

Hypoalbuminemia as a Predictor of Adverse Outcome in Critically Ill Children: A Prospective Cohort Study

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Abstract

Background

hypoalbuminemia is a common finding in critically ill patients associated with a high risk of mortality, but there is lack of data on its role in pediatric patients. The aim of this study is to investigate the effect of low albumin levels in pediatric patients on poor prognosis and high risk of mortality in the pediatric intensive care unit (PICU).

Methods

This was a prospective cohort study conducted at the PICU at El-Bagour hospital from November 2018 to November 2020. The aim was to evaluate low albumin level as a predictor of poor prognosis and clinical outcome in 150 critically ill children aged one month up to 18 years. ROC curve was used to assess the discriminatory ability of scoring systems for patients' mortality.

Results

148 patients were included in the final analysis where the incidence of hypoalbuminemia in the 1st 48-h postadmission was 44.6% with an overall mean serum albumin level of 3.34 ± 0.78 . Hypoalbuminemia was an independent factor of mortality prediction. Moreover, we found children with hypoalbuminemia had higher mortality rate (p-value < 0.001), higher PICU stays (p-value = 0.016), lower galscow coma score (GSC) (p-value = 0.0017), and more need of mechanical ventilation (p-value < 0.001).

Conclusion

hypoalbuminemia may be used as a significant predictor of mortality and risk assessment in critically ill children.

1. Introduction

Albumin represents the most abundant protein in plasma with more than two-third of plasma protein composition, thus it contributes about 75% or higher of the colloid osmotic pressure of plasma [1]. Also, albumin plays an important role in the transport and binding of many molecules such as bilirubin, bile salts, hormones and even drugs [2]. About two-thirds of albumin remains in the extra-vascular space with only one-third in the intra-vascular space as it is highly water-soluble [2].

Hypoalbuminemia is a complex disease characterized by either lack of synthesis in malnutrition, malabsorption, and even hepatic dysfunction or excessive loss, which happens in nephropathy, or protein-losing enteropathy [3]. In critical illness, the permeability of capillaries increases much caused by pro-

inflammatory mediators such as histamine, or bradykinin or by damage to the integrity of capillaries structures so that they may become leakier. Thereby there is an exchange between albumin in the extra-vascular and intra-vascular compartments so hypoalbuminemia is a common finding in critical ill patients [4].

A recent meta-analysis study, has been conducted on critically ill patients, showed that hypoalbuminemia was associated with higher mortality rate, higher length of PICU stay along with the higher need of mechanical ventilation [5]. It also showed that hypoalbuminemia is anchored with adverse outcome in adults [6]. There is a paucity of data regarding the incidence and significance of hypoalbuminemia in critically ill children, but show conflicting results [7–9]. Therefore, the aim of this study is to evaluate the incidence of hypoalbuminemia as a predictor of clinical outcome in critically ill pediatric patients.

2. Patients And Methods

2.1 Study Design:

This was a prospective observational cohort study conducted at the Pediatric intensive care unit (PICU) of Menofia teaching hospital from November 2018 to November 2020. The study protocol was approved by the Ethical committee of Menofia Hospital under the code of 9114485, as well as a written confirmed consent was gained from guardians before the inclusion process after explanation of the study.

2.2 Inclusion Criteria:

Our inclusion criteria were children who were critically ill and admitted to the PICU aged one month up to 18 years. We also excluded children in whom hypoalbuminemia was expected to be a result of preexisting diseases such as severe protein-energy malnutrition characterized by either weight or height < 3rd centile according to the WHO guidelines in 2007 [10]. Also, children who had chronic diseases such as chronic liver disease and chronic kidney disease. Children who experienced second and third burn degrees, or who had received blood product or albumin within the last 4 weeks before admission were excluded too.

2.3 Study Process:

All children had done the admission albumin level test within the first 48 hours of admission. The exact estimation of the albumin level in plasma was done according to the guidelines (dye-binding method) [11]. We defined hypoalbuminemia based on the guidelines as serum albumin level < 2.5 g/dl for children < 7 months in age and < 3.4 g/dl for whom age are > 7 months [12].

