



Implication of Hypoalbuminemia in Early Postoperative Complications

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Abstract

Background: Serum albumin is a marker of nutrition and inflammation. Currently, hypoalbuminemia is used as a marker of inflammation and a predictor of outcome in post-surgical patients. It is associated with increased morbidity and mortality in patients having surgery for cancer disease.

Objectives: to evaluate the implication of hypoalbuminemia on early postoperative complications in major cancer surgery.

Methods: 40 patients undergoing elective major cancer surgery were included in the study. 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. Major postoperative complications and length of stay in ICU (Intensive care unit) were documented.

Results: Postoperative complications were higher in number and percentage in group II (serum albumin ≤ 35 g/L) compared to group I (serum albumin > 35 g/L). Furthermore, the length of ICU was significantly longer in group II (serum albumin ≤ 35 g/L) (9.60±3.59 days) compared to group I (serum albumin > 35 g/L) (6.95±0.69 days) (P= 0.002).

Conclusion: The current study revealed that preoperative hypoalbuminemia increases the risk of postoperative complications and length of stay in ICU after major cancer surgery, as such, accounts for high proportion of ICU budget.

Introduction

The prevalence of protein-energy malnutrition in surgical patients is high, ranging from 10% to 54%. The correct assessment of the nutritional status of such patients is crucial since malnourishment is a risk factor for morbidity and mortality [1]. The identification of patients with a high surgical risk is essential in the operative indications and decisions, often limited by the potential morbidities and mortality related to the procedure. Hence, the clinical and laboratory parameters which may point out higher risk for postoperative complications are important [2]. Malnourishment is reported in 40% to 50% of hospitalized patients, with higher risk factor for postoperative infections and healing complications in patients who undergo major surgeries [3]. Hypoalbuminemia (serum albumin less than 3.5 g/dL) often reflects malnourishment [4].

Malnutrition also impairs cell mediated immunity and resistance to infection [5]. 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 [6]. Hypoalbuminemia is one of the risk factors for anastomotic dehiscence in colorectal surgery and healing remains a process depending more on the patient than on any aspect of the surgical technique [7]. Although extreme hypoalbuminemia by itself was associated with increased ICU (Intensive care unit) and postoperative stay, complications were the greatest predictor of resource use such as postoperative stay, ICU stay, and NPO (Nil per Os) days [8]. Sepsis, need for vasopressors and need for mechanical ventilation was observed more frequently in patients with serum albumin concentrations <20 g/L, suggesting that low albumin levels may increase the incidence of organ dysfunction and infections in critically ill patients with cancer [9].

The aim of this work is to evaluate the implication of hypoalbuminemia in early postoperative complications.

Patients and Methods

This is a prospective observational study that was carried out in the Intensive Care Unit of South Egypt Cancer Institute (SECI-ICU), Assiut University, Assiut, Egypt. After Institutional Ethics Committee approval and written informed consent, 40 patients underwent elective major oncological surgery 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.

Inclusion criteria: All cancer patients undergoing elective major cancer surgery and requiring ICU admission > 24 hours were evaluated.

Exclusion criteria: Patients with ICU stay of <24 hours, no preoperative mechanical bowel preparation, previous intra-abdominal surgery, recurrent tumor, liver cirrhosis or jaundice; patients undergoing laparoscopic surgery; patients undergoing palliative tumor resection or adjacent organ resection and acute complicated conditions such as colonic obstruction or perforation were excluded from the study

All the patients provided routine perioperative care with antibiotic prophylaxis, multimodal analgesia, DVT prophylaxis and early mobilization.

After surgery, patients were monitored daily for major postoperative complications, including, Acute Respiratory Distress Syndrome (ARDS), sepsis, multiorgan dysfunction syndrome (MODS), renal failure, heart failure, respiratory failure, pneumonia/respiratory tract infection, major thromboembolic event, wound infection / dehiscence, anastomotic leak, fistula formation, and in-hospital mortality cause of death were documented. Furthermore, the length of stay in the ICU was measured as the number of days from admission up till discharge from the ICU.

Rigid objective criteria were established defining each complication to avoid subjective bias. Fistulae were radiographically documented. Pneumonia was documented by positive sputum culture of clear 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. Respiratory failure was defined as the requirement of mechanical ventilation beyond 24 h. after surgery. Circulatory insufficiency when unstable blood pressure requiring extra fluid or cardiac stimulant. ARDS was diagnosed as by recent Berlin definition of ARDS by

The ARDS Definition Task Force [10]. The details of this definition are shown in Appendix A. Presence of sepsis was diagnosed according to the criteria of American College of Chest Physicians / Society of Critical Care Medicine (ACCP/ SCCM) [11], which can be found in Appendix B.

Statistical analysis

A data entry file, using EXCEL® 2007 program, was detected. Data were processed and analyzed using SPSS® ver.19. The frequencies, percentages, mean and standard deviation were computed. t- test was used to compare quantitative data between the two groups. Chi-square test was used to compare qualitative data between the two groups. P-value of < 0.05 was considered as significant.

