

Pediatric Hypoprotienemia and its Implications on Surgical Outcome, Vital Organs Function and Immunity after Cancer Surgeries

Wegdan A. Ali MD¹, Al Shima Ismael Roushdy¹, Alaa Ali M. Elzohry MD^{2*}

¹Department of Anesthesia and ICU, Faculty of Medicine, Minia University, Egypt.

²Department of Anesthesia, ICU and Pain Relief, South Egypt Cancer Institute, Assiut University.
alaa.zohiry@hotmail.com

***Corresponding Author:** Alaa Ali M. Elzohry, MD., Department of Anesthesia, ICU and Pain Relief, South Egypt Cancer Institute, Assiut University, Arab Republic of Egypt.

Abstract

Background: Hypoprotienemia is associated with poor outcomes in adult critical illness, but whether this association exists in pediatric patients remains unclear. There is a paucity of data evaluating serum albumin level on admission as a predictor of outcome in critically ill children.

Objectives: To determine or to investigate the effect of hypoprotienemia in surgical outcome, vital organs function and immunity in patients undergoing major cancer surgery.

Study Design: A Randomized double-blinded trial.

Setting: Academic medical center.

Methods: Forty pediatric patients underwent elective oncological surgery were divided into two groups. Group I: serum albumin >35 g/L and Group II: serum albumin ≤ 35 g/L. Preoperative level of IL1, total lymphocytic count and neutrophilic count were determined. patients were monitored daily for major postoperative complications, including, renal failure, heart failure, respiratory failure, pneumonia/respiratory tract infection, major thromboembolic event, wound infection / dehiscence, anastamotic leak and fistula formation.

SOFA score was recorded on the day of admission to the ICU and every 48 hours until discharge. The length of stay in the ICU was measured from admission to the ICU until discharge. Complete blood picture liver function, interleukin IL6 and kidney function were done on first, third, fifth and seventh postoperative day.

Results: Postoperative complications were more frequent in group II compared to group I. Also, the length of ICU stay was proved to be significantly longer in group II (10.60 ± 3.59 days) compared to group I (7.95 ± 0.69 days) (P = 0.002**). Serum IL6 levels were significantly higher in group II compared to group I on first, third and seventh postoperative days (P = 0.001**). There was no statistically significant difference between two groups in Total lymphocytic count in all follow up days and statistically significant increase in neutrophilic count on group II compared to group I on first, third and seventh postoperative days. Finally there was a statistically significant increase in SOFA score in group II compared to group I in all follow up days.

Limitations: This study is limited by its small sample size.

Conclusion: Hypoprotienemia increases the risk of postoperative complications and impaired vital organs dysfunction leading to prolongation of ICU stay in ICU after pediatric cancer surgery.

Keywords: Hypoprotienemia; ICU; pediatric cancer surgery; SOFA score.

INTRODUCTION AND AIM OF THE WORK

Albumin is the most abundant protein in blood plasma, usually constituting up to two-thirds of total plasma protein.¹ It contributes about 80% of the plasma colloid osmotic pressure and is responsible for the transport and binding of many molecules. Albumin is highly water soluble and resides in the extracellular space, with one third in the intravascular space and two thirds in the extra-vascular space. The prevalence of hypoalbuminemia in pediatric surgical cancer patients is high, ranging reaching up to 35%. (1-4)

Hypoalbuminemia is associated with poor outcomes in adult critical illness, but whether this association exists in pediatric patients remains unclear. There is a paucity of data evaluating serum albumin level on admission as a predictor of outcome in critically ill children. (5-6)

The correct assessment of the nutritional status of such patients is crucial since malnourishment is a risk factor for morbidity and mortality (7). Hypoalbuminemia (serum albumin less than 3.5 g/dL) often reflects malnourishment (8). Malnourished pediatric patients have a higher risk of mortality; complications and prolonged hospital stay.

