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Preoperative Low Serum Albumin Levels Increase the Requirement of Renal Replacement Therapy after Cardiac Surgery

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ABSTRACT

Background: Acute kidney injury is a common complication of cardiac surgery that increases morbidity and mortality. The aim of the present study is to analyze the association of preoperative serum albumin levels with acute kidney injury and the requirement of renal replacement therapy after isolated coronary artery bypass graft surgery (CABG).

Methods: We retrospectively reviewed the prospectively collected data of 530 adult patients who underwent isolated CABG surgery with normal renal function. The perioperative clinical data of the patients included demographic data, laboratory data, length of stay, in-hospital complications and mortality. The patient population was divided into two groups: group I patients with preoperative serum albumin levels <3.5 mg/dL; and group II pateints with preoperative serum albumin levels ≥3.5 mg/dL.

Results: There were 413 patients in group I and 117 patients in group II. Postoperative acute kidney injury (AKI) occured in 33 patients (28.2%) in group I and in 79 patients (19.1%) in group II. Renal replacement therapy was required in 17 patients (3.2%) (8 patients from group I; 9 patients from group II; P = .018). 30-day mortality occurred in 18 patients (3.4%) (10 patients from group I; 8 patients from group II; P = .037). Fourteen of these patients required renal replacement therapy. Logistic regression analysis revealing the presence of lower serum albumin levels preoperatively was shown to be associated with increased incidence of postoperative AKI (OR: 1.661; 95% CI: 1.037-2.661; P = .035). Logistic regression analysis also revealed that DM (OR: 3.325; 95% CI: 2.162-5.114; P = .000) was another independent risk factor for AKI after isolated CABG.

Conclusion: Low preoperative serum albumin levels result in severe acute kidney injury and increase the rate of renal replacement therapy and mortality after isolated CABG.

INTRODUCTION

Acute kidney injury (AKI) is a common complication after cardiac surgery and is associated with significant morbidity and mortality, as well as increased cost due to increased length of hospital stay [Lassnigg 2004; Mao 2013]. The development of AKI after cardiac surgery remains common and occurs in up to 30% of patients [Schopka 2014]. The requirement for renal replacement therapy (RRT) in patients with postoperative AKI occurs in about 2-15% of cases, and is associated with increased mortality up to 60% [Lassnigg 2004; Mangano 1998; Abel 1976]. In an effort to reduce these adverse consequences, significant increases in mortality and morbidity [Lassnigg 2004], many researches have focused on identifying prophylactic strategies as well as biomarkers for subclinical AKI after cardiac surgery [Mao 2013]. A thorough understanding of the mechanisms and risk factors underlying the development of AKI may aid in identifying useful biomarkers and designing preventative methods. Serum albumin, which is an acute phase reactant, is suggested to be associated with morbidity and mortality after various surgical procedures [Ataseven 2015; Koertzen 2013]. The purpose of this study is to analyze the association of preoperative serum albumin levels with AKI and the requirement of renal replacement therapy after coronary artery bypass graft surgery (CABG).

METHODS

Patients

After we received institutional review board approval, we retrospectively reviewed the prospectively collected data of 530 adult patients who underwent isolated CABG surgery with normal renal function (baseline serum creatinine value <1.4 mg/dL) from January 2011 to February 2015. All patients had previously granted permission for use of their medical records for research purposes. The clinical data of the patients included demographic data, laboratory data, length of hospital stay, in-hospital complications, and mortality. For the present study, the patient population was divided into two groups on the basis of preoperative serum albumin levels according to a cutoff level of 3.5 g/dL (group I: patients with preoperative serum albumin levels <3.5 mg/dL; group II: patients with preoperative serum albumin levels ≥3.5 mg/dL). The primary outcome was the development of AKI. Kidney injury was interpreted according to Acute Kidney Injury Network (AKIN) criterias [Mehta 2007], which are explained as Stage I, Stage II, and Stage III according to the changes in serum creatinine levels within 48 hours of surgery (Table 1). Patients who were on either hemodialysis or

