Postoperative hypoalbuminemia as a predictor of acute kidney injury after open repair of ruptured abdominal aortic aneurysm

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ABSTRACT

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Objectives: Perioperative hypoalbuminemia has a prognostic effect on mortality and morbidity in various cohorts. Patients undergoing open repair of ruptured abdominal aortic aneurysms (rAAA) are at a high risk of hypoalbuminemia due to bleeding and underlying diseases. Hence, this study aimed to investigate the predictive value of hypoalbuminemia for the risk for acute kidney injury (AKI) in patients undergoing open rAAA repair.

Methods: We retrospectively reviewed 143 patients with rAAA between January 2008 and May 2022. The patients were divided into two groups according to the presence of postoperative AKI. The perioperative serum albumin levels of the two groups were compared. The patients were further divided into two groups based on the median postoperative albumin level (2.4 g/dL). The incidence of AKI was compared between the two groups. Multivariate logistic regression analysis was performed to assess the predictors of postoperative AKI.

Results: Postoperative serum albumin was significantly lower in the AKI group than in the non-AKI group (2.59 ± 0.62 g/dL vs. 2.11 ± 0.62 g/dL, $p < 0.001$). The incidence of postoperative AKI was significantly higher in patients with albumin ≤ 2.4 g/dL than in patients with albumin > 2.4 g/dL (27.7% vs. 53.8%, $p = 0.002$). Postoperative albumin level (Odds ratio, 0.310; 95% confidence interval: 0.165–0.583, $p < 0.001$) was an independent predictor of AKI.

Conclusions: Postoperative hypoalbuminemia was an independent predictor of postoperative AKI in patients with rAAA, suggesting the need for measurement of postoperative serum albumin level and intraoperative albumin replacement to increase postoperative serum albumin level may have beneficial effects into preventing the development of AKI in patients undergoing surgery with rAAA.

Key words : albumin, hypoalbuminemia, aortic repair, ruptured abdominal aortic aneurysm, acute kidney injury

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I. INTRODUCTION

Patients undergoing open repair of ruptured abdominal aortic aneurysms (rAAAs) have substantial risks of developing postoperative renal dysfunction due to unstable hemodynamics, hypovolemia, nephrotoxic contrast agent use, and renal ischemia during the perioperative period.[1,2] The incidence of acute kidney injury (AKI) after rAAA repair has been reached 75%.[1,3] Therefore, various studies, which have been conducted to predict the prognosis of rAAA, found that disease severity and blood loss during surgery were risk factors.[4]

Serum albumin is a major protein in the blood that acts as a binding agent for various drugs and regulates fluid movement between body compartments through oncotic pressure. Moreover, serum albumin levels are associated with inflammation, thrombosis, platelet activation, and oxidative stress. Hypoalbuminemia reflects overall health due to malnutrition, systemic inflammation, and liver and kidney diseases. Its presence was also observed in patients with cardiac insufficiency, malignant tumors, sepsis, and renal disease.[5,6] Serum albumin level is also reduced by hemodilution and massive bleeding. In addition, it was also associated with the occurrence of AKI after surgery including coronary artery bypass, non-cardiac, and brain tumor surgeries.[7-10] Considering these, albumin may potentially play an important role as a predictor of prognosis in patients undergoing open rAAA repair; however, studies on this are lacking.

Therefore, we investigated the predictive value of postoperative hypoalbuminemia for the occurrence of AKI in patients undergoing surgery for rAAA.

II. MATERIALS AND METHODS

1. Study population

The study was approved by the institutional review board of Yonsei University Health System, Seoul, South Korea. The need for informed consent was waived because of the retrospective nature of the study. A total of 157 patients who underwent open rAAA repair at Gangnam Severance Hospital between January 2008 and May 2022 were retrospectively reviewed. Patients with chronic kidney disease (n = 14) were excluded. Finally, 143 patients were included in the study (Figure 1). According to serum albumin level measured in the immediate postoperative period, the patients were divided into two groups based on the median values (albumin > 2.4 g/dL [n=65] and albumin ≤ 2.4 g/dL [n = 78]). Subgroup analysis was performed to exclude the effect of synthetic colloids or exogenous albumin on renal function, excluding patients who were administered with synthetic colloids or exogenous albumin.

