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Effect of preoperative hypoalbuminemia on postoperative mortality and morbidity in liver transplant surgery

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ABSTRACT

Aim: In this study, it isaimed to retrospectively evaluatethe effect of serum albumin levels on postoperative mortality and morbidity in patients with end-stage liver failure with hypoalbuminemia who underwent follow-up liver transplant surgery.

Material and Method: After the approval of the ethics committee, the patients who underwent liver transplant surgery between April 2011 and September 2016 were divided into two groups as with preoperative albumin values <3.5 g/dl and ≥3.5 g/dl. Demographic characteristics of the patients, preoperative and postoperative arterial blood gases, posteroanterior chest radiographs, tracheal aspirate cultures, preoperative and postoperative serum creatinine levels, mechanical ventilation and intensive care unit length of stay, transfusion of blood and blood products, and early postoperative complications (30 days) were determined and compared retrospectively.

Result: It was observed that mechanical ventilation, intensive care hospitalization and discharge times were higher in the group with low albumin levels ($p<0.05$). More blood and blood products were used in the group with low albumin levels ($p<0.05$). Postoperative pulmonary complications and acute kidney injury were more common in the group with low albumin levels ($p<0.05$). Complications in the early postoperative period were more common in the group with low albumin levels.

Conclusion: As a result, it isconcluded that the preoperative serum albumin level can be used as a guide and a valuable parameter in the postoperative follow-up in the detection of perioperative and postoperative complications in liver transplant recipients.

Keywords: Hypoalbuminemia, liver transplantation, mortality, morbidity

INTRODUCTION

Hypoalbuminemia is a picture encountered in many acute or chronic clinical conditions. In 20% of hospitalizations, patients are hypoalbuminemia. Low albumin levels are accepted as an indicator of poor prognosis. However, it has been shown that preoperative hypoalbuminemia is a strong indicator of mortality and morbidity in the early postoperative period in patients undergoing cardiac surgery, gastrointestinal surgery, orthopedic surgery, sepsis and major infections (1).

Albumin is a plasma protein responsible for most of the plasma oncotic pressure and is also a negative acute phase reactant. Albumin levels are an informative parameter for the general condition of the patient, both as an acute phase reactant and as an indirect indicator of the patient's metabolic status and organ functions (such as liver). Patients with liver failure are frequently found to have low plasma albumin. It is characterized by impaired hepatocellular functions and a decrease in albumin synthesis up to 60-80% in advanced stages of cirrhosis (2). Albumin has found its place as a prognostic marker in various diseases. Albumin levels are frequently used for estimating the clinical course and survival of patients, since it is a relatively cheaper and accessible test compared to special tests, which are checked in routine biochemical tests.

Based on these effects of albumin, the present study was arrangedwith the hypothesis that serum albumin level may play a role in predicting postoperative morbidity and mortality in patients with end-stage chronic liver disease who are scheduled for liver transplantation with hypoalbuminemia.

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MATERIAL AND METHOD

The study was initiated with the approval of the Uludağ University Medical Faculty Clinical Researches Ethics Committee (Date: 2017, Decision No: 4/37). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was conducted by retrospectively scanning the files of liver transplant recipients who were performed at Uludağ University Faculty of Medicine between April 2011 and September 2016. The obtained 136 files were examined. Patients over the age of 18, who underwent liver transplantation were included intothis study, while patients who were hospitalized in the intensive care unit in the preoperative period, patients under the age of 18 and those who died in the first 24 hours postoperatively were excluded. In this context, 9 patient files were excluded from the study, since 3 patients were under the age of 18, 4 patients were operated under preoperative intensive care treatment and 2 patients died within 24 hours postoperatively.

Age, gender and MELD (Model For End-stage Liver Disease) scores of the patients were recorded in order to determine the differences between the study groups of the patients' demographic characteristics and the severity of their current disease.

In order to determine the effects of serum albumin level on postoperative mortality and morbidity, 127 screened patient files were divided into two groups according to their preoperative serum albumin level.

Group I: patients with preoperative serum albumin level below 3.5 g/dL

Group II: patients with preoperative serum albumin level of 3.5gr/dL and above

In order to compare the respiratory functions and postoperative respiratory complications, posteroanterior (PA) chest X-ray and tracheal aspirate cultures were evaluated on postoperative day 1, and mechanical ventilation times were recorded.

Preoperative, postoperative 1st day and postoperative 2nd day creatinine levels of the patients were also recorded and the creatinine increase between the groups and acute kidney injury rates were tried to be compared by using the AKIN (Acute Kidney Injury Network) classification. (**Table 1**)

In addition, numbers of erythrocyte suspension, fresh frozen plasma and thrombocyte suspension transfused in the perioperativeperiod,the duration of intensive care unit stay and the period from the end of the operation to the discharge were documented.