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Table 1. Acute Kidney Injury Network (AKIN) Criteria

Stage	SCr	UO
1	↑SCr ≥26.5 µmol/L (≥0.3mg/dL) or ≥SCr≥150 a 200% (1.5 a 2x)	<0.5 mL/kg/h (>6 h)
2	↑SCr>200 a 300% (>2 a 3x)	<0.5 mL/Kg/h (>12 h)
3*	↑SCr>300% (>3x) or if baseline SCr ≥353.6 µmol/L (≥4 mg/dL) ↑ SCr ≥44.2 µmol/L (≥0.5 mg/dL)	<0.3 mL/kg.h (24h) or anuria (12 h)

SCr, serum creatinine; UO urine ouput.
*Stage 3 also includes patients requiring RRT independent of the state

peritoneal dialysis, patients with peripheral vascular disease, recent myocardial infarction, emergent surgery, and patients undergoing operations other than or in conjunction with CABG were excluded from the study.

Preoperative serum albumin levels were measured using the bromocresol green dye-binding method. The reference range of serum albumin at our institution is 3.5-5.2 g/dL. The cutoff value of preoperative serum albumin was set at 3.5g/dL.

CABG Procedure

All operations were performed with a standardized approach by a Terumo roller pump (Terumo Advanced Perfusion System 1, USA) and membrane oxygenators (Dideco Compactflo Evo, USA). Mild to moderate (28-32°C) hypothermia and pulsatile flow of 2.2-2.4 L/m^2 were used. Myocardial protection was achieved with tepid antegrade blood cardioplegia and a "hot shot" (250-500 mL) was delivered just prior to the removal of the aortic cross clamp. The perfusion pressure was kept over 70 mmHg at all times. Induction and maintenance of general anesthesia with endotracheal intubation were standardized for all patients (phentanyl, midazolam, and isoflurane in oxygen with air). The same surgical team performed all operations.

Postoperative Management

Postoperatively, patients were followed in the intensive care unit (ICU) according to the protocols of our institution. Electrocardiography, systemic mean arterial pressure, central venous pressure, pulmonary artery and wedge pressures, cardiac output and index, arterial blood gases, chest tube output, and hourly urine output were monitored. Serum electrolytes were measured in conjunction with arterial blood gas measurement. Fluid and electrolyte imbalances were corrected immediately with appropriate management. Hematocrit values <25% were corrected with erythrocyte suspension administration.

Daily blood urea nitrogen (BUN), serum and urea creatinine, and serum electrolytes were measured uniformly in all patients until discharge from the hospital. Preoperative and postoperative creatinine clearances and peak creatinine clearance were calculated according to the formulations reported in the literature [Lassnigg 2000; Cockcroft 1976].

Our staff nephrologists determined the indication criteria for RRT, and they were the same for both of the study groups. These criteria included hyperkalemia (>6 mmol/L), anuria or oliguria <0.5mL/kg/h for 12 hours, and metabolic acidosis.

Vascular access was with a dual lumen catheter via a central venous vein. Patients were heparinized to achieve activated clotting time of 200 seconds. Fresenius polysulfone filter (Fresenius Medical Care, Bad Homburg, Germany) was used for filtration.

Statistical Analysis

All statistics were performed using SPSS version 17.0 for Windows (IBM, New York, USA). Continous variables were expressed as mean ± SD and were compared by unpaired Student t test or the Pearson chi-square test. The effect of preoperative serum albumin levels on AKI after CABG was determined using logistic regression analysis and the results were expressed as odds ratio with a 95% confidence interval. Kaplan-Meier analysis with the log-rank test was used to evaluate mortality rates between the groups according to the serum albumin cut-off level. A P value <.05 was considered statistically significant.