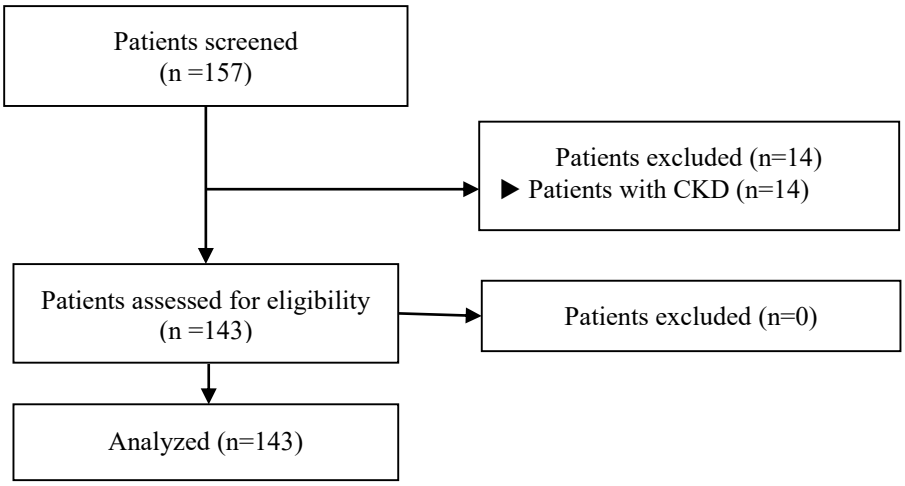

Figure 1. Flowchart depicting patient enrollment

2. Perioperative management

All patients received standardized anesthetic care according to the institutional protocol. After arriving at the operating room, five-lead electrocardiography and pulse oximetry were performed, and the radial artery was cannulated to monitor arterial pressure. Anesthesia was induced with midazolam or ketamine, sevoflurane, and remifentanil (0.2–0.5 mcg/kg.) Anesthesia was maintained with sevoflurane and remifentanil infusion. Transesophageal echocardiography was performed to evaluate cardiac function and volume status. All patients received balanced crystalloid solutions intraoperatively. A balanced synthetic colloid (Volulyte; Fresenius Kabi, Bad Homburg, Germany) was used at the anesthesiologist's option when blood loss was significant. Exogenous albumin was administered at the anesthesiologist's discretion when preoperative albumin value < 3.0 g/dL or supplementation was deemed necessary because of acute blood loss. The mean arterial pressure was maintained with norepinephrine, vasopressin, or nicardipine. During surgery, a cell salvage device was used in all patients, and the salvaged blood was reinfused into the patients before the end of surgery. Packed red blood cell (pRBC) transfusion was performed according to the anesthesiologist's discretion if hemoglobin level < 8 g/dL even after salvaged blood administration or if the blood loss during surgery was significant. Following the completion of the surgery, all patients were transferred to the intensive care unit (ICU).

3. Study endpoint

The primary endpoint was the incidence of AKI, which was defined using the Kidney Disease Improving Global Guidelines and Clinical Practice Guidelines.[11] The secondary endpoint was the incidence of postoperative complications. Postoperative infection was defined as the presence of pneumonia, sepsis, peritonitis, or urinary tract infections. Pulmonary complications were defined as the presence of respiratory failure or pneumonia that required prolonged mechanical ventilation (> 24 h) in the postoperative period. Furthermore, the incidence of postoperative complications including reintubation, duration

of mechanical ventilation beyond 24 hours, ICU readmission, reoperation, requirement of renal replacement therapy (RRT), pulmonary complications, infections, AKI, myocardial infarction (MI), and CVA were recorded. Moreover, the duration of hospitalization, ICU stay, and mortality rate were recorded.

4. Other assessments

Baseline patient characteristics, including sex, age, body mass index (BMI), comorbidities such as hypertension, diabetes mellitus, cerebrovascular accident (CVA), coronary artery occlusive disease (CAOD), chronic obstructive pulmonary disease (COPD), preoperative medications, and smoking status, were retrospectively collected. Preoperative shock was defined and recorded when vasopressor support was required before surgery or when systolic blood pressure < 90 mmHg. Perioperative laboratory data including complete blood count, C-reactive protein (CRP), blood urea nitrogen (BUN), creatinine (Cr), and estimated glomerular filtration rate (eGFR) were recorded. Albumin levels were recorded before surgery, upon ICU arrival, and on postoperative days 1 and 2. Intraoperative data, including intake and output during surgery, and total duration of surgery and anesthesia, were recorded. Aneurysm location (suprarenal, juxtarenal, pararenal, or infrarenal) was also recorded.

5. Statistical analyses

IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA) was used for all the statistical analyses. All results are expressed as means ± standard deviations or percentages (%). Normality was assessed using the Kolmogorov–Smirnov test. Independent t-test or the Mann–Whitney U test was used to compare continuous variables. Categorical variables were compared using the chi-squared or Fisher's exact test. Moreover, logistic regression analysis was performed to evaluate the predictors of AKI. Variables with p-value < 0.2 in the univariate analysis were selected for the multivariate analysis. Predictability was expressed as odds ratios (OR) and 95% confidence intervals (CI). A p-

value <0.05 was considered statistically significant.

III. RESULTS

A total of 157 patients were reviewed during the study period, and 143 patients were finally analyzed. Figure 2 shows the change in serum albumin levels from before surgery to the second day after surgery, depending on the presence or absence of AKI. The group × time interaction for perioperative serum albumin levels was statistically significant (p < 0.001).

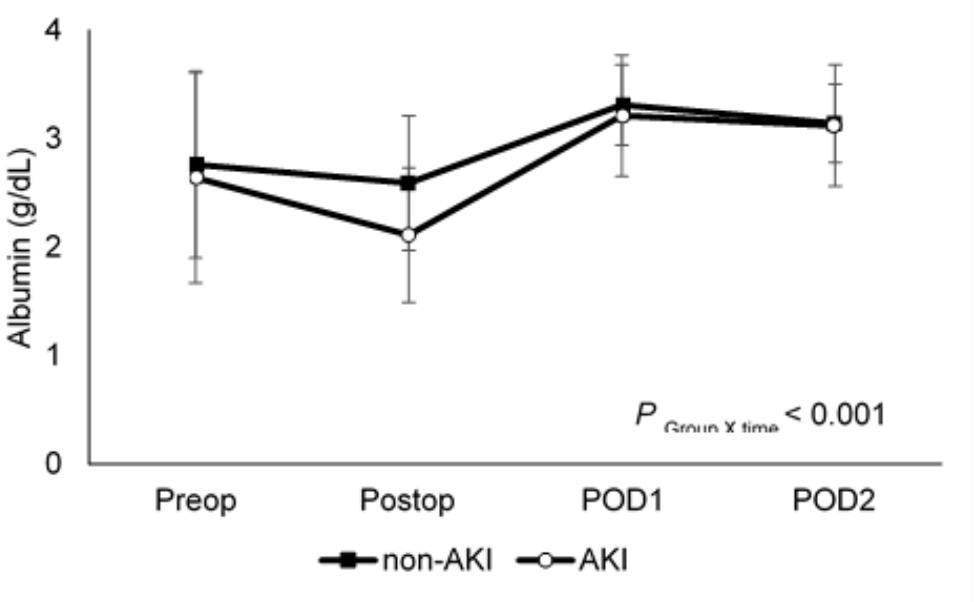

Figure 2. Perioperative serum albumin levels. Values are mean ± SD. $P_{Group\ x\ Time}$, P-value for the group x time interaction in the linear mixed model.

