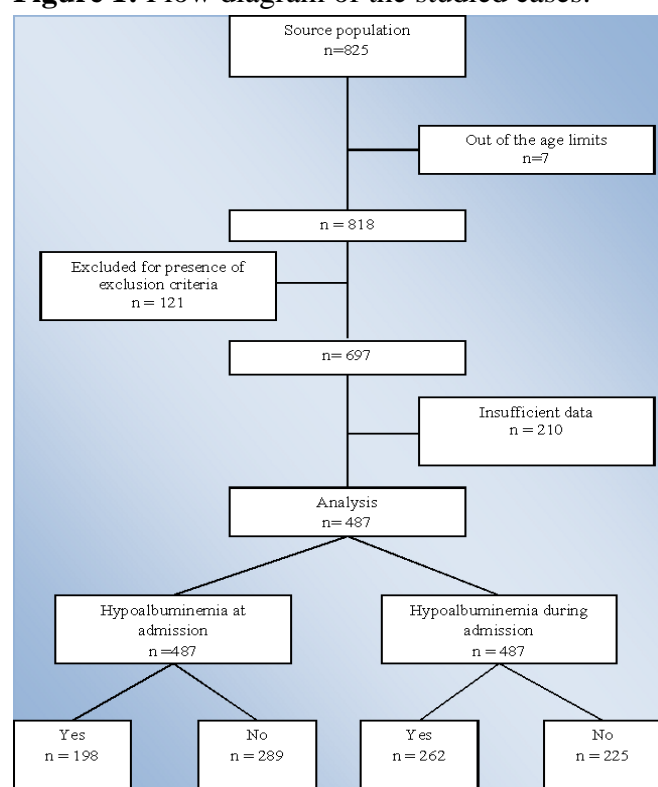


Table I: Distribution of the studied cases according to demographic data (n = 487)

	Value
Sex	
Male, n (%)	256 (52.57)
Age (Months) [§]	9(4-28)
Weight (kg) [§]	7.8 (5-12)
Height(cm) [§]	67 (57-82)
Length of PICU stay (days) [§]	4 (2-9)
Mechanical ventilation, n (%)	287 (59.93)
Duration of ventilation (days) [§]	4 (2-8)
PELOD [§]	1 (1-13)
PIM-2 [§]	33.50 (12-64)
Hypoalbuminemia at admission, n (%)	198 (40.66)
Hypoalbuminemia during admission, n (%)	262 (53.8)
Serum albumin (g/dL) [§]	3.1 (2.6-3.6)
Mortality, n (%)	125 (25.67)

§: Data expressed as median and interquartile range.

Table II: Distribution of the studied cases according to primary disease (n = 487)

Primary disease	(n=487)	
	n	%
Cardiology	36	7.39
Respiratory	118	24.23
Neurology	61	12.53
Renal	14	2.87
Metabolic And Diabetes	49	10.06
Hematology	39	8.01
Sepsis	94	19.3
Gastrointestinal	55	11.29
Others	21	4.31

Figure 3: Kaplan-Meier survival analysis of patients with and without hypoalbuminemia during admission.

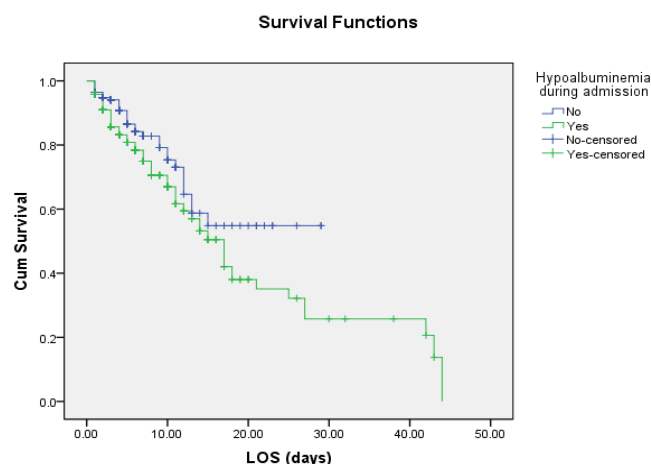


Figure 2: Kaplan-Meier survival analysis of patients with and without hypoalbuminemia at admission.