Table 1. Classification of acute kidney injury AKIN

Stage	Serum creatinine	Urine output
1	0.3 mg/dl or 1.5-2 times increase in serum creatinine compared to baseline	<0.5 ml/kg per hour for 6 hours
2	2-3 times increase in serum creatinine compared to baseline	<0.5 ml/kg per hour for 12 hours
3	3-fold increase in serum creatinine compared to baseline or 0.5 mg/dl increase in creatinine with serum creatinine ≥4 mg/dl	12 hour anuria or <0.3 ml/kg/hour for 24 hours or renal replacement therapy

When the clinical course and epicrisis of the patients were examined, a table was created from the complications observed in the postoperative 30 days that would prolong the most common mortality, morbidity and hospital stay, and the complications observed in the clinical course of the patients were recorded.

Statistical Analysis

In thisstudy, mean, standard deviation, median, lowest, highest, frequency and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured viaKolmogorov-Smirnov test. The Mann-Whitney U test was used for the analysis of quantitative independent data. Wilcoxon test was used for the analysis of dependent quantitative data. Fischer test was used when Chi-square test was not provided qualitative independent datain the analysis. The value of $p<0.05$ was considered statistically significant. The SPSS 22.0 softwarewas used forthe analysis.

RESULTS

Of 136 patient scheculed for liver transplantation, 127 were included (**Figure 1**). In the study, 127 patients in which 80 male (63%) and 47 female (37%) were scanned. As a result, statistically no significant differences were observed between the demographic characteristics and MELD scores of the patient groups (**Table 2**).

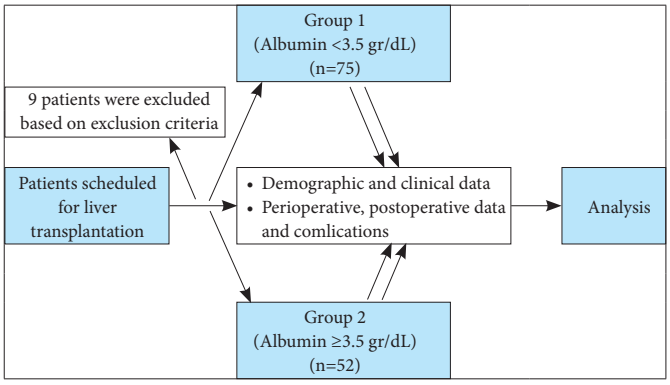

Figure 1. Flow diagram of study

The patients' postoperative mechanical ventilation times (weaning), intensive care unit stay, and time to discharge were compared, it was found that the durations were longer in the group with low albumin levels (**Table 2**).

Table 2. Demographic and clinical characteristics

	Group I		Group II		p
	Mean±SD /n-%	Median	Mean±SD /n-%	Median	
Demographic characteristics and MELD scores					
Age	54.2±12.0	57.0	53.3±13.0	57.0	0.693
Gender					
Male	49-65.3%		31–59.6%		0.512
Female	26-34.7%		21–40.4%		
MELD Skoru	21.1±4.6	20.0	20.7± 4.7	20.0	0.486
MV, ICU and Hospital stay					
MV duration (day)	2.3±1.4	2.0	1.2±0.4	1.0	0.000
ICU duration (day)	6.1±3.4	5.0	3.3±1.1	3.0	0.000
Length of hospital stay (day)	15.0±5.6	13.0	10.1±3.1	9.5	0.000
Use of blood and blood products					
ES	6.5±3.9	5.0	3.8±1.8	3.5	0.000
FFP	8.5±5.0	7.0	5.7±2.2	5.0	0.000
PS	2.1±1.3	2.0	2.1±1.3	2.0	0.936
Postoperative pulmonary complications					
Pleural effusion	50–66.7%		8–15.4%		0.000
Atelectasis	33–44.0%		2–3.8%		0.000
Pneumonia	23–30.7		2–3.8%		0.000
Creatinine levels					
Preoperative	0.78±0.26	0.7	0.73±0.23	0.7	0.279
Postoperative 1st day	1.03±0.49	0.9	0.74±0.28	0.7	0.000
Postoperative 2nd day	1.3±0.58	1.2	0.78±0.41	0.7	0.000
Acute Kidney Injury					
Stage I	29–38.7%		1–1.9%		0.000
Stage II	15–20%		2–3.8%		0.000
Stage III	5–6.7%		0–0.0%		0.000

MELD: Model for end-stage liver disease, MV: Mechanical ventilation, ICU: Intensive care unit ES: Erythroid suspension, FFP: Fresh frozen plasma, PS: Platelet suspension

In case of the blood and blood products used during operation in the patient groups, it was observed that the use of erythrocyte suspension and fresh frozen plasma was higher in the group with low albumin levels, and this difference was statistically significant too. Furthermore, there was no significant difference between the groups in the use of platelet suspension (**Table 2**).