The data collected from children were age, sex, weight, height, diagnosis categorized regarding the organ system, complete blood count (CBC), C-reactive protein (CRP), GCS, blood glucose, Na, K, urea Creatinine, SGOT, SGPT & blood culture.

Children were allocated into two groups based on their albumin level to hypoalbuminemic group (children with low level of albumin) and Normo-albuminemic group (children with normal albumin level). Based on the purpose of analysis, children were also assigned to two sub-groups regarding the age into (< 7 months and > 7 months). Children who were discharged against medical advice were excluded from the final analysis of outcome.

2.4 Outcomes:

Our primary outcomes were the length of PICU stay, the need for mechanical ventilation, and the fate of patients in PICU. Pediatric Risk of mortality 2 (PRISM2), Pediatric Logistic Organ Dysfunction 2 (PELOD2), and Pediatric Index of Mortality 2 (PIM2) scoring systems were used to assess the severity of illness at admission.

2.5 Statistical analysis:

SPSS software version 25.0 was used to perform the analysis. All continuous data were expressed as mean \pm standard deviation and dichotomous data were expressed as frequency (percentage).

Independent sample t-test and Fisher's exact test were used to compare albumin levels with PDR and duration of PICU stay. Mortality risk scores were analyzed using Pearson's Chi-square test.

The area under curve (AUC) of the receiver operating characteristics (ROC) was also carried out using SPSS to measure discrimination. P value less than 0.05 along with a 95% confidence interval (CI) was considered to be significant.

3. Results

3.1. Baseline Data

150 children were included out of 167 children admitted to the PICU during the study time. 17 children were excluded from our study [Fig. 1]. The mean age for all children was 4.03 ± 4.35 years (range: 1.5 month – 15 years). 73 children (48.7%) were male and 77 (51.3%) were female. The mean serum albumin for all children was 3.34 ± 0.78 g/dL.

The incidence of hypoalbuminemia was found in 67 children (44.6%) out of 150 children. When the children were allocated regarding their age, it was found that 13 out of 36 (36.1%) children in the younger group were hypoalbuminemic whereas 54 out of 114 (47.4%) in the older group were hypoalbuminemic making the incidence of hypoalbuminemia in children older than 7 months significantly higher (p-value = 0.26, RR = 0.76). The incidence of hypoalbuminemia in children with PDR > 5% (55.4%) was higher than the incidence observed in children with PDR calculated by PIM2 < 1% (23%) (p < 0.001, RR = 2.399) [Table 1].

Table 1
Baseline demographics data of the study population at admission.

Population N = 150	Hypo-albuminemic group (n = 67)	Normal Albuminemic group (n = 83)	P value
Age group 1 (1–7 months) [n = 36]	13 (36.1%)	23 (63.9%)	0.26
Age group 2 (7 month- 18 years) [n = 114]	54 (47.4 %)	60 (52.6%)	
weight (kg)	14.72 ± 10.46	17.67 ± 14.74	0.169
height (cm)	90.31 ± 29.28	95.55 ± 36.46	0.342
serum albumin (gm/dl)	2.67 ± 0.5	3.88 ± 0.5	< 0.001
PDR < 1% (n = 13)	3 (23%)	10 (77%)	< 0.001
PDR 1%-5% (n = 81)	33 (40.7%)	48 (59.3%)	
PDR > 5% (n = 56)	31 (55.4%)	25 (44.6%)	
Independent Sample t-test, PDR: Predicted death rate.			
Mean ± SD was used for continuous data, and frequency (percentage) was used for dichotomous data.			

3.2 Diagnostic Categories:

The diagnostic categories of 150 children showed that the incidence of hypoalbuminemia in the neurological disease category was higher than other illnesses (20 out of 40) followed by the respiratory disease category (20 out of 43), while in Normo-albuminemic group, the respiratory disease category has the highest number of pediatric patients (23 out of 43) then the neurological disease category (20 out of 40) [Table 2].