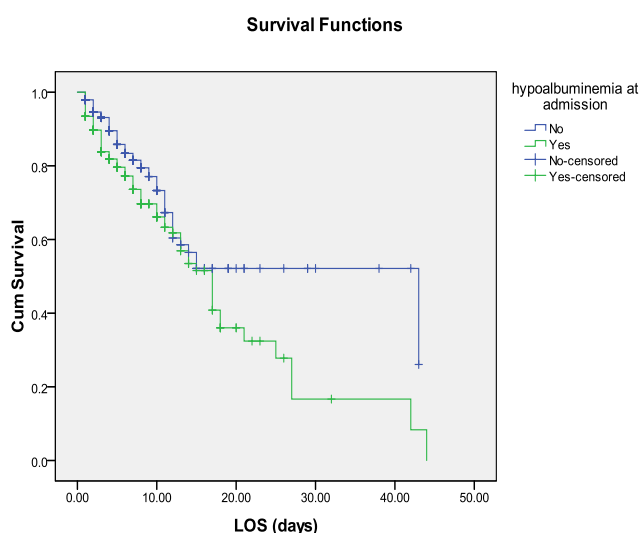


Table III: Demographic and clinical data of patients with and without hypoalbuminemia at admission.

	Non hypoalbuminemia (n = 289)		Hypoalbuminemia (n = 198)		Test of significant	P
	No.	%	No.	%		
Male	158	54.67	98	49.49	$X^2=1.263$	0.261
Age (Months) [§]	7 (3-14)		15 (6-48)		$Z_{(MW)}=6.52$	0.000*
Weight (kg) [§]	7 (4.8-10)		9.4 (6.5-15)		$Z_{(MW)}=5.594$	0.000*
Height (cm) [§]	63 (55-75)		74 (62-93)		$Z_{(MW)}=5.685$	0.000*
Length of PICU stay (day) [§]	4 (2-8)		6 (3-10)		$Z_{(MW)}=3.143$	0.002*
Mechanical ventilation n(%) n=287	170 (58.82)		117 (59.09)		$X^2=0.003$	0.953
Duration of mechanical Ventilation (day) [§]	4 (2-8)		5 (2-11)		$Z_{(MW)}=1.335$	0.182
PELOD [§]	2 (0-12)		11 (1-21)		$Z_{(MW)}=4.221$	0.000*
PIM-2 [§]	32.5 (12.8-61.1)		34.45 (11.1-68.3)		$Z_{(MW)}=0.742$	0.458
Mortality n(%)	53 (18.34)		72 (36.36)		$X^2=20.008$	0.000*

χ^2 , p: χ^2 and p values for Chi-square test for comparing between the two groups, Z, p: Z and p values for Mann Whitney test for comparing between the two groups

*: Statistically significant at $p < 0.05$, §: Data expressed as median and interquartile range.

Table IV: Demographic and clinical data of patients with and without hypoalbuminemia during admission

	Non hypoalbuminemia (n = 225)		Hypoalbuminemia (n = 262)		Test of significant	P
	No.	%	No.	%		
Male	118	52.44	138	52.67	$\chi^2=0.003$	0.96
Age (Months) [§]	6 (3-10)		15 (6-42)		$Z_{(MW)}=7.742$	0.000 [*]
Weight (kg) [§]	6.5 (4.5-9)		9.25 (6.5-14)		$Z_{(MW)}=6.733$	0.000 [*]
Height (cm) [§]	61 (53-70)		73 (61-93)		$Z_{(MW)}=6.79$	0.000 [*]
Length of PICU stay (day) [§]	4 (2-7)		6 (3-10)		$Z_{(MW)}=6.733$	0.000 [*]
Mechanical ventilation n(%) n=287	120 (53.33)		167 (63.74)		$\chi^2=5.417$	0.02 [*]
Duration of mechanical Ventilation (day) [§]	4 (2-7)		4 (2-10)		$Z_{(MW)}=1.615$	0.106
PELOD [§]	2 (0-12)		11 (2-21)		$Z_{(MW)}=6.008$	0.000 [*]
PIM-2 [§]	30 (9.7-53.1)		38.75 (17.5-69.4)		$Z_{(MW)}=3.363$	0.001 [*]
Mortality n(%)	34 (15.11)		91 (34.73)		$\chi^2=24.427$	0.000 [*]

χ^2 , p: χ^2 and p values for Chi-square test for comparing between the two groups, Z, p: Z and p values for Mann Whitney test for comparing between the two groups