RESULTS

In this study, 413 patients (78%) had preoperative serum albumin levels ≥3.5g/dL and 117 patients (22%) had preoperative serum albumin levels <3.5g/dL. Patient demographics and operative data are shown in Table 2. Preoperative patient characteristics and intraoperative data did not assure statistical significance between the two groups other than for BMI. Body mass index was significantly lower in patients with lower preoperative serum albumin levels (group I: 26.88 ± 5.05 and group II: 27.92 ± 4.64 respectively; P = .037). Postoperative AKI occured in 33 patients (28.2%) in group I whereas in 79 patients (19.1%) in group II. On logistic regression analysis, the presence of lower serum albumin levels preoperatively was shown to be associated with increased incidence of postoperative AKI (OR: 1.661, 95% CI: 1.037-2.661; P = .035). Logistic regression analysis also revealed that DM (OR: 3.325, 95% CI: 2.162-5.114; P = .000) was the other independent risk factor for AKI after isolated CABG in this study.

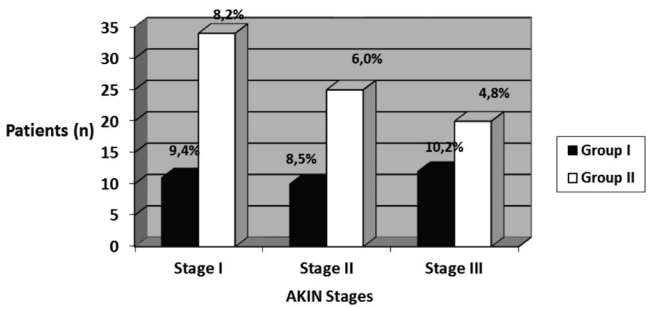

Figure 1. The comparison of Group I versus Group II AKIN stages.

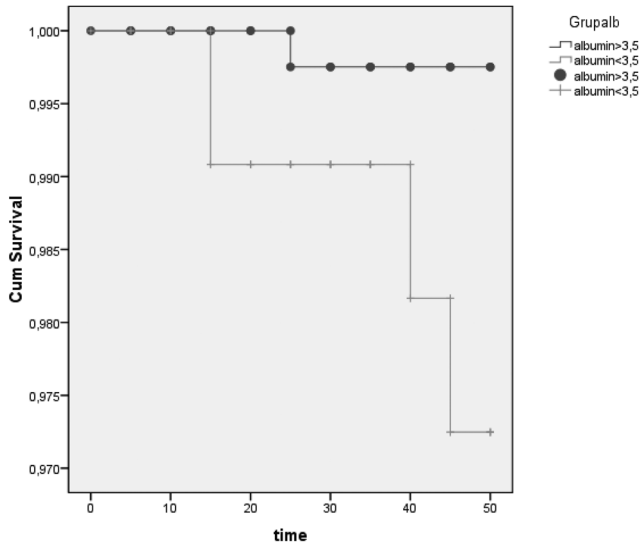

Figure 2. Four-year Kaplan-Meier survival curve in group 1 and group 2, respectively.
(Three patients in group 1 and one patient in group 2, $\chi^2 = 6.94$, $P = .008$ in Log rank test.)

Table 2. Baseline and Perioperative Characteristics of Patients

	Group 1* (n = 117)	Group 2† (n = 413)	*P*
Age, y	62.1 ± 10.9	61.1 ± 10.3	.335
Female, n	25	98	.622
Body mass index, kg/m^2	26.8 ± 5.0	27.9 ± 4.6	.037
Hypertension, n	78	253	.169
Diabetes mellitus, n	45	147	.587
Hyperlipidemia, n	77	239	.074
Smoking, n	68	242	.504
CPB time, min	110.7 ± 43.3	102.4 ± 38.5	.063
Cross-clamp time, min	63.1 ± 24.6	59.6 ± 23.7	.168
LV function, %	52.4 ± 10.7	54.4 ± 9.4	.052
Serum creatinine, mg/dL	0.95 ± 0.2	0.92 ± 0.2	.219
Creatinine clearance, mL/min	84.1 ± 35.9	90.1 ± 35.2	.156
Blood urea nitrogen, mg/dL	19.6 ± 9.2	18.3 ± 7.0	.093

*Group I: patients with preoperative serum albumin levels <3.5 mg/dL,
†Group II: patients with preoperative serum albumin levels ≥3.5 mg/dL.