Table 2
Diagnostic categories between studied groups.

diagnostic categories n = 150	Hypo-albumin (n = 67)	Normal Albumin (n = 83)
neurological (n = 40)	20	20
Respiratory (n = 43)	20	23
Cardiovascular (n = 14)	6	8
sepsis (n = 6)	5	1
renal (n = 8)	6	2
Gastro-intestinal (n = 5)	1	4
Hemato-oncological (n = 5)	3	2
Metabolic and Diabetes (n = 12)	0	12
Post-arrest (n = 5)	3	2
Others (n = 12)	3	9
total (n = 150)	67	83

3.3 Outcomes:

148 children included in the final analysis in which two children were excluded due to discharge against medical advice. The duration of the PICU stay was significantly higher in the hypoalbuminemic group than that in the normal albuminemic group (p-value = 0.016, mean difference= [-8.08] [95% CI -14.64 to -1.52]). The essential need for Mechanical ventilation was significantly higher in hypo-albuminemic as compared to the normal group (OR = 4.54 [95% CI 2.22 to 9.26], p-value < 0.001). Moreover, mean serum albumin in ventilated children (55 child) was 2.92 ± 0.76 , and 3.58 ± 0.69 in non-ventilated children (113 child), and mean difference was 0.66 (p = < 0.001). In terms of GCS, there was a lower score in the hypoalbuminemic group compared to the normal group with mean of 11.71 ± 2.3 , and 12.93 ± 2.32 respectively, and mean difference of 1.22 [95% CI 0.464 to 1.975] (p-value = 0.0017). Children with hypo albumin levels had a mortality rate of 43.9% (29 out of 66) which was 2.78 times greater than the normal albumin group 15.8% (13 out of 82) (OR = 4.16 [95% CI 1.93 to 8.95] (p = 0.0003) [Table 3].

Table 3

Comparison of albumin level groups with reference to duration of PICU stay, GCS score, mechanical ventilation and outcome

Compare (N = 148)	Hypo-albuminemic group (n = 66)	Normo-albuminemic group (n = 82)	MD [95% CI]	P value
Duration of PICU stay (days)	19.03 ± 27.66	10.95 ± 10.62	-8.08 [-14.64 to -1.52]	0.016
GCS	11.71 ± 2.3	12.93 ± 2.32	1.22 [0.464 to 1.975]	0.0017
Need for Mechanical ventilation (n = 55)	37	18	OR = 4.54 [2.22 to 9.26]	< 0.001
Fate of patients	29 (69%)	13 (31%)	OR = 4.16 [1.93 to 8.95]	0.0003
Died (n = 42)	37 (34.9%)	69 (65.1%)		
discharged (n = 106)				
Independent Sample t-test, Fisher's exact test. PICU: Pediatric intensive care unit, MD = Mean difference, OR = Odds Ratio.				
Mean ± SD was used for continuous data, and frequency (percentage) was used for dichotomous data.				

We also assessed a comparison between survivors and non-survivors children regarding serum albumin level, PRISM2, PIM2, and PELOD2. Mean PRISM2 score in non-survivors group (13.74 ± 6.58) was higher compared to survivors group (8.42 ± 4.96) with mean difference of -5.32 [95% CI -7.28 to -3.358] (p-value < 0.0001). Mean PELOD2 score in non-survivors children (6.33 ± 2.99) was higher than survivors children (2.71 ± 1.94), and mean difference of -3.62 [95% CI -4.439 to -2.8] (p-value < 0.0001). Mean PIM2 score in non-survivors group (2.64 ± 0.49) was higher compared to survivors group (2.15 ± 0.61) with mean difference of -0.49 [95% CI -0.698 to -0.28]. When using an independent sample t-test for comparing the mean serum level in survivors and non-survivors children, it was found that the mean in survivors was 3.54 ± 0.7 , and 2.82 ± 0.76 in non-survivors with mean difference of 0.72 [95% CI 0.46 to 0.977] (p-value < 0.0001) [Table 4].