The postoperative pulmonary complications were compared by examining the postoperative pulmonary radiographs and tracheal aspirate cultures of the patients, it was observed that the development of pleural effusion, atelectasis and pneumonia was significantly higher in patients with low serum albumin levels (**Table 2**).

The increase between the preoperative and postoperative creatinine levels of the patients werecompared. Consequently, a significant difference was observed between the groups (**Table 2**).

When the serum creatinine levels of the patients on the 1st and 2nd postoperative days were evaluated and acute kidney injuries were compared using the AKIN classification, it was observed that the development of stage I and stage II acute kidney injury was significantly higher in patients with low serum albumin levels (**Table 2**).

When the complications occuredin the early postoperative first 30 days of the patients were compared, it was observed that sepsis, acute kidney failure, unsuccessful weaning, bleeding-transfusion requirement, pneumonia, pulmonary edema, urinary tract infection, retransplantation and exitus development were significantly higher in patients with low serum albumin levels (**Table 3**).

Table 3. Early postoperative complications

	Grup I		Grup II		p
	n	%	n	%	
sepsis	21	28%	1	1.9%	0.000
Acute Renal Failure	30	40%	3	5.8%	0.000
Pneumonia	23	30.7%	2	3.8%	0.000
Bleeding / Transfusion	20	26.7%	2	3.8%	0.001
Failed weaning	11	14.7%	0	0%	0.004
Reintubation	4	5.3%	0	0%	0.144
Pulmoneredema	5	6.7%	0	0%	0.057
Urinary tract infection	15	20%	0	0%	0.001
Cardiac problems	8	10.7%	1	1.9%	0.059
Retransplantation	3	4.0%	0	0%	0.269
Eksitus	4	5.3%	0	0%	0.144

DISCUSSION

The frequency of hypoalbuminemia has been shown to be 30-40% in adult critically ill patients. Acute hypoalbuminemia as a result of albumin leakage into the interstitial space has been associated with high mortality, as the degree of capillary hyperpermeability is probably related to the degree of systemic inflammatory response (3). In patients with sepsis and other inflammatory conditions, the increased vascular permeability increases the transcapillary loss of albumin, participating into the development of hypoalbuminemia (4).

Albumin level is one of the main determinants of plasma oncotic pressure as well as reflecting nutritional status and being a negative acute phase reactant. In case of hypoalbuminemia, due to low oncotic pressure, it leaks into the interstitial space and causes hypovolemia. Therefore, hypovolemia developing during surgery in a patient with hypoalbuminemia requires more blood and blood product transfusions (5).

Many mechanisms cause hypoalbuminemia in patients who are followed up with the diagnosis of end-

stage liver failure and received liver transplantation. Decreased albumin synthesis, protein leakage to the interstitial area, blood loss in the perioperative period, relocation of the protein pool, peroperative and postoperative fluid resuscitation, and postoperative immunosuppressive agents are included in the etiology of hypoalbuminemia (6).

The most common complications in the postoperative period are pulmonary complications. The only laboratory test can predict the postoperative pulmonary complications that may develop in the preoperative period is the serum albumin value. The oxidation and degradation of albumin affect bioactive lipid mediators, which play an important role in antimicrobial defense and repair. Therefore, albumin level affects the development of postoperative infection, and the level of hypoalbuminemia is considered to be correlated with the severity of infection (7). Haskins et al. (8) reported that preoperative hypoalbuminemia increased the rate of pneumonia and reintubation in the postoperative period and caused prolonged mechanical ventilation in their study on patients with colon cancer. Yang et al. (9) also found in their study that hypoalbuminemia prolongs the duration of mechanical ventilation and it is one of the markers predicting the success of weaning in patients on mechanical ventilation support. It has been determined that, patients with hypoalbuminemia in the pediatric intensive care unit have longer mechanical ventilation periods and lower discharge rates from the intensive care unit. (10) It has been reported that, preoperative hypoalbuminemia increases the dependence on mechanical ventilator in patients undergoing coronary bypass surgery. (11), In another study, it was reported that, hypoalbuminemia increased all cardiac and pulmonary complications and the rate of emergency intubation. (12)

In this study, the rate of postoperative pulmonary complications (atelectasis, pleural effusion, pneumonia) was found to be higher in the patient group with low serum albumin levels. At the same time, weaning times were found to be longer in this group too. However, no significant difference was found in arterial blood gas samples taken to evaluate the postoperative pulmonary functions. It can be explained as the reason for this is close follow-up of mechanical ventilation settings and electrolyte values and the application of rapid replacement in order to keep the monitoring parameters within physiological limits.