The preoperative mean serum creatinine level was 0.95 ± 0.23 mg/dL in group I and 0.92 ± 0.21 mg/dL in group II ($P = .219$). Postoperative peak serum creatinine levels were higher in group I patients than in group II (1.19 ± 0.52 mg/dL and 1.09 ± 0.41 mg/dL, respectively; $P = .035$).

When results were compared according to the AKIN stage, the 33 patients in group I included 11 patients (9.4%) in AKIN stage I, 10 patients (8.5%) in AKIN stage II, and 12 patients (10.2%) in AKIN stage III; 79 patients in group II included 34 patients (8.2%) in AKIN stage I, 25 patients (6%) in AKIN stage II, and 20 patients (4.8%) in AKIN stage III (Figure 1).

Renal replacement therapy was required in 3.2% (n = 17) of patients (8 patients in group I, and 9 patients in group II; $P = .018$). The creatinine value before commencement of RRT was 3.85 ± 0.73 mg/dL. RRT was started 36-50 hours after surgery and used for 5 days. The mean creatinine level was 1.29 ± 0.91 mg/dL prior to hospital discharge and none of the patients became hemodialysis dependent.

The mean ICU time was 66.02 ± 36.09 hours in group I and 59.01 ± 28.00 hours in group II ($P = .026$); in-hospital stay time was 7.73 ± 2.99 days in group I and 7.06 ± 2.68 days in group II ($P = .022$). The intraaortic balloon pump support was required in 3.8% of patients (9 patients in group I and 11 patients in group II; $P = .007$). Prolonged ventilatory support was necessary in 4% of patients and the mean ventilatory support time was 7.92 ± 6.40 in group I and 11.44 ± 16.76 in group II ($P = .001$); one patient required tracheotomy. The 30-day mortality rate was 3.4% (n = 18, 10 patients in group I and 8 patients in group II; $P = .037$). Fourteen patients died due to low cardiac output and multiorgan failure and these patients required RRT. Two patients died due to cerebrovascular accident and 2 patients died due to mesentery artery ischemia. Log-rank test for survival revealed a higher overall mortality for patients with lower preoperative serum albumin levels ($\chi^2 = 6.947$; $P = .008$) (Figure 2).

DISCUSSION

Renal dysfunction after cardiac surgery is a frequent and devastating complication. Many preoperative biomarkers were studied to predict which patients would have postoperative AKI and/or RRT. In our study, we analyzed the effect of preoperative serum albumin levels as a biomarker on RRT requirement, morbidity, and mortality after CABG.

There have been many valuable studies in recent years reporting the association between hypoalbuminemia and AKI [Wedermann 2010; Lee 2012]. Albumin is one of the main proteins in plasma and is responsible from 70-80% of plasma oncotic pressure [Fanali 2012]. Aside from the effect of albumin on intravascular volume, it has andioxidant, anticoagulant, anti-inflammatory, and antiapoptotic effects [Gabay 1999; Yap 2002]. Albumin also plays an important role in transport process and has a direct effect on pharmacokinetics of many drugs. Hypoalbuminemia points out liver and kidney dysfunction [Rothschild 1998; Ha 2013]. Hypoalbuminemia is common in critically ill patients and is suggested to be a biomarker of acute illness in a metaanalysis of 90 cohort studies [Vincent 2003]. In this metaanalysis, hypoalbuminemia was reported to be associated with mortality, morbidity, and length of stay in hospital. In our study, group 1, which had albumin levels <3.5 mg/dL, showed a statistically significant 30-day mortality rate of 6.8%.

In a study which analyzed 5168 cardiac surgery patients [Engelman 1999], it was reported that plasma albumin levels

<2.5 mg/dL were associated with mortality; additionally, plasma albumin levels <3.5 mg/dL were associated with renal dysfunction, atrial fibrillation, prolonged ventilatory support, length of stay in ICU and length of stay in hospital. In another study by Montazerghaem and Safaie Nezhad, which analyzed 345 CABG patients [Montazerghaem 2014], it was reported that ventilatory support times and mortality were higher in patients with plasma albumin levels <2.5 mg/dL and <3.5 mg/dL. We found in our study that the critical serum albumin level was 3.5 mg/dL. Among the 530 patients operated for CABG in our study, prolonged stay in the ICU and hospital, prolonged ventilatory support, and increased incidence of renal failure were found with statistical significance, particularly in the study group of patients with critically low serum albumin levels.