Table 4

Comparison between survivors and non-survivors regarding scores and serum albumin level

Compare	non-survivors (n = 42)	survivors (n = 108)	MD [95% CI]	P value
Serum albumin (g/dl)	2.82 ± 0.76	3.54 ± 0.7	0.72 [0.46 to 0.977]	< 0.0001
PRISM2 score	13.74 ± 6.58	8.42 ± 4.96	-5.32 [-7.28 to -3.358]	< 0.0001
PIM2	2.64%±0.49	2.15%±0.61	-0.49 [-0.698 to -0.28]	< 0.0001
PELOD2 score	6.33 ± 2.99	2.71 ± 1.94	-3.62 [-4.439 to -2.8]	< 0.0001
Pearson's Chi-square test, MD = mean difference, CI = Confidence interval.				
Mean ± SD was used for continuous data				

Univariate binary logistic regression was performed to check whether hypo-albuminemia at admission was considered to be independently in relation to mortality. We assessed any factor that could be associated with mortality such as age < 1 year at admission, GCS < 8, PIM2 score, and the need for mechanical ventilation. GCS < 8, PIM2 score, and need for mechanical ventilation were significantly associated with mortality at admission (p-value < 0.001), except age < 1 year which wasn't significantly associated (p-value = 0.2) [Table 5].

Table 5

Univariate binary logistic regression of variables potentially associated with mortality

Variables	OR (95% CI)	P value
Hypoalbuminemia	4.16 (1.93–8.95)	< 0.001
PDR (PIM2) score	4.57 (2.24–9.3)	< 0.001
Age < 1 year	0.57 (0.27–1.17)	0.12
need for MV	17.2 (6.95–42.58)	< 0.001
GCS < 8	0.08 (0.02–0.31)	< 0.001
OR: odds ratio, CI: Confidence interval.		

3.4 Statistical relations:

We measured the correlation between albumin level and other parameters to assess the strength of the relationship between this variable and other parameters [Table 6]. A non-significant correlation was found between Serum Albumin level and GCS < 8, and PRISM2 score (Rho=-0.128, 0.105 respectively, p-value > 0.05), and a positive correlation between Serum Albumin level and PIM2 score, PELOD2 score, need for

mechanical ventilation, the mortality rate, and length of PICU stay (Rho = 0.216, 0.306, 0.351, 0.31, and 0.235 respectively, p-value < 0.05).

Table 6
Correlation between serum albumin level and other parameters

Parameters	Serum Albumin	
	Correlation coefficient	P-value
PIM2	0.216	0.008
GCS	-0.128	0.121
PRISM2 score	0.105	0.2
PELOD2 score	0.306	< 0.001
Length of ICU stay	0.235	0.004
Need for MV	0.351	< 0.001
Mortality	0.31	< 0.001
Rho = Spearman's correlation.		

3.5 Diagnostic Accuracy:

The optimal cut-off PIM2 score was at > 1.6%, with 92.9% sensitivity and 75.5% specificity and area under ROC curve of 0.78 (p-value < 0.001). The optimal cut-off PRISM2 score was at > 4.5 with 92.9% sensitivity and 72.6% specificity and area under ROC curve of 0.73 (p-value < 0.001). Also, the optimal cut-off PELOD2 score was at > 1.5 with 95.2% sensitivity and 84.9% specificity and area under ROC curve of 0.844 (p-value < 0.001) that yielded a good discrimination on predicting mortality and morbidity in the PICU [Table 7].

Table 7
the prognostic scoring performance for PIM2, PRISM2, and PELOD2 scores regards mortality

Scores	Cutoffs	Specificity	Sensitivity	AUC	P-value
PIM2	> 1.6%	75.5	92.9	0.78	< 0.001
PRISM2	> 4.5	72.6	92.9	0.73	< 0.001
PELOD2	> 1.5	84.9	95.2	0.844	< 0.001
AUC: Area under curve, PIM2: Pediatric index mortality 2, PRISM2: Pediatric Risk of Mortality2, PELOD2: Pediatric logistic organ dysfunction 2.					
Level of significant is 0.5					

4. Discussion

Despite of the availability of many severity scores systems that can predict the mortality, there were only few studies that assess the mortality and morbidity in PICU in critically ill patients presented with hypoalbuminemia. This study focused on the incidence of hypoalbuminemia in PICU in critically ill pediatrics, as hypoalbuminemia is a common problem associated with higher mortality and morbidity rate [13]. In critical illness, the permeability of blood vessels increases much by the action of inflammatory mediators, as a result, there is a dramatic change in albumin level between extra-vascular and intra-vascular. There is about 300% rise in albumin escape rate as a result of albumin balance alteration. Also, there is a huge decrease in albumin synthesis in liver by the effect of these inflammatory mediators especially IL-6 and TNF-alpha [7, 14].