1. Baseline characteristics and laboratory data, stratified according to the occurrence of AKI.

Table 1 summarizes the baseline characteristics of the patients, compared with the occurrence of postoperative AKI. The postoperative albumin level (2.59 ± 0.62 g/dL *vs*. 2.11 ± 0.62 g/dL, $p < 0.001$) was significantly lower in the AKI group than in the non-AKI group, while the preoperative albumin level was similar between the groups (2.76 ± 0.86 g/dL *vs*. 2.64 ± 0.97 g/dL, $p = 0.434$). The preoperative Cr level (1.16 ± 0.62 mg/dL *vs*. 1.40 ± 0.75 mg/dL, $p = 0.039$) and, eGFR (73.20 ± 22.03 mL/min/1.73 m^2 *vs*. 58.08 ± 22.48 mL/min/1.73 m^2, $p = 0.001$) were significantly higher in the AKI group than in the non-AKI group. The location of aneurysm was similar between the groups. The proportion of patients with intraoperative platelet transfusion was higher in patients with AKI (13.3% *vs*. 26.7%, $p = 0.043$). The amount of crystalloid (3.21 ± 1.37 L *vs*. 3.92 ± 2.30 L, $p = 0.040$), colloid (0.29 ± 0.49 L *vs*. 0.64 ± 0.87 L, $p = 0.006$), pRBC (2.60 ± 2.05 pack *vs*. 5.43 ± 5.73 pack, $p < 0.001$), fresh frozen plasma (1.78 ± 1.84 pack *vs*. 3.38 ± 3.65 pack, $p = 0.002$), platelet concentrate (1.23 ± 3.35 pack *vs*. 3.25 ± 6.08 pack, $p=0.022$) transfusions and intraoperative bleeding (1.04 ± 1.35 L *vs*. 2.30 ± 2.60 L, $p = 0.002$) were significantly higher in the AKI group. The anesthesia time (179.70 ± 66.19 min *vs*. 207.95 ± 92.13 min., $p=0.045$) was also significantly longer in the AKI group, while the aorta cross clamp time (42.86 ± 18.12 min *vs*. 42.14 ± 19.43 min., $p = 0.854$) was similar between the two groups (Table 1).

Table 1. Baseline characteristics and laboratory data, stratified according to the occurrence of acute kidney injury.

	Non-AKI (n=83)	AKI (n=60)	*p*-value
Female sex	15 (18.1%)	6 (10.0%)	0.178
Age (years)	72.35±9.14	72.80±9.62	0.776
BMI (kg/m^2)	23.82±2.98	23.04±3.58	0.176
Preoperative shock	51 (61.4%)	31 (52.5%)	0.290
Smoking	32 (38.6%)	26 (43.3%)	0.566
Comorbidities			

Hypertension	50 (60.2%)	38 (63.3%)	0.708
Diabetes mellitus	15 (18.1%)	11 (18.3%)	0.968
Cerebrovascular accident	7 (8.4%)	9 (15.0%)	0.219
CAOD	11 (13.3%)	11 (18.3%)	0.406
COPD	4 (4.8%)	0	0.139
Laboratory test results			
Preop WBC (10^3/μL)	13668.92±5457.08	14725.67±6042.59	0.277
Preop hemoglobin (g/dL)	9.38±2.38	9.51±2.39	0.737
Preop hematocrit (%)	28.62±6.79	28.84±6.98	0.850
Preop platelet (/μL)	165072.29 ±71638.79	152833.33 ±76493.09	0.329
Preop PT (INR)	1.57±2.52	1.46±0.54	0.740
Preop CRP (mg/L)	29.03±59.63	18.27±27.23	0.275
PreopBUN (mg/dL)	21.17±10.67	23.63±9.99	0.170
Preop Cr (mg/dL)	1.16±0.62	1.40±0.75	0.039*
Preop eGFR (mL/min/1.73 m^2)	73.20±22.03	58.08±22.48	0.001*
Preop albumin (g/dL)	2.76±0.86	2.64±0.97	0.434
Postop albumin (g/dL)	2.59±0.62	2.11±0.62	<0.001*
POD1 albumin (g/dL)	3.31±0.37	3.21±0.56	0.215
POD2 albumin (g/dL)	3.14±0.36	3.12±0.56	0.782
Location of aneurysm			
Suprarenal	2 (2.4%)	2 (3.3%)	1.000
Juxtarenal	3 (3.6%)	2 (3.3%)	1.000
Pararenal	2 (2.4%)	0	0.510
Infrarenal	76 (91.6%)	56 (93.3%)	0.761
Intraoperative variables			

Amount of crystalloid (L)	3.21±1.37	3.92±2.30	0.040*
Amount of colloid (L)	0.29±0.49	0.64±0.87	0.006*
Urine output (L)	0.46±0.46	0.36±0.34	0.206
Cell saver (L)	0.30±0.33	0.44±0.71	0.248
Bleeding (L)	1.04±1.35	2.30±2.60	0.002*
pRBC transfusion (pack)	2.60±2.05	5.43±5.73	<0.001*
FFP transfusion (pack)	1.78±1.84	3.38±3.65	0.002*
PLT conc transfusion (pack)	1.23±3.35	3.25±6.08	0.022*
Operative time (min)	142.60±64.37	158.37±80.60	0.196
Anesthesia time (min)	179.70±66.19	207.95±92.13	0.045*
Aorta cross clamp time (min)	42.86±18.12	42.14±19.43	0.854

Values are presented as means ± standard deviations or number of patients (%).