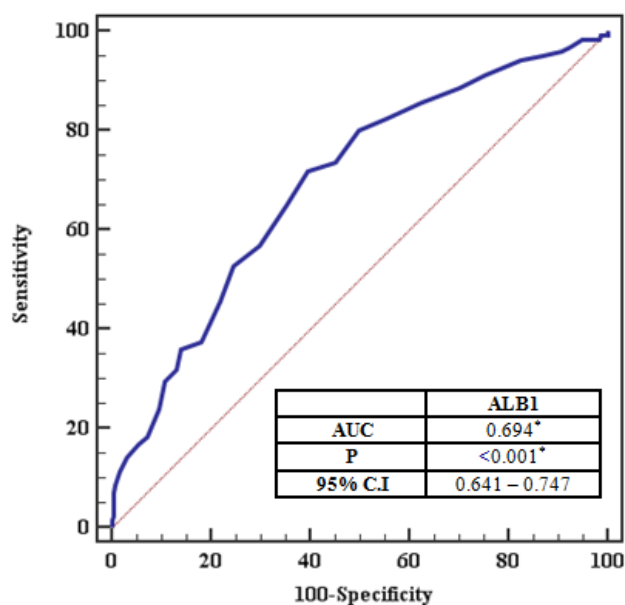
*: Statistically significant at $p < 0.05$, §: Data expressed as median and interquartile range.

Table V: Multivariate logistic regression analysis for death

	B	OR	95% CI	p value
Age	0.017	0.009	1.094-3.734	0.025 [*]
Weight	-0.07	0.042	0.859-1.012	0.093
Hypoalbuminemia at admission	0.703	0.313	1.094-3.734	0.025 [*]
Hypoalbuminemia during admission	0.345	0.329	0.741-2.693	0.294
PIM2	0.016	0.005	1.006-1.026	0.002 [*]
Need for mechanical ventilation	1.658	0.394	2.425-11.357	0.000 [*]
PELOD	0.062	0.013	1.038-1.092	0.000 [*]
Length of PICU stay	-0.019	0.018	0.947-1.017	0.291
Model significance	$\chi^2=160.837, p=0.000$ [*]			
Classification accuracy	74.3%			

B: Unstandardized Coefficients, OR: Odds ratio, CI: Confidence interval, χ^2 , p: χ^2 and p values for Chi square test, *: Statistically significant at $p < 0.05$

Figure 4: ROC curve for serum albumin level at admission to predict deceased cases.



Discussion

Low albumin levels result in decreased carrier capacity for substances that are primarily transported by albumin (some medications, bilirubin, and free radicals). Because of albumin’s importance in maintaining plasma colloid oncotic pressure, severe hypoalbuminemia may result in extravascular fluid accumulation.¹³ Also low serum albumin level is predictive of energy, with a resultant higher incidence of infection and mortality. This is attributed to the decreased anti-inflammatory and antioxidant effects of albumin.¹⁴ The incidence of hypoalbuminemia in the pediatric population is frequent. The prevalence of hypoalbuminemia in critically ill children in the previous studies ranged from 21–76%.^{1,3,5,6,15,16} This might be contributed to the differences in the study population and the definition of hypoalbuminemia.

In the current study, hypoalbuminemia was defined as a serum albumin level of less than 2.5 g/dL in infants less than one year and a level less than 3.4 g/dL in older children. Different definitions of hypoalbuminemia were used in the previous studies. Horowitz and Tai⁵, Kattisakmontri et al.⁶, and Kumar et al.¹⁶ defined hypoalbuminemia as a serum albumin level of less than 2.5 g/dL in infants less than 7 months and a level less than 3.4 g/dL in older children. Durward et al.³ defined it as lower than 3.3 g/dL. Pons Leite et al.¹⁵ defined it as less than 3.5 g/dL while Tiwari et al.¹ defined it as less than 2.5 g/dL.

Also, there were differences in the timing of measurement that had been studied. Some of the authors used the measurement in the first 24 hours of admission in their analysis, while others used serum albumin within the first 48 hours of admission. Tiwari et al.¹ studied hypoalbuminemia in the first 48 hours of admission and at any time during PICU stay. In the present study, hypoalbuminemia was analyzed within 24 hours of admission and again at any time of PICU stay. Due to these differences, a clear definition of hypoalbuminemia according to age should be made.