Malnutrition also impairs cell mediated immunity and resistance to infection. In hypoalbuminemia, alteration in cytokine metabolism especially impairs interleukin-1 activity and defects in the complement system have also been detected. Therefore, in the hypoalbuminemic group, surgical site infections and remote infections such as pneumonia were commonly found. (9-10)

The aim of this work was to evaluate the implication of hypoproteinemia on outcome, vital organ function and immune function in pediatric patients undergoing cancer surgery.

PATIENTS AND METHODS

This is a prospective observational study that was carried out in the South Egypt Cancer Institute, Assiut University, Assiut, Egypt. After Hospital Ethics Committee approval and written informed consent from parents, 40 pediatric patients underwent elective cancer surgery (abdominal operations) were included in the study. Preoperative serum albumin was measured and these patients were divided according to their serum albumin level into two groups. Group I: with serum albumin >35 g/L and Group II: with serum albumin ≤ 35 g/L.

Patients with preoperative mechanical bowel preparation, previous intra-abdominal surgery, recurrent tumor, liver cirrhosis or jaundice, patients undergoing laparoscopic surgery, and acute complicated conditions such as colonic obstruction or perforation were excluded from the study.

Preoperative level of IL6, total lymphocytic count and neutrophilic count were determined.

Parameters Assessed

After surgery, all patients were monitored daily for postoperative complications, including: renal failure, heart failure, respiratory failure, pneumonia/ respiratory tract infection, major thromboembolic event, wound infection / dehiscence, anastomotic leak and fistula formation.

Pneumonia was documented by positive sputum culture, or clinical and radiographic evidence of consolidation. The presence of a wound infection was defined by culture and operative or spontaneous drainage of purulent materials. A wound dehiscence is diagnosed when operative re-closure of the wound is required. Acute kidney injury (AKI) was defined as a 50% or 0.3 mg/dL increase in plasma creatinine above baseline level.

The presence of organ dysfunction was assessed using the sequential organ failure assessment (SOFA) score recorded on the day of admission to the ICU and every 48 hours until discharge. The data required to calculate SOFA score included PaO₂ and FIO₂ (to calculate PaO₂/FIO₂ ratio), platelet count, bilirubin concentration, mean arterial pressure and need for vasoactive drugs, Glasgow Coma Scale score, creatinine concentration, and urine output. In the calculation of the score the worst values of each parameter in the 24 hour period were used. The length of stay in the ICU was measured as the number of days from admission to the ICU until discharge from the ICU.

Laboratory Investigations

Complete blood picture, liver and renal function tests were done on first, third, fifth and seventh postoperative day.

Serum IL-6 was measured by EVOLIS fully automated ELISA processor which is manufactured by Bio- Rad, using enzyme linked immunosorbent assay (Human IL-1b ELISA KIT, AVIBION). The lower detection limits for these kits is 10 pg/ml.

Pediatric Hypoproteinemia and its Implications on Surgical Outcome, Vital Organs Function and Immunity after Cancer Surgeries

Statistical Analysis

A data entry file, using EXCEL® 2019 program, was prepared. Data were processed and analyzed using SPSS® ver.21. The frequencies, percentages, mean and standard deviation were computed. Mann-Whitney test was used to compare quantitative data between the two groups. Wilcoxon Signed Rank test was used to compare quantitative data between each time and the preoperative level in the same group. Chi-square test was used to compare qualitative data between the two groups. P-value of < 0.05 was considered as significant.

RESULTS

Regarding demographic data, there were no statistically significant differences between the two groups in age, sex, weight and height (P>0.05) (Table 1). Postoperative complications were higher in number and percentage in group II compared to group I. In group I, there were 2 patients (10%) had pneumonia/ respiratory tract infection, one patient (5%) had respiratory failure; one patient (5%) had renal failure and one patient (5%) had wound infection/ dehiscence. In group II, there were 7 patients (35%) had pneumonia/ respiratory tract infection, 1 patient (5%) had heart failure, 2 patients (10%) had renal failure, 1 patient (5%) had major thromboembolic events, 3 patients (15%) had wound infection /dehiscence, 4 patients (20%) developed fistula, 4 patients (20%) complicated by sepsis and 2 (10%) had multiple organ dysfunction syndrome.