The incidence of hypoalbuminemia in this study was 44.6% of children admitted to the PICU and this comes with the alignment of a study by (*Horowitz and Tai 2007*) that mentioned the incidence of hypoalbuminemia which was about 33% at admission [8]. (*Durward et al. 2003*) found that hypoalbuminemia was 57% at admission but after 1 day, it was progressed to 76% [7]. The frequency of hypoalbuminemia in another study by (*Tiwari et al. 2014*) was 21% at admission, then it increased to 34% after one week, and about 37% during the rest of the PICU stay [14]. We couldn't perform repeated serum albumin to all children due to the lack of commitment from guardians, so we measured only the incidence of hypoalbuminemia at admission.

We used PIM2, PRISM2 and PELOD2 scores to assess the severity of illness 48-h postadmission [15–17]. Pediatric Index of Mortality 2 (PIM2) was found in a previous study by (*Qureshi et al. 2007*) to be the most effective pediatric scoring system with the highest accuracy rate among all other scores [17]. Pediatric Risk of mortality 2 (PRISM2) and Pediatric Logistic Organ Dysfunction 2 (PELOD2) were also used to assess the severity of illness and give the highest accuracy rate in assessing the risk mortality as well.

There was a strong relation between hypoalbuminemia and mortality rate as PRISM2 score was much higher in the hypoalbuminemic group rather than the normal albumin level group (10.82 vs 7.71, $p = 0.13$) despite of the non-statistically significance in p-value, and high PELOD2 score in the hypoalbuminemic group versus the other group (3.24 vs 1.35, $p = 0.04$). As regards the need for mechanical ventilation, there was a highly significant difference in favor of the hypoalbuminemic group (56% vs 21.9% $p < 0.001$) and a high mortality rate in the hypo albumin level group compared to the normal group (43.9% vs 15.8% $p < 0.001$). This comes with the alignment of another study by (*Tiwari et al. 2007*) which stated that hypoalbuminemic children had higher PRISM2 scores compared to normal ones (12.9 vs 7.5, $P < 0.001$) with prolonged PICU stay (13.8 vs 6.7, $p < 0.001$); and a higher need for mechanical ventilation was observed in the hypoalbuminemic group compared to normal group (84.8% vs 28.8%, $p < 0.001$) and a high risk of mortality between both groups in favor of hypoalbuminemic group (25.6% vs 17.7% $p < 0.001$) [14].

Our findings on PRISM2 score offered good discriminative power with the area under the ROC curve being 0.73 (95% CI, [0.638–0.822]) which comes in alignment with other studies that mentioned the ROC curve analysis of PRISM (0.78, 0.90, 0.87, 0.86, 0.95) as mentioned by (Qureshi et al. 2007, Pollack et al. 2016, Martha et al. 2005, Verma et al. 2017, and Choi et al 2005, respectively) [17–21]. Also there was a significant correlation between PELOD2 score and PIM2 score with (0.84, 95% CI, [0.767–0.921]; and 0.78, 95% CI, [0.691–0.86] respectively, $p < 0.001$). So overall these three scores rendered good discriminative relation between survivors and non-survivors and further it may be used as a tool for prognostic evaluation beside their use in assessing the risk of mortality.

4.1 Limitations and Recommendations:

This study had several limitation. It was a single-center study with a small number of participants in each group. Also we couldn't perform repeated serum albumin so we can assign the incidence of hypoalbuminemia in whole study duration. We recommend further high number of participants and multi-center studies to be approached, so we can conclude a better evaluation of such disease. We also recommend prospective studies and randomized controlled trials to be performed not retrospective, so we can get the highest possible accuracy.

5. Conclusion

There is a strong relation between hypoalbuminemia in PICU and high mortality and morbidity rates as patients with hypoalbuminemia tend to have bad adverse outcomes and hence giving that high mortality rates.

Declarations

Ethics approval and consent to participate: The study was approved by the Ethical committee of Menofia Hospital. A written consent of participation was obtained from guardians after discussing the measures of the study and its importance. All Methods of the study were performed in accordance with Menofia Hospital guidelines and their regulations.