It is expected to see that hypoalbuminemia prevalence increases as the time of PICU stay increases as it reflects the progression and severity of the state of critical illness. In the current study, the incidence of hypoalbuminemia at admission was 40.66%. This increased to 53.8% during the rest of PICU stay. Durward et al.³ reported that incidence of hypoalbuminemia increased from 57% on admission to 76% at 24 hours while Tiwari et al.¹ found it increased from 21% on admission to 34% at the end of the first week and to 37% during the rest of PICU.

In this study; 36.36% of patients with hypoalbuminemia at admission died which was consistent with that of Kumar et al.²² as they reported mortality of 32%. This was higher than the data from previous studies of Tiwari et al.¹ and Kattisakmontri et al.⁶ as they reported that 25.6% to 27.5% of their patients of hypoalbuminemia at

admission died. On the other hand; Durward et al.³ reported that only 12.5% of their patients with hypoalbuminemia at admission died. Regarding hypoalbuminemia during admission, the present study showed that 34.73% of them died. Tiwari et al.¹ reported a lower percentage of death in the patients with hypoalbuminemia at any time of PICU stay; 23.9%. This could be explained by the differences in the patient profile.

In the current study; patients with hypoalbuminemia at and during admission had significantly worse survival than patients without which was consistent with Horowitz and Tai⁵, Kattisakmontri et al.⁶, Pons et al.¹⁵ and Kumar et al.¹⁶ as they proved that patients with hypoalbuminemia had significantly lower survival rate. Two studies found no statistically significant difference in mortality rate between patients with hypoalbuminemia and those with normal serum albumin level.^{1,3} This might be attributed to the difference in definitions of hypoalbuminemia used in different studies

In adults, extensive investigations into the efficacy of hypoalbuminemia as a predictor of critical illness have been demonstrated a clear association with clinical outcomes including mortality. In the APACHE III, IV scores, albumin was added as one of the important variables in predicting prognosis.¹⁷

Regarding mortality prediction, by using multivariate analysis, the present study found that hypoalbuminemia at admission was an independent risk factor for death. Similarly, Kattisakmontri et al.⁶, Pons et al.¹⁵ and Kumar et al.¹⁶ reported the same results. Also in one large cohort study where serum albumin was one of the covariates in the regression analysis, hypoalbuminemia was a significant predictor of mortality in critically ill children.¹⁸

The present study also showed that serum albumin level at admission was an important discriminator of mortality with an AUC of 0.694. In contrast; Durward et al.³ reported that the discriminatory ability of serum albumin level at admission was poor for detecting PICU mortality.

Comparing the length of PICU stay, the current study found that PICU stay was longer in patients with hypoalbuminemia at admission and during rest of PICU stay. Similarly, many previous studies reported that patients with hypoalbuminemia at admission had a longer length of PICU stay.^{1,3,5,6,16}

As regards to severity and progression to multi-organ dysfunction syndrome, the present study found that patients with hypoalbuminemia at admission had a significantly higher PELOD score. Similarly; Tiwari et al.¹ reported that hypoalbuminemic patients had higher PRISM scores and higher likelihood progression to multi-organ dysfunction syndrome. Also, Horowitz and Tai⁵ found that they had a higher number of organ failures.

In contrast to some other studies;^{1,5,6,15,16} the current study was unable to document the difference in the patients regarding the number of ventilated cases, length of ventilation, and PIM-2 as they were similar between patients with and without hypoalbuminemia at admission.

In the present study, it was found that patients with hypoalbuminemia at any time during admission had a longer length of PICU stay, higher PIM-2, worse PELOD and more likelihood to need mechanical ventilation, but they showed no difference in duration of mechanical ventilation. Similarly; Tiwari et al.¹ studied hypoalbuminemia during PICU admission. They found that patients with hypoalbuminemia had higher Pediatric Risk of Mortality scores, prolonged PICU stay; higher requiring mechanical ventilation, prolonged duration of mechanical ventilation and progression to multi-organ dysfunction syndrome.

The two limitations of the present study were: First, this study was a single center study; multicenter studies are needed to be done. Second, being a retrospective study, 210 patients (25.4%) of the source population did not participate in the study because of incomplete data.

Conclusions

We found that hypoalbuminemia is a frequent feature in critically ill children in PICU. We also found that hypoalbuminemia at admission demonstrated a statistically significant association with clinical outcomes; longer length of PICU stay, higher PELOD score and higher mortality. Hypoalbuminemia at admission is an independent predictor of PICU mortality and serum albumin is a good discriminator for detecting mortality.

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