Bhamidipati et al compared mortality and albumin levels in 2794 patients [Bhamidipati 2011]. They found the highest mortality rate in the group of patients with serum albumin levels <3 mg/dL, whereas the mortality rate was lowest in the group of patients with serum albumin levels >4 mg/dL. Together with the studies mentioned above, and many others in accordance with the results obtained in our study [Koertzen 2013; Rapp-Kesek 2004; Rady 1998], there are also several studies with different results. De la Cruz et al found a significant increase in the incidence of 30-day mortality in the group of patients with serum albumin levels <3.5 mg/dL [De la Cruz 2011]. Acute kidney injury following cardiac surgery is frequent with an average incidence of 15-30% [Schopka 2014; Loef 2005]. In our study group with hypoalbuminemia, the changes in preoperative and postoperative serum creatinine levels were significant. There are reports mentioning that a 0.3 mg/dL increase of serum creatinine in the early stages of AKI is associated with increased mortality and prolonged stay in hospital [Lassnigg 2004; Lafrance 2010; Chertow 2005; Englberger 2011]. The need for intraaortic balloon pump counterpulsation in the intraoperative period was found to be significantly higher in the hypoalbuminemia group than in the control group in our study.

In our study, the incidence of AKI was 28% in the study group of patients with serum albumin levels lower than 3.5 mg/dL and 19% in the control group of patients with serum albumin levels higher than 3.5 mg/dL, where the difference was statistically significant. There was a statistically significant difference in the number of Stage III AKI patients between the study group with 12 (10%) and the control group with 20 (4%) patients.

Postoperative renal dysfunction affects not only mortality, but also the quality of life in the short- and long-term. AKI plays an important role in postoperative mortality and morbidity in cardiac surgery patients. In multicentral and international studies, the rate of renal replacement therapy (RRT) was approximately 6% in patients with a high prevalence of AKI [Uchino 2005]. There are studies concerning treatment modalities for lowering the need for RRT [Kunt 2009]. The aim of continuous RRT is to treat acute kidney failure by maintaining hemodynamic stability, acid-base, and electrolyte balances in critically ill patients with a very high risk of mortality. Among the patients who developed AKI, RRT was applied to 25% of the patients in our study group with hypoalbuminemia and 11% of the patients in our control group, where the difference was statistically significant. It is important to think about many clinical, biochemical, and physiologic factors and make a decision for patients with AKI prior to initiation of RRT. There is not a complete consensus regarding course of action [Gibney 2008]. There are many studies regarding the timing of RRT and which RRT to apply; the decisions regarding these factors were made together with our nephrologists in this study [Bouman 2002; Demirkılıç 2004; Sugahara 2004; Elahi 2004; Iyem 2009; Manche 2008].

The 30-day mortality was 3.4% (n = 18) in our study. The mortality rate was 6.8% (n = 8) in the hypoalbuminemia group and 2.4% (n = 10) in the control group. There are reports mentioning mortality rates up to 60-70% in patients treated with RRT. This rate was 71% (n = 12) in our study.

The mortality rates are high in patients who require RRT. Hypoalbuminemia is frequent in patients who are candidates for open cardiac surgery. The number of reports regarding increased mortality and morbidity following open cardiac surgery in patients with hypoalbuminemia has been increasing recently. We emphasize in our study that the need for RRT and mortality are significantly increased, particularly in patients with hypoalbuminemia. Further studies with larger populations are required.

Conclusion

Low preoperative serum albumin levels increase the incidence of RRT following cardiac surgery. Hypoalbuminemia results in more severe AKI, increases the frequency of RRT and mortality rate, and changes quality of life.

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