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ORIGINAL INVESTIGATION

Investigating preoperative myoglobin level as predictive factor for acute kidney injury following cardiac surgery with cardiopulmonary bypass: a retrospective observational study

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Abstract
Background: Early identification of patients at risk of AKI after cardiac surgery is of critical importance for optimizing perioperative management and improving outcomes. This study aimed to identify the association between preoperative myoglobin levels and postoperative acute kidney injury (AKI) in patients undergoing valve surgery or coronary artery bypass graft surgery (CABG) with cardiopulmonary bypass.
Methods: This retrospective study included 293 patients aged over 17 years who underwent valve surgery or CABG with cardiopulmonary bypass. We excluded 87 patients as they met the exclusion criteria. Therefore, 206 patients were included in the final analysis. The patients' demographics as well as intraoperative and postoperative data were collected from electronic medical records. AKI was defined according to the Acute Kidney Injury Network classification system.
Results: Of the 206 patients included in this study, 77 developed AKI. The patients who developed AKI were older, had a history of hypertension, underwent valve surgery with concomitant CABG, had lower preoperative hemoglobin levels, and experienced prolonged extracorporeal circulation (ECC) times. Multivariate logistic regression analysis revealed that preoperative myoglobin levels and ECC time were correlated with the development of AKI. A higher preoperative myoglobin level was an independent risk factor for the development of cardiac surgery-associated AKI.
Conclusions: Higher preoperative myoglobin levels may enable physicians to identify patients at risk of developing AKI and optimize management accordingly.

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Introduction

Acute kidney injury (AKI) is a common complication in patients who have undergone cardiac surgery.[1] Postoperative AKI is a major cause of prolonged intensive care unit stay and increased operative mortality.[2] Morgan et al. reported an 18.7% incidence of AKI after cardiac surgery, while Hobson et al. reported an incidence rate between 5% and 42%.[3,4] In another study, cardiac surgery-associated AKI augmented the mortality rate to over 60%.[5]

Grams ME et al. noted that early identification of patients with cardiac surgery-associated AKI is of critical importance in optimizing perioperative management and improving the outcomes of patients undergoing cardiac surgery.[3,6] The risk factors and predictors of cardiac surgery-associated AKI include older age, female sex, obesity, valve replacement surgery, history of myocardial infarction within 30 days of surgery, intraoperative diuretic administration, transfusion of blood products, low cardiac output, history of heart failure, hypertension, diabetes, chronic obstructive pulmonary disease, and chronic kidney disease.[6–9]

The mechanisms underlying the development of cardiac surgery-associated AKI are complex, multifactorial, and have not been elucidated.[10] Nevertheless, epidemiologic studies on cardiac surgery-associated AKI are important because they allow for early diagnosis of AKI and facilitate the implementation of more effective strategies to prevent this complication, decreasing its subsequent morbidity and mortality.[11] This study aimed to determine the risk factors, protective factors, and incidence of AKI in patients undergoing valve surgery or coronary artery bypass graft surgery (CABG) with cardiopulmonary bypass.

The mechanisms underlying the development of cardiac surgery-associated AKI are complex, multifactorial, and have not been elucidated.[10] The traditional risk factors of cardiac surgery-associated AKI include older age, female sex, obesity, valve replacement surgery, history of myocardial infarction within 30 days of surgery, intraoperative diuretic administration, transfusion of blood products, low cardiac output, history of heart failure, hypertension, diabetes, and chronic obstructive pulmonary disease.[6–9] Preoperative biomarkers have been studied to predict cardiac surgery-associated AKI[12–14] because early identification of patients with cardiac surgery-associated AKI facilitates the optimization of pre- and postoperative management to improve outcomes for patients undergoing cardiac surgery.[6]

However, to the best of our knowledge, much as myoglobin is a commonly measured biomarker, few reports have presented its potential as a predictive factor of cardiac surgery-associated AKI.

This study aimed to identify the association between preoperative myoglobin levels and postoperative AKI in patients undergoing valve surgery or CABG with cardiopulmonary bypass.

Methods

This study was approved by the Institutional Review Board of Korea University Ansan Hospital (IRB No. 2019AS0064). Informed consent was not required because of the retrospective study design. This study included elective surgery patients over the age of 17 years who underwent valve surgery or CABG with cardiopulmonary bypass at Korea University Ansan Hospital between March 2008 and December 2019. The surgical procedures included valve surgery, CABG, and combined valve surgery and CABG. The exclusion criteria were preoperative serum creatinine > 2.0 $mg.dL^{-1}$, end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, and incomplete data. The patients' demographics as well as intraoperative and postoperative data were collected from an electronic medical records database of the hospital.

Postoperative AKI was defined according to the Acute Kidney Injury Network criteria: a postoperative increase of > 0.3 $mg.dL^{-1}$ in serum creatinine (SCr) levels on comparison with preoperative values; percent increase in SCr levels of > 50% on comparison with preoperative values; and urine output < 0.5 $mL.kg^{-1}.h^{-1}$ for more than 6 hours. Preoperative SCr values were defined as the most recent SCr values measured within seven days before surgery. Peak postoperative SCr values were defined as the highest creatinine levels within 48 hours after surgery.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 12 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as median or mean ± standard deviation. Categorical variables are presented as percentages. Continuous variables were compared using the Mann-Whitney U test or Student's *t*-test, and Bonferroni corrections were applied when appropriate. Categorical variables were compared using the chi-squared and Fisher's tests.

Univariate analysis was performed to evaluate the risk factors and protective factors related to cardiac surgery-associated AKI. Variables with a *p*-value < 0.1 were selected for further multivariate analysis. Multivariate analysis was performed using logistic regression to identify the variables that were independently predictive of cardiac surgery-associated AKI.

Results

A total of 293 patients who underwent valve surgery or CABG at our center between March 2008 and December 2019 were selected for this study. We excluded three patients who underwent off-pump CABG surgery and 12 patients who were undergoing regular dialysis due to ESRD. The data were incomplete for 72 patients. Therefore, data from 206 patients were included in the final analysis (Fig. 1). In this study, the incidence of cardiac surgery-associated AKI was 37%. The demographic data and clinical characteristics of the study population are presented in Table 1.

Patients who developed cardiac surgery-associated AKI were older ($p = 0.003$) and were more likely to have a history of hypertension ($p = 0.004$) (Table 1). There was a significant increase in the incidence of cardiac surgery-associated AKI among patients undergoing valve surgery and concomitant CABG ($p = 0.028$) (Table 1). Patients who experienced cardiac surgery-associated AKI had lower preoperative hemoglobin levels ($p = 0.002$) and higher preoperative myoglobin levels ($p = 0.001$) (Table 2).

Patients with cardiac surgery-associated AKI did not differ significantly from those without cardiac surgery-