Table 1. Patient's demographic data

	Group I (n= 20)	Group II (n= 20)	P-value
Age (year):			0.386
Mean ± SD	4.35 ± 2.31	5.45 ± 4.08	
Range	1.5 - 8.0	1.0 - 9.0	
Sex: No. (%)			0.749
Male	9 (45.0%)	8 (40.0%)	
Female	11 (55.0%)	12 (60.0%)	
Weight (kg):			0.058
Mean ± SD	9.60 ± 14.01	10.80 ± 5.73	
Range	7.0 – 95.0	6.5 – 70.0	
PO serum albumin(mg/dl)			0.000*
Mean ± SD	39.45 ± 2.87	30.66 ± 3.99	
Range	35.0 – 45.0	22.0 – 35.0	

Data were expressed by mean ±SD, range, number and percentage

PO preoperative

P-value comparison between groups (t- test)

* Statistically significant difference

Table 2. Postoperative complications in group I and II

Complications	Group I (n= 20)		Group II (n= 20)		P- value
	No.	%	No.	%	
Respiratory tract infection	2	10.0	7	35.0	0.130
Respiratory failure	1	5.0	7	35.0	0.048*
Renal failure	1	5.0	2	10.0	1.000
Major thromboembolic events	0	0.0	1	5.0	1.000
Wound infection/ dehiscence	1	5.0	3	15.0	0.598
Fistulas	0	0.0	4	20.0	0.114
Sepsis	0	0.0	4	20.0	0.114
MODS	0	0.0	2	10.0	0.468

Data were expressed by number and percentage

P-value comparison between groups (Chi-square test)

* Statistically significant difference

MODS= Multiple organ dysfunction syndrome

Table 3. Length of ICU stay in the study groups (in days)

	Group I (n= 20)	Group II (n= 20)	P-value
Mean ± SD	7.95 ± 0.69	10.60 ± 3.59	0.002*
Range	5.0 - 8.0	7.0 - 20.0	

Data were expressed by mean ±SD and range

P-value comparison between groups (t-test)

* Statistically significant difference

Regarding serum level of IL6, there was a significant increase in serum IL6 levels in group II compared to group I on first, third and seventh postoperative days. On first day after surgery, serum IL6 levels had a mean

Pediatric Hypoprotienemia and its Implications on Surgical Outcome, Vital Organs Function and Immunity after Cancer Surgeries

of 2.20 ± 4.10 pg/ml in group II compared to 0.90 ± 1.86 in group I ($p=0.001$), on third day it had a mean of 3.15 ± 4.11 in group II and 0.93 ± 1.75 in group I ($p=0.000$) and on seventh postoperative day had a mean of 5.16 ± 4.48 in group II while 0.42 ± 0.73 in group I ($p=0.000$).

When comparing group I (serum albumin > 35 g/L) and group II (serum albumin ≤ 35 g/L) there were a statistically significant increase in SOFA score in

group II compared to group I in all follow up days. On first postoperative day SOFA score had a mean of 1.50 ± 1.43 in group II compared to 0.40 ± 0.82 in group I ($p=0.009$), on third postoperative day had a mean of 1.90 ± 1.59 in group II and 0.40 ± 0.75 in group I ($p=0.001$), on the fifth postoperative day it had a mean of 2.25 ± 2.45 in group II and a mean of 0.30 ± 0.92 in group I ($p=0.000$) and on seventh postoperative day had a mean of 2.70 ± 3.33 in group II while 0.30 ± 1.13 in group I ($p=0.001$). (figure 2).