BMI: body mass index, CAOD: coronary artery occlusive disease, COPD: chronic obstructive pulmonary disease, Preop: preoperative, WBC: white blood cell, PT: prothrombin time, INR: international normalized ratio, CRP: C-reactive protein, BUN: blood urea nitrogen, Cr: creatinine, eGFR: estimated glomerular filtration rate, Postop: postoperative, POD: postoperative day, pRBC: packed red blood cell, FFP: fresh frozen plasma, PLT conc: platelet concentration, * $p < 0.05$.

2. Baseline characteristics and laboratory data, stratified according to postoperative albumin level

The patients were divided into two groups based on the median values (albumin >2.4 g/dL, ≤2.4 g/dL) of immediate postoperative serum albumin level. The baseline characteristics, including sex, age, BMI, comorbidities, and preoperative laboratory data, were similar between the groups. Only a medical history of diabetes mellitus was more frequent in the albumin ≤ 2.4 g/dL group (10.8% *vs*. 24.4%, $p < 0.036$).

Table 2. Baseline characteristics and laboratory data, stratified according to postoperative albumin level

	Albumin >2.4 (n=65)	Albumin ≤2.4 (n=78)	*p*-value
Female sex	11 (16.9%)	10 (12.8%)	0.490
Age (years)	71.94±8.95	73.04±9.63	0.484
BMI (kg/m^2)	23.98±3.19	23.08±3.26	0.112
Smoking	30 (46.2%)	28 (35.9%)	0.214
Preoperative shock	34 (53.1%)	48 (61.5%)	0.313
Comorbidities			
Hypertension	37 (56.9%)	51 (65.4%)	0.300
Diabetes mellitus	7 (10.8%)	19 (24.4%)	0.036*
Cerebrovascular accident	5 (7.7%)	11 (14.1%)	0.226
CAOD	11 (16.9%)	11 (14.1%)	0.642
COPD	1 (1.5%)	3 (3.8%)	0.626
Medications			
Beta blocker	8 (14.5%)	5 (8.6%)	0.324
Calcium channel blocker	14 (25.0%)	15 (25.4%)	0.958
RASi	12 (21.4%)	16 (27.1%)	0.477
Statin	12 (21.4%)	15 (25.4%)	0.613
Diuretics	7 (12.3%)	5 (8.5%)	0.501
Preoperative laboratory test results			
WBC ($10^3/\mu L$)	13988.15±5663.93	14215.77±5788.62	0.813
hemoglobin (g/dL)	9.35±2.32	9.51±2.44	0.692
hematocrit (%)	28.62±6.76	28.80±6.95	0.877
platelet (/μL)	161246.15±72371.01	158846.15±75236.61	0.847
PT (INR)	1.32±0.45	1.70±2.64	0.249
CRP (mg/L)	19.45±32.85	31.07±63.70	0.210

BUN (mg/dL)	21.12±10.22	23.11±10.59	0.263
Cr (mg/dL)	1.16±0.53	1.34±0.79	0.118
eGFR (mL/min/1.73 m^2)	68.24±22.98	67.33±23.81	0.843
Albumin (g/dL)	2.80±0.82	2.64±0.97	0.318

Values are presented as means ± standard deviations or number of patients (%).

BMI: body mass index, CAOD: coronary artery occlusive disease, COPD: chronic obstructive pulmonary disease, RASi: Renin-angiotensin system inhibitor, WBC: white blood cell, PT: prothrombin time, INR: international normalized ratio, CRP: C-reactive protein, BUN: blood urea nitrogen, Cr: creatinine, eGFR: estimated glomerular filtration rate. pRBC: packed red blood cell, FFP: fresh frozen plasma, * $p < 0.05$.

3. Operation related data

Significant differences in the location of aneurysms between the two groups was not observed. The amount of colloid (0.15 ± 0.36 L *vs*. 0.67 ± 0.80 L, $p = 0.001$), cell saver (0.25 ± 0.31 L *vs*. 0.44 ± 0.62 L, $p = 0.049$), bleeding (1.13 ± 1.44 L *vs*. 1.91 ± 2.40 L, $p = 0.026$), and pRBC transfusions (2.83 ± 2.39 pack *vs*. 4.59 ± 5.20 pack, $p = 0.009$) were significantly greater in the albumin ≤2.4 g/dL group. The duration of aorta cross clamp (47.94 ± 18.25 min *vs*. 36.86 ± 17.11 min, $p = 0.002$) was significantly longer in the albumin > 2.4 g/dL group (Table 3).

Table 3. Operation related data

	Albumin >2.4 (n=65)	Albumin ≤2.4 (n=78)	*p*-value
Location of aneurysm			
Suprarenal	1 (1.5%)	3 (3.8%)	0.626
Juxtarenal	3 (4.6%)	2 (2.6%)	0.659
Pararenal	2 (3.1%)	0	0.205
Infrarenal	59 (90.8%)	73 (93.6%)	0.529

Intraoperative variables

Amount of crystalloid (L)	3.54±1.27	3.47±2.24	0.821
Amount of colloid (L)	0.15±0.36	0.67±0.80	<0.001*
Urine output (L)	0.47±0.46	0.37±0.36	0.140
Cell saver (L)	0.25±0.31	0.44±0.62	0.049*
Bleeding (L)	1.13±1.44	1.91±2.40	0.026*
pRBC transfusion (pack)	2.83±2.39	4.59±5.20	0.009*
FFP transfusion (pack)	2.32±.07	2.56±3.37	0.616
PLT conc transfusion (pack)	2.22±4.50	1.96±5.02	0.753
Operative time (min)	156.43±68.37	143.21±74.39	0.274
Anesthesia time (min)	195.42±72.04	188.33±84.82	0.596
Aorta cross clamp time (min)	47.94±18.25	36.86±17.11	0.002*

Values are presented as means ± standard deviations or number of patients (%).

pRBC: packed red blood cell, FFP: fresh frozen plasma, PLT conc: platelet concentration, * $p < 0.05$.