Results

There were no significant differences between the two groups in demographic data as regards age, sex, weight and height ($P>0.05$) (Table 1). The diagnosis and type of surgeries included in the study is shown in Table 2. Postoperative complications and in hospital mortality 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, 7 patient (35%) had respiratory failure, 2 patient had acute respiratory distress syndrome (10%), 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. There were 3 patients died postoperatively in hospital, 2 of them died from MODS and one patient died from sepsis (Table 3). Also, when comparing the two groups the increase in the length of stay was proved to be statistically significant in group II (9.60 ± 3.59 days) compared to group I (6.95 ± 0.69 days) ($P = 0.002$) (Table 4).

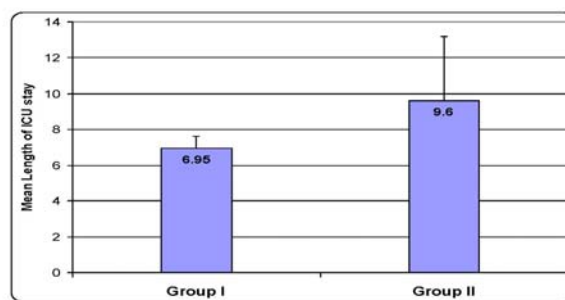


Figure (1): Length of stay in ICU/ day

Table (1): Patient's Personal characteristics

	Group I	Group II	P-value
	serum albumin > 35 g/L. (n= 20)	serum albumin ≤ 35 g/L. (n= 20)	
Age (year):			
Mean ± SD	53.35 ± 12.31	58.45 ± 9.08	0.386
Range	27.0 - 70.0	45.0 - 75.0	
Sex: No. (%)			
Male	9 (45.0%)	8 (40.0%)	0.749
Female	11 (55.0%)	12 (60.0%)	
Weight (kg):			
Mean ± SD	64.60 ± 14.01	56.80 ± 5.73	0.058
Range	40.0 – 95.0	50.0 – 70.0	
Height (cm):			
Mean ± SD	166.95 ± 8.33	162.60 ± 6.18	0.084
Range	150.0 - 180.0	150.0 - 175.0	
PO serum albumin(mg/dl)			
Mean ± SD	39.45 ± 2.87	30.66 ± 3.99	0.000*
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): The diagnosis and type of surgeries included in the study

Number of patients	Diagnosis	Surgery
7	Stomach cancer	Subtotal gastrectomy and gastrojejunostomy
6	Esophageal cancer	Total esophagectomy and gastric pullup
6	Colon cancer	3 Right hemicolectomy and 3 Left hemicolectomy
11	Rectal cancer	Anterior resection of Dixon
2	Hypopharyngeal cancer	Total pharyngolaryngectomy
6	Pancreatic cancer	Whipple operation
2	Bladder cancer	Orthotopic bladder reconstruction

Table (3): Postoperative complications in group I and II

	Group I		Group II		P- value
	serum albumin > 35 g/L.		serum albumin ≤ 35 g/L.		
	No.	%	No.	%	
Pneumonia/ respiratory tract infection	2	10.0	7	35.0	0.130
Respiratory failure	1	5.0	7	35.0	0.048*
ARDS	0	0.0	2	10.0	0.468
Heart failure	0	0.0	1	5.0	1.000
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
In-hospital mortality	0	0.0	3	15.0	0.230

Data were expressed by number and percentage

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

* Statistically significant difference

ARDS= Acute respiratory distress syndrome

MODS= Multiple organ dysfunction syndrome

Table (4): Length of stay in ICU/ day

	Group I serum albumin > 35 g/L. (n= 20)	Group II serum albumin ≤ 35 g/L. (n= 20)	P-value
Mean ± SD	6.95 ± 0.69	9.60 ± 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

Discussion

Serum albumin is a good and simple predictor of surgical risk and has a close correlation with the degree of malnutrition [4]. It has the highest positive predictive value of all the nutritional assessment methods for predicting associated complications and mortality [14].

In our study postoperative complications were higher in number and percentage in group II (serum albumin ≤ 35 g/L) compared to group I (serum albumin > 35 g/L). Also, serum albumin ≤ 35 g/L was associated with statistically significant increase in the mean length of stay in ICU (p= 0.002).

The result of our study were in agreement with, Lohsiriwat et al. [6] who demonstrated a higher rate of overall postoperative complications and a longer hospital stay associated with hypoalbuminaemia. A more recent study was conducted by Chandrasinghe et al. [15] 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.

Heys et al. [16] in the earliest available study of 481 patients with colon and rectal cancer demonstrated a significant association between preoperative serum albumin and survival in large bowel cancer. Pre-operative hypoalbuminemia is an independent risk factor for postoperative complications following rectal cancer surgery. Hypoalbuminemic patients also have a non-statistically significant tendency to delayed recovery of postoperative bowel function. Low serum albumin may be used as a simple and low-cost prognostic tool to predict the risk of adverse surgical outcomes [17].

Cheng-Chou et al. [18] conducted a study to determine the relation of preoperative malnutrition and postoperative outcomes of cancer colon patients were reported that hypoalbuminemia is an independent risk factor for postoperative mortality, morbidity, as well as complications related to wounds, lungs, urinary system, and anastomosis, but not the gastrointestinal system or other complications. They concluded that hypoalbuminemia is a predictor of poor surgical outcomes of colon cancer patients. It is also a poor prognosis factor for long-term survival of colon cancer patients after curative operation.