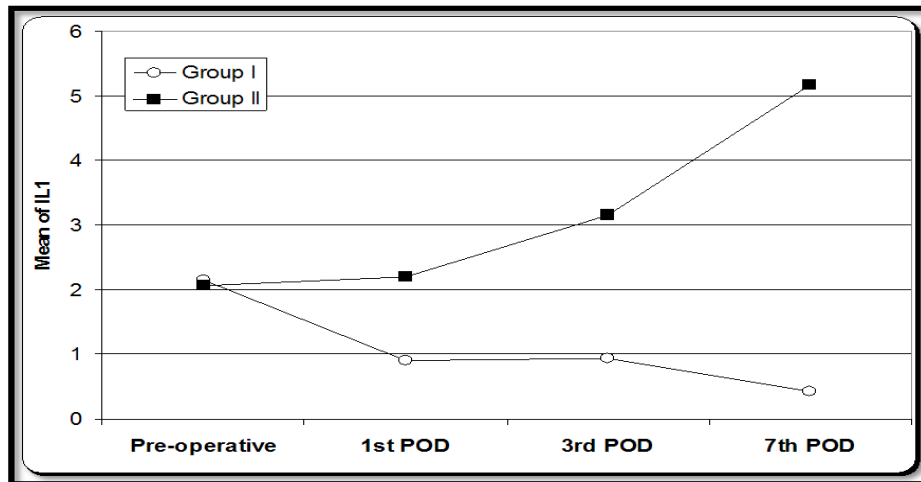


Figure 1. IL6 (pg/ml) level in group I and II in follow up days

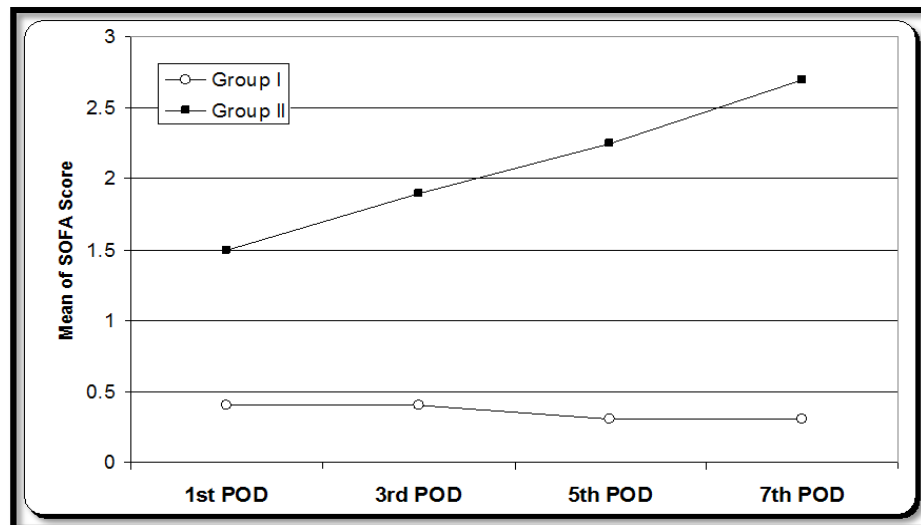


Figure 2. SOFA Score in group I and group II in follow up days

DISCUSSION

Hypoprotienemia is not an infrequent event in the critically ill child. Not every Patients admitted to our PICU do not undergo a comprehensive metabolic profile or albumin level determination; therefore, the true incidence of hypoalbuminemia in our population

is not known. There is a paucity of data in this regard. In the only other comparable study, Durward et al found a hypoalbuminemia incidence of 56.7%. Whatever the cause of low albumin levels, the decreased plasma colloid osmotic pressure compromises the intravascular volume, placing the child at risk for inadequate blood flow to vital organs. (12)

Pediatric Hypoproteinemia and its Implications on Surgical Outcome, Vital Organs Function and Immunity after Cancer Surgeries

The current study showed an association between preoperative hypoalbuminemia and increased incidence of postoperative complications. Also, using SOFA score as a tool for assessing the degree of organ dysfunction, preoperative hypoalbuminemia was associated with statistically significant higher scores in all follow up days.