Acute kidney injury is one of the major complications after liver transplantation. Its frequency is variable due to the variety of tests used in patient selection, classification, and evaluation of renal function. However, the common result in the studies shows that acute kidney injury and failure are common after liver transplantation which is found to be associated with increased cost, mortality, and morbidity. Wiederman et al. in the meta-analysis study (13), it was stated that serum albumin level could be used as an independent marker in the prediction of acute kidney injury, and it was also reported that the rate of acute kidney injury increased by 134% for each 1 g/dL decrease in serum albumin level. Preoperative hypoalbuminemia has been independently associated with acute kidney injury in non-cardiac surgeries. (14) Sang et al. it was shown in a study by AKI that postoperative hypoalbuminemia is associated with AKI. (15) In this study, it was found that 48-hour creatinine levels were higher in patients in the hypoalbuminemia group and the development of acute kidney injury was higher in these patients.

In patients with end-stage liver failure, hemostasis balance is impaired in favor of coagulopathy with physiopathological changes. When major surgery such as liver transplantation is added to the existing coagulopathy, massive blood transfusion is frequently appliedfor these patients. Although the use of blood has decreased continuously with the development of surgical and anesthesia techniques, better graft preservation, preoperative anemia treatment, better intraoperative monitoring of coagulation status, and pharmacological treatment of fibrinolysis, orthotopic liver transplantation often presents with an increased need for transfusion. Although it is difficult to predict the need for transfusion, studies have shown that the preoperative albumin level can be used to predict the amount of intraoperative transfusion. Kim et al. (5) reported that, preoperative hypoalbuminemia increased peroperative erythrocyte suspension transfusion in patients who underwent radical nephrectomy. Erdost et al. (16) in his study reported that, the use of intraoperative erythrocyte suspension and fresh frozen plasma increased in patients with preoperative hypoalbuminemia who developed acute kidney injury. Similarly, studies in which hypoalbuminemia and increased transfusion rate are reported in literature. (12,17) In this study, the rate of intraoperative erythrocyte suspension and fresh frozen plasma transfusion was found to be higher in the patient group with preoperative hypoalbuminemia.

Gibbs et al. reported that a decrease below 1 g/L in serum albumin level is associated with an increase in mortality rates from 1% to 29% and morbidity rates from 10% to 65% in non-cardiac surgeries. They also reported that hypoalbuminemia is a better indicator of some types of morbidity, especially sepsis and major infections. (1)

In the study in which the results were compared according to albumin levels of 30,676 patients who had colorectal cancer surgery, in the hypoalbuminemia group 30-day mortality was 3.7%, DVT 2.7%, pneumonia 4%, sepsis 4.1%, acute renal failure 0.9%, and these values were found to be significantly higher than the normal albumin level group (17). In another study, the 30-day mortality was found to be 16.3% in the hypoalbuminemia group, and significantly higher than the normal albumin level group (4.3%) (18). In the study, in which 204819 patient data from 16 major operations were included, postoperative 30-day mortality was 3.81%, pulmonary complications 8.78%, and sepsis 8.09% in the hypoalbuminemia group (19). In this study, sepsis was 28%, pneumonia was 30.7%, and 30-day mortality was 5.3%. It was thought that the high complication rates obtained were related to the long duration of the liver transplant operation, the high need for blood and blood products, and the longer length of stay in the intensive care unit and hospital.

CONCLUSION

As a result; Albumin is the most abundant protein in the plasma and undertakes many important functions. The measurement of this protein level, which is easily accessible and cost-effective, has become one of the routine laboratory tests evaluated preoperatively. In this study, the relationship between preoperative serum albumin level and postoperative mortality and morbidity were examined, and revealed that preoperative hypoalbuminemia causes many postoperative complications and is a strong indicator of early mortality. Based on these effects, it is concluded that albumin can be used as a guide and a valuable parameter in postoperative follow-up in the detection of perioperative and postoperative complications.

The retrospective nature and the inaccessibility of some patient files are the main limitations of the study.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Uludağ University Medical Faculty Clinical Researches Ethics Committee (Date: 2017, Decision No: 4/37).

Informed Consent: Because of retrospective design of the study, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version

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