Malnutrition also impairs cell mediated immunity and resistance to infection [5]. 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 [6]. Roxburgh and McMillan [19] in a review looking in to role of the systemic inflammatory response (SIR) in predicting survival for patients with cancer using biochemical or haematological markers recognised hypoalbuminaemia to be significant as an inflammatory marker along with C-reactive protein (CRP), neutrophils and lymphocyte/ platelet ratio .

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 [20]. Therefore, wound infection, remote infections such as pneumonia, and anastomotic leakage are commonly observed in hypoalbuminaemic patients [21].

Our results were in agreement with an early study conducted by Gibbs et al. [22] and demonstrated that hypoalbuminemia preoperatively or pretrauma is independently associated with the development postoperative complications, especially the development of infective complications. In upper gastrointestinal cancer surgery, low preoperative serum albumin levels have significantly correlated with anastomotic leak as well as major morbidity and in-hospital mortality [23].

A more recent study by Lohsiriwat et al. [17] found that in hypoalbuminemic patients, wound infection, remote infections such as pneumonia, and anastomotic leakage, were commonly found. In a large multi-center study by Hennessey et al. [24] the authors determined hypoalbuminemia (defined as albumin level 35 g/dL) to be an independent predictor of surgical site infection in patients undergoing colorectal surgery which is applied to our work.

The mechanisms of increase in infectious etiologies in hypoalbuminemia are multifactorial and likely include impairment of tissue healing, decreased collagen synthesis and granuloma formation. The immune response in hypoalbuminemia is also compromised through impairment of macrophage activation and induction of macrophage apoptosis [5, 20]. These factors together could explain the higher risk

of surgical site infections in hypoalbuminemic patients [12]. Furthermore, more recently, Thieme et al. [13] found a significant association between low serum albumin and non-infectious complications.

Patients at nutritional risk have higher complication rates after surgery for colorectal cancer. Especially, malnutrition increases the rate of anastomotic leakage and wound infection. Malnutrition was also a significant risk factor for the length of hospital stay [25].

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 [26]. A more recent study conducted by Slivio et al. [27] concluded that sepsis, need for vasopressors and need for mechanical ventilation was observed more frequently in patients with serum albumin concentrations <20 g/L, suggesting that low albumin levels may increase the incidence of organ dysfunction and infections in critically ill patients with cancer.

Shitanshu et al. [12] concluded that albumin level below 3 g/dL help identify a high-risk surgical population. Although the causes of low albumin are multifactorial, identification of this subset of patients and aggressive optimization of nutritional status preoperatively or using alternative treatment strategies for patients who are extremely high risk for open surgery may improve surgical outcomes in this population.

Conclusion

The current study revealed that preoperative hypoalbuminemia increases the risk of postoperative complications and length of stay in ICU after major cancer surgery, as such, accounts for high proportion of ICU budget. Some limitations are present in this study, including lack of follow up of patients after discharge from ICU and from hospital and small number of patients studied in a single institution, limiting the globalization of the conclusions. We believe that the results of this study give reasons for raising attention about using serum albumin level as a simple and low-cost prognostic tool to predict the risk of adverse surgical outcome and consequently, decreasing the incidence of postoperative complications and ICU stay.

Abbreviations

ICU:	Intensive care unit
NPO:	Nil per Os
AKI:	Acute kidney injury
ARDS:	Acute respiratory distress syndrome
MODS:	Multiple organ dysfunction syndrome
DVT:	Deep venous thrombosis
SIR:	Systemic inflammatory response
CRP:	C-reactive protein
ACCP/ SCCM:	American College of Chest Physicians / Society of Critical Care Medicine

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Appendix A:

Berlin definition of acute respiratory distress syndrome (The ARDS Definition Task Force, 2012)

The Berlin definition of acute respiratory distress syndrome	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging	Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (eg., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation	
Mild	200 mmHg < PaO ₂ /FIO ₂ ≤300 mmHg with PEEP or CPAP ≥5 cmH ₂ O
Moderate	100 mmHg < PaO ₂ /FIO ₂ ≤200 mmHg with PEEP ≥5 cmH ₂ O
Severe	PaO ₂ /FIO ₂ ≤100 mmHg with PEEP ≥5 cmH ₂ O

Abbreviations: CPAP, continuous positive airway pressure; FIO₂, fraction of inspired oxygen; PaO₂, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; a- Chest radiograph or computed tomography scan; b-If altitude is higher than 1,000 m, the correction factor should be calculated as follows: [PaO₂/FIO₂ (barometric pressure/760)]; c-This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Appendix B:

The criteria of Members of American College of Chest Physicians / Society of Critical Care Medicine (ACCP/ SCCM), 1992 include 2 or more of the following:

- Core Temperature ≥=38°C or ≤= 36°C.
- Heart Rate ≥=90bpm.
- Respiratory Rate ≥=20bpm or PaCO₂ ≤=32mmHg.