Many studies found that hypoalbuminemia was a significant marker of morbidity and mortality in critically ill children. Additional pediatric studies are needed to confirm this, although the adult literature is in agreement. Replacement is very likely to be beneficial in some circumstance (eg, for septic shock) and not of value (for burns) or detrimental (eg, for head trauma) in others. (13-15)

In our study the increase in postoperative complications in group II compared to group I and the significant increase in the length of ICU stay ($p=0.002$) were in agreement with, Lohsiriwat et al. 2007 who demonstrated a higher rate of overall postoperative complications and a longer hospital stay associated with hypoalbuminaemia. (16)

Chandrasinghe et al. 2013, showed a significant association between a low preoperative serum albumin of less than 35 g/L, with a reduction in overall survival for patients undergoing surgery for rectal cancer. They concluded that albumin can be used as a cost effective and a sensitive marker to predict survival in rectal cancer compared to other available inflammatory markers. (17)

According to Campos et al., 2008, several factors affect post-surgical wound healing such as protein malnutrition that can adversely affect wound healing. Collagen is the most abundant protein in human body and provides strength, integrity and structure. Besides protein, wound healing is stimulated by an adequate amount of energy, vitamins A, C, E and B complex, zinc, copper, and selenium. Malnutrition influence in wound healing quality and duration and serum effects proteins, such as albumin, are important to this process. (18)

The mechanism of increased postoperative complications in hypoalbuminemic group can be the fact that hypoalbuminaemia is associated with poor tissue healing, decreased collagen synthesis in surgical wounds or at anastomoses, and impairment

of immune responses, such as macrophage activation and granuloma formation (19). Therefore, wound infection, remote infections such as pneumonia, and anastomotic leakage are commonly observed in hypoalbuminaemic patients (20).

This result was in agreement with a study conducted by **Kanda et al., 2011** and they reported that preoperative total lymphocyte count, haemoglobin and platelet count did not reflect patient outcome in their study. (21)

In addition to a more recent study conducted by **Thieme et al., 2013** to investigate methods of evaluation of the nutritional status that better correlate with postoperative complications and the length of hospital stay in patients submitted to gastrointestinal or abdominal wall surgeries. They reported that the immunologic status, analysed by total lymphocytes count was not correlated to postoperative outcomes, suggesting that this is not an adequate parameter to predict postoperative complications. (22)

Currently, available outcome prediction models such as the Sequential Organ Failure Assessment (SOFA) score reflects changing organ physiology with continuing intensive therapy have been used to predict the outcomes of critical illness (23).

The SOFA score has been validated for a number of different critical illnesses and is known to have good correlation with patient outcome. There have been few reported prognostic indicators in patients with cancer admitted to the ICU (24).

A meta-analysis was performed of observational clinical studies evaluating the relationship between serum albumin level and occurrence of acute kidney injury. This meta-analysis provided an evidence that hypoalbuminemia is a significant independent predictor of both acute kidney injury and of death following of acute kidney injury development (25).

In hypoalbuminemic patients, acute renal failure commonly occurred in postoperative period especially associated with massive blood loss. Serum albumin is responsible for 75–80% of the plasma colloid osmotic pressure (COP). Albumin is thus the major determinant of the plasma COP component of Starling's equation for fluid flux across the capillary wall (26). Inadequate fluid replacement and low plasma COP lead to insufficient intravascular volume and poor splanchnic

Pediatric Hypoproteinemia and its Implications on Surgical Outcome, Vital Organs Function and Immunity after Cancer Surgeries

blood supply. Many investigations, however, do not support the correction of albumin as useful, either on the basis of plasma COP changes or on outcome (27).

CONCLUSION

Hypoproteinemia increases the risk of postoperative complications and impaired vital organ function leading to prolongation of length of stay in ICU after pediatric cancer surgery.

Study Limitations

They were lack of follow-up patients after discharge from ICU and from hospital as some postoperative complications might manifest later after discharge and these data were not evaluated. Also, small number of patients studied in a single institution, limiting the generalization of the conclusion.

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Pediatric Hypoproteinemia and its Implications on Surgical Outcome, Vital Organs Function and Immunity after Cancer Surgeries

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