Consent for publication: Not applicable.

Availability of data and materials: • All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Figures

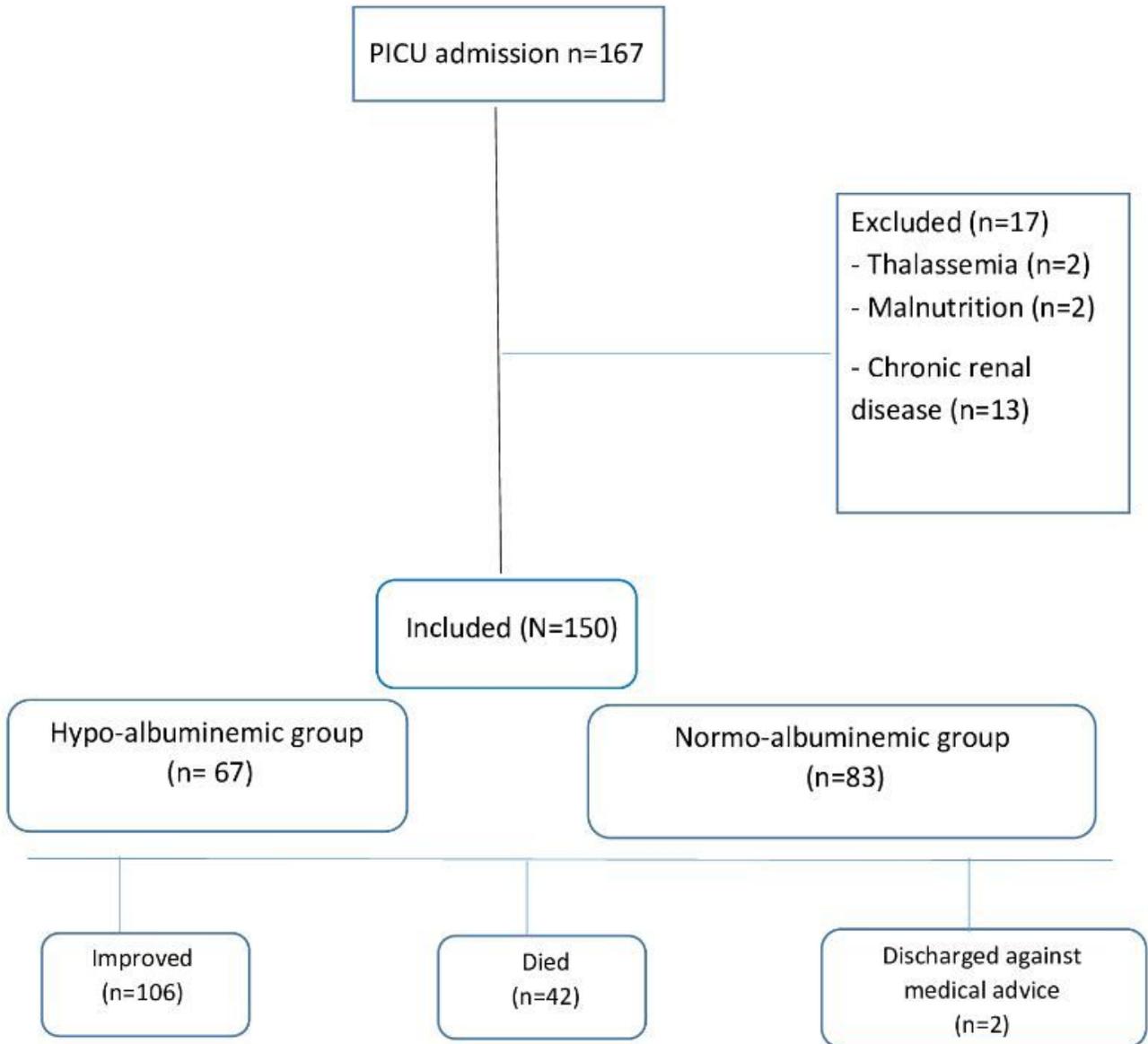


Figure 1

Temporal Profile of subject admitted to Pediatric intensive care unit

Supplementary Files

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