4. Postoperative morbidity and mortality

The incidence of postoperative complications including reintubation (6.5% *vs*. 27.3%, $p = 0.001$), requirement of RRT (1.5% *vs*. 14.1%, $p=0.007$), and AKI (27.7% *vs*. 53.8%, $p = 0.002$) was significantly higher in the albumin ≤ 2.4 g/dL group. The incidence of in-hospital mortality (6.2% *vs*. 19.2%, $p = 0.022$) and 30-day mortality (1.5% *vs*. 14.1%, $p=0.007$) was also significantly higher in the albumin ≤ 2.4 g/dL group (Table 4).

Table 4. Postoperative morbidity and mortality

	Albumin >2.4 (n=65)	Albumin ≤2.4 (n=78)	*p*-value
Reintubation	4 (6.5%)	21 (27.3%)	0.001*
MV >24 h	28 (43.8%)	38 (48.7%)	0.555
ICU readmission	2 (3.1%)	7 (9.0%)	0.182

Reopen for bleeding	2 (3.1%)	9 (11.5%)	0.111
Requirement of RRT	1 (1.5%)	11 (14.1%)	0.007*
Pulmonary complication	10 (15.4%)	22 (28.2%)	0.067
Infection	5 (7.7%)	13 (16.7%)	0.107
Acute kidney injury	18 (27.7%)	42 (53.8%)	0.002*
Myocardial infarction	2 (3.1%)	3 (3.8%)	1.000
Cerebrovascular accident	1 (1.5%)	0	0.455
Hospital stay (days)	12.60±5.76	17.68±16.57	0.350
ICU stay (days)	6.29±8.65	8.88±10.67	0.122
Inhospital mortality	4 (6.2%)	15 (19.2%)	0.022*
Mortality in 30days	1 (1.5%)	11 (14.1%)	0.007*

Values are presented as means ± standard deviations or number of patients (%).
MV: mechanical ventilation, ICU: intensive care unit, RRT: renal replacement therapy, * $p < 0.05$.

5. Logistic regression analysis for the predictors of AKI after open rAAA repair.

Table 5 summarizes the results of the logistic regression analysis for the predictors of postoperative AKI after open rAAA repair. In the univariate analysis, the preoperative Cr and postoperative albumin levels were significantly different ($p < 0.2$) and selected for multivariate analysis. Postoperative albumin level (OR, 0.310; 95% CI, 0.165–0.583; $p < 0.001$) was an independent predictor of postoperative AKI. These results were the same when patients administered with exogenous albumin and synthetic colloids were excluded. An increase in albumin by 1 g/dL was associated with a decrease in the incidence of AKI, both in patients without exogenous albumin replacement during the operation (OR, 0.426; 95% CI, 0.190–0.952; $p = 0.038$) and patients without synthetic colloid replacement during the operation (OR, 0.160; 95% CI, 0.049–0.533; p=0.003).

Table 5. Logistic regression analysis for the predictors of acute kidney injury after rAAA open repair.

	Univariate OR (CI)	*p*-value	Multivariate OR (CI)	*p*-value
Age	1.005 (0.970-1.042)	0.775		
Smoking	1.219 (0.620-2.395)	0.566		
Hypertension	1.140 (0.575-2.261)	0.708		
Diabetes mellitus	1.018 (0.430-2.406)	0.968		
CVA	1.916 (0.671-5.472)	0.225		
CAOD	1.469 (0.591-3.655)	0.408		
Preop Cr	1.747 (0.995-3.065)	0.052	1.504 (0.844-2.681)	0.166
Preop shock	0.695 (0.353-1.365)	0.291		
Postop albumin	0.281 (0.150-0.527)	<0.001	0.310 (0.165-0.583)	<0.001*
Subgroup analysis – patients without exogenous albumin replacement during operation (n=108)				
	Univariate OR (CI)	p-value	Multivariate OR (CI)	p-value
Age	1.006 (0.965-1.048)	0.793		
Smoking	1.557 (0.714-3.396)	0.266		
Hypertension	1.189 (0.550-2.572)	0.660		
Diabetes mellitus	0.767 (0.307-1.916)	0.570		
CVA	1.857 (0.612-5.636)	0.274		
CAOD	1.328 (0.493-3.579)	0.575		
Preop Cr	1.910 (0.997-3.661)	0.051	1.617 (0.859-3.043)	0.136
Preop shock	0.989 (0.464-2.108)	0.977		
Postop albumin	0.357 (0.163-0.783)	0.010	0.426 (0.190-0.952)	0.038*
Subgroup analysis – patients without synthetic colloid replacement during operation (n=86)				
	Univariate OR (CI)	p-value	Multivariate OR (CI)	p-value
Age	1.040 (0.989-1.095)	0.125	1.030 (0.969-1.095)	0.346

Smoking	1.056 (0.411-2.712)	0.911		
Hypertension	0.941 (0.378-2.345)	0.896		
Diabetes mellitus	0.369 (0.075-1.813)	0.220		
CVA	2.250 (0.519-9.756)	0.279		
CAOD	2.429 (0.758-7.781)	0.135	2.448 (0.608-9.858)	0.208
Preop Cr	1.867 (0.763-4.568)	0.172	2.226 (0.788-6.292)	0.131
Preop shock	0.816 (0.326-2.040)	0.663		
Postop albumin	0.165 (0.054-0.504)	0.002	0.161 (0.049-0.533)	0.003*

Values are presented as odds ratios (95% confidence intervals).

CVA: cerebrovascular accident, CAOD: coronary artery occlusive disease, Preop: preoperative, Cr: creatinine, Postop: postoperative, * $p < 0.05$.

IV. DISCUSSION

We found that the postoperative albumin level was significantly lower in patients with postoperative AKI than in those without AKI. An increase in the albumin level by 1 g/dL after surgery reduced the incidence of AKI by 0.310 times.

AKI commonly occurs in patients undergoing open rAAA repair and is associated with adverse postoperative outcomes including prolonged hospitalization and ventilator support and mortality.[1-3] The causes of AKI after open rAAA repair are multifactorial, including unstable hemodynamics, hypovolemia, nephrotoxic contrast agent use, and renal ischemia during the perioperative period.[1 4]

Meanwhile, albumin is a negative acute-phase reactant synthesized by the liver. The serum albumin level is affected by albumin synthesis, catabolic or anabolic rates, redistribution between the various fluid compartments of the body, and loss.[12] Hypoalbuminemia is associated with inflammation, nutritional status, oxidative stress, colloid oncotic pressure, and liver disease.[13] It has also been associated with AKI in various cohorts such as in orthopedic and cardiac surgery.[8 10 14-18] Although the prognostic impact of hypoalbuminemia on AKI has been demonstrated, studies in patients undergoing open

rAAA repair have not been conducted.

The mechanisms by which hypoalbuminemia causes AKI are as follows. The pharmacodynamic properties of human albumin with renal-protective potential include the mitigation of the nephrotoxicity of medications, restoration of balanced net fluid balance, protection against loss of glycocalyx, and maintenance of glomerular filtration[19]. Through various signal transduction pathways, endogenous albumin is involved in maintaining the integrity and function of proximal tubule cells[20].

The most characteristic feature of rAAA is acute massive blood loss due to aortic rupture. Thereafter, hemodilution and albumin loss cause hypoalbuminemia, which is consequently related to the development of AKI. The results of a study, which showed that AKI occurs frequently with the decrease in albumin levels after surgery in patients with no difference in albumin levels before surgery, suggest that blood loss during surgery and its management are important factors. This is similar to a previous study in which intraoperative hypotension was the only risk factor for AKI in patients with AAA.[21]

Some evidence showed that intravenous albumin replacement may reduce the risk of AKI in a particular patient population. A previous prospective randomized controlled trial in cardiac surgery demonstrated that the correction of low albumin levels is associated with a lower increase in Cr, suggesting improved renal function with human albumin therapy.[22] The use of albumin-containing solutions was associated with lower mortality compared with other fluid resuscitation regimens in a previous meta-analysis conducted in patients with sepsis.[23] A recent retrospective study suggested that albumin replacement after the development of AKI may also promote renal recovery.[17] A meta-analysis, which evaluated the effect of hyperoncotic colloids on AKI in various clinical cases, including ascites, surgery, sepsis, and spontaneous bacterial peritonitis, demonstrated that the administration of hyperoncotic albumin solutions could decrease the odds of AKI by 76%.[24] Albumin-mediated renoprotection may be explained by several mechanisms, including the maintenance of renal perfusion, promotion of proximal tubular integrity and function, binding of endogenous toxins and nephrotoxic drugs, prevention of oxidative damage, and

binding and delivery of protective lysophosphatidic acid [16]. In the context of these studies, intraoperative albumin replacement may potentially be a renoprotective strategy in patients undergoing surgery for rAAA.

The possible association between synthetic colloid use and AKI is another concern because two large randomized control trials conducted in critically ill patients reported an increased risk of renal injury in patients receiving hydroxyethyl starch.[25 26] However, the results of these studies may not be applied to surgical patients with acute blood loss because they only included critically ill patients. Consistent with this, studies on patients undergoing major abdominal and cardiac surgeries did not show different hydroxyethyl starch and saline effects on AKI.[27 28] In our study, more synthetic colloids were used in patients with AKI, which was thought to be related to hypovolemia, massive blood loss, and renal ischemia rather than colloid-induced AKI, as reported in previous studies. In addition, colloids were frequently used in patients with low postoperative albumin levels; therefore, a subgroup analysis was conducted excluding patients who used colloids. Consequently, hypoalbuminemia was found to be associated with AKI although colloids were not used. Although the relationship between colloids and AKI is beyond the scope of this study, we found that colloids did not contribute to the association between low albumin levels and AKI.

Previous studies on hypoalbuminemia and AKI have used different cut-off values at different time points. In a study conducted in patients who underwent cardiac surgery, preoperative albumin levels of 3 and 4 g/dL were used as cut-off values.[8 18] Preoperative albumin level < 3.75 g/dL was independently associated with AKI after non-cardiac surgery[9]. Albumin level < 3.0 g/dL on the postoperative second day and albumin level < 2.9 g/dL during the first two postoperative days were both associated with AKI occurrence after orthopedic surgery.[14 15] Thus, in our study, the albumin change during the perioperative period was assessed, and the postoperative albumin level, which showed a difference in the occurrence of AKI, was used as a standard. In addition, since there was significant blood loss and hemodilution in patients with rAAA and there were no known cut-off values for

these patients, the median value was used as the standard. The median value used was 2.4 g/dL, which was lower than what was used in previous studies, because it was the postoperative value of patients with significant blood loss.

The strength of this study is that the predictive value of postoperative hypoalbuminemia for AKI in patients undergoing surgery for rAAA, which has not been addressed before, was determined. Furthermore, we observed the changes in albumin levels before and after surgery, with and without AKI.

However, our study had some limitations. First, adjustments for possible confounding factors such as liver disease, inflammatory status, and comorbidities were not performed. Second, we had no fixed principle of controlling the fluid infused into the patient during the surgery. This was left to the discretion of each anesthesiologist in charge of the surgery. Finally, the relatively small sample size of participants may be another concern. However, considering that the incidence of rAAA is low and preoperative mortality cases are considerably high, our study may still provide valuable insights since we followed up patients who underwent open rAAA repair at one institution for 15 years.

V. CONCLUSION

In conclusion, postoperative serum albumin level was an independent prognostic factor of AKI in patients undergoing rAAA. Our results suggest that measurement of postoperative serum albumin level is important. moreover, increasing it through intraoperative albumin replacement may have beneficial effects in preventing the development of AKI in patients undergoing surgery with rAAA. However, further research is needed on this issue.

REFERENCES

1. Kopolovic I, Simmonds K, Duggan S, et al. Risk factors and outcomes associated with acute kidney injury following ruptured abdominal aortic aneurysm. *BMC Nephrol* 2013;14:99. doi: 10.1186/1471-2369-14-99 [published Online First: 2013/05/03]

2. van Beek SC, Legemate DA, Vahl A, et al. Acute kidney injury defined according to the 'Risk,' 'Injury,' 'Failure,' 'Loss,' and 'End-stage' (RIFLE) criteria after repair for a ruptured abdominal aortic aneurysm. *J Vasc Surg* 2014;60(5):1159-67 e1. doi: 10.1016/j.jvs.2014.04.072 [published Online First: 2014/07/08]

3. Jalalzadeh H, Indrakusuma R, Vogt L, et al. Long-term survival after acute kidney injury following ruptured abdominal aortic aneurysm repair. *J Vasc Surg* 2017;66(6):1712-18 e2. doi: 10.1016/j.jvs.2017.04.049 [published Online First: 2017/09/14]

4. Ambler GK, Coughlin PA, Hayes PD, et al. Incidence and Outcomes of Severe Renal Impairment Following Ruptured Abdominal Aortic Aneurysm Repair. *Eur J Vasc Endovasc Surg* 2015;50(4):443-9. doi: 10.1016/j.ejvs.2015.06.024 [published Online First: 2015/07/21]

5. Vincent JL, Dubois MJ, Navickis RJ, et al. Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. *Ann Surg* 2003;237(3):319-34. doi: 10.1097/01.SLA.0000055547.93484.87 [published Online First: 2003/03/05]

6. Jantti T, Tarvasmaki T, Harjola VP, et al. Hypoalbuminemia is a frequent marker of increased mortality in cardiogenic shock. *PLoS One* 2019;14(5):e0217006. doi: 10.1371/journal.pone.0217006 [published Online First: 2019/05/17]

7. Wiedermann CJ, Wiedermann W, Joannidis M. Causal relationship between hypoalbuminemia and acute kidney injury. *World J Nephrol* 2017;6(4):176-87. doi: 10.5527/wjn.v6.i4.176 [published Online First: 2017/07/22]

8. Aksoy R, Adademir T, Yilmaz E, et al. Is Hypoalbuminemia a Predictor for Acute Kidney Injury after Coronary Bypass Grafting in Diabetes Mellitus Patients? *Braz J*

Cardiovasc Surg 2019;34(5):565-71. doi: 10.21470/1678-9741-2018-0291 [published Online First: 2019/06/06]

9. Li N, Qiao H, Guo JF, et al. Preoperative hypoalbuminemia was associated with acute kidney injury in high-risk patients following non-cardiac surgery: a retrospective cohort study. *BMC Anesthesiol* 2019;19(1):171. doi: 10.1186/s12871-019-0842-3 [published Online First: 2019/09/04]
10. Kim K, Bang JY, Kim SO, et al. Association of preoperative hypoalbuminemia with postoperative acute kidney injury in patients undergoing brain tumor surgery: a retrospective study. *J Neurosurg* 2018;128(4):1115-22. doi: 10.3171/2016.11.JNS162237 [published Online First: 2017/05/06]
11. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care* 2013;17(1):204. doi: 10.1186/cc11454 [published Online First: 2013/02/12]
12. Doweiko JP, Nompleggi DJ. The role of albumin in human physiology and pathophysiology, Part III: Albumin and disease states. *JPEN J Parenter Enteral Nutr* 1991;15(4):476-83. doi: 10.1177/0148607191015004476 [published Online First: 1991/07/01]
13. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: Pathogenesis and Clinical Significance. *JPEN J Parenter Enteral Nutr* 2019;43(2):181-93. doi: 10.1002/jpen.1451 [published Online First: 2018/10/06]
14. Kim HJ, Koh WU, Kim SG, et al. Early postoperative albumin level following total knee arthroplasty is associated with acute kidney injury: A retrospective analysis of 1309 consecutive patients based on kidney disease improving global outcomes criteria. *Medicine (Baltimore)* 2016;95(31):e4489. doi: 10.1097/md.0000000000004489 [published Online First: 2016/08/09]
15. Shin KH, Han SB. Early postoperative hypoalbuminemia is a risk factor for postoperative acute kidney injury following hip fracture surgery. *Injury* 2018;49(8):1572-76. doi: 10.1016/j.injury.2018.05.001 [published Online First:

2018/06/18]

16. Wiedermann CJ, Wiedermann W, Joannidis M. Hypoalbuminemia and acute kidney injury: a meta-analysis of observational clinical studies. *Intensive Care Med* 2010;36(10):1657-65. doi: 10.1007/s00134-010-1928-z [published Online First: 2010/06/03]
17. Yu M-y, Lee SW, Baek SH, et al. Hypoalbuminemia at admission predicts the development of acute kidney injury in hospitalized patients: A retrospective cohort study. *PLOS ONE* 2017;12(7):e0180750. doi: 10.1371/journal.pone.0180750
18. Lee EH, Baek SH, Chin JH, et al. Preoperative hypoalbuminemia is a major risk factor for acute kidney injury following off-pump coronary artery bypass surgery. *Intensive Care Med* 2012;38(9):1478-86. doi: 10.1007/s00134-012-2599-8 [published Online First: 2012/05/24]
19. Wiedermann CJ, Joannidis M. Nephroprotective Potential of Human Albumin Infusion: A Narrative Review. *Gastroenterol Res Pract* 2015;2015:912839. doi: 10.1155/2015/912839 [published Online First: 2015/07/03]
20. Dixon R, Brunskill NJ. Activation of mitogenic pathways by albumin in kidney proximal tubule epithelial cells: implications for the pathophysiology of proteinuric states. *J Am Soc Nephrol* 1999;10(7):1487-97. doi: 10.1681/asn.V1071487 [published Online First: 1999/07/15]
21. Brinkman R, HayGlass KT, Mutch WA, et al. Acute Kidney Injury in Patients Undergoing Open Abdominal Aortic Aneurysm Repair: A Pilot Observational Trial. *J Cardiothorac Vasc Anesth* 2015;29(5):1212-9. doi: 10.1053/j.jvca.2015.03.027 [published Online First: 2015/08/16]
22. Lee EH, Kim WJ, Kim JY, et al. Effect of Exogenous Albumin on the Incidence of Postoperative Acute Kidney Injury in Patients Undergoing Off-pump Coronary Artery Bypass Surgery with a Preoperative Albumin Level of Less Than 4.0 g/dl. *Anesthesiology* 2016;124(5):1001-11. doi: 10.1097/ALN.0000000000001051 [published Online First: 2016/02/19]

23. Delaney AP, Dan A, McCaffrey J, et al. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. *Crit Care Med* 2011;39(2):386-91. doi: 10.1097/CCM.0b013e3181ffe217 [published Online First: 2011/01/21]

24. Wiedermann CJ, Dunzendorfer S, Gaioni LU, et al. Hyperoncotic colloids and acute kidney injury: a meta-analysis of randomized trials. *Crit Care* 2010;14(5):R191. doi: 10.1186/cc9308 [published Online First: 2010/10/30]

25. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012;367(2):124-34. doi: 10.1056/NEJMoa1204242 [published Online First: 2012/06/29]

26. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012;367(20):1901-11. doi: 10.1056/NEJMoa1209759 [published Online First: 2012/10/19]

27. Futier E, Garot M, Godet T, et al. Effect of Hydroxyethyl Starch vs Saline for Volume Replacement Therapy on Death or Postoperative Complications Among High-Risk Patients Undergoing Major Abdominal Surgery: The FLASH Randomized Clinical Trial. *Jama* 2020;323(3):225-36. doi: 10.1001/jama.2019.20833 [published Online First: 2020/01/22]

28. Nagore D, Candela A, Bürge M, et al. Hydroxyethyl starch and acute kidney injury in high-risk patients undergoing cardiac surgery: A prospective multicenter study. *J Clin Anesth* 2021;73:110367. doi: 10.1016/j.jclinane.2021.110367 [published Online First: 2021/06/06]

ABSTRACT(IN KOREAN)

파열된 복부 대동맥류의 개복술 후 급성 신장 손상의 예측인자로서의 수술 후 저알부민혈증

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수술 전후의 저알부민혈증은 다양한 코호트 연구에서 환자의 사망률과 이환율과 관련된 예후를 예측할 수 있는 것으로 보고된 바 있다. 파열된 복부 대동맥류(rAAA) 개복술을 받는 환자는 출혈 및 기저 질환으로 인한 저알부민혈증의 위험이 높다. 따라서 본 연구에서는 복부대동맥류 파열로 인조 혈관 치환술을 시행받는 환자에서 수술 후 저알부민혈증이 급성 신손상(AKI)의 발생을 예측할 수 있는지 알아보고자 하였다.

강남 세브란스 병원에서 2008년 1월부터 2022년 5월까지 복부 대동맥류 인조 혈관 치환술을 시행 받은 환자 143명을 대상으로 후향적 연구를 진행하였으며 대상자들은 중앙값인 수술 직후 혈청 알부민 수치 2.4g/dL를 기준으로 두 군으로 나누어 수술 후 급성 신손상의 유무 및 환자의 예후를 비교하였다. 또한 급성 신 손상의 발생 여부에 따라 두 군으로 나누어 수술 후 혈청 알부민 값에 유의한 차이가 있는지 비교하였다.

수술 후 급성신손상의 발생은 저알부민혈증 군에서 유의미하게 높았으며 (27.7% *vs*. 53.8% p=0.002) 저알부민혈증 군에서 기관삽관 재시도, 신장대체요법, 병원내 사망, 수술 후 30일 이내 사망한 비율이 모두 높게 확인되었다.

급성신손상이 발생한 군의 혈청 알부민 농도 역시 발생하지 않은 군에 비하여 유의미하게 낮게 나타났다. (2.59 ± 0.62 *vs*. 2.11 ± 0.62, p < 0.001) 다변수 로지스틱 회귀분석에서도 수술 후 저알부민혈증이 급성신손상의 독립적인 예측변수로 확인되었다. (odds ratio: 0.310, 95% confidence interval: 0.165–0.583, p<0.001)

수술 후 저 알부민혈증은 복부대동맥류 파열로 수술을 받은 환자들에서 급성 신손상을 위한 독립적인 예측 변수로 생각할 수 있으며, 이는 수술 후 혈청 알부민 수치의 파악 및 수술 후 혈청 알부민 수치의 상승을 위한 수술 중 알부민 보충이 환자의 급성신손상을 막고 나쁜 예후를 줄이는 데에 도움이 될 수 있음을 시사한다.

핵심되는 말 : 알부민, 저알부민혈증, 대동맥 치환술, 파열된 복부 대동맥류, 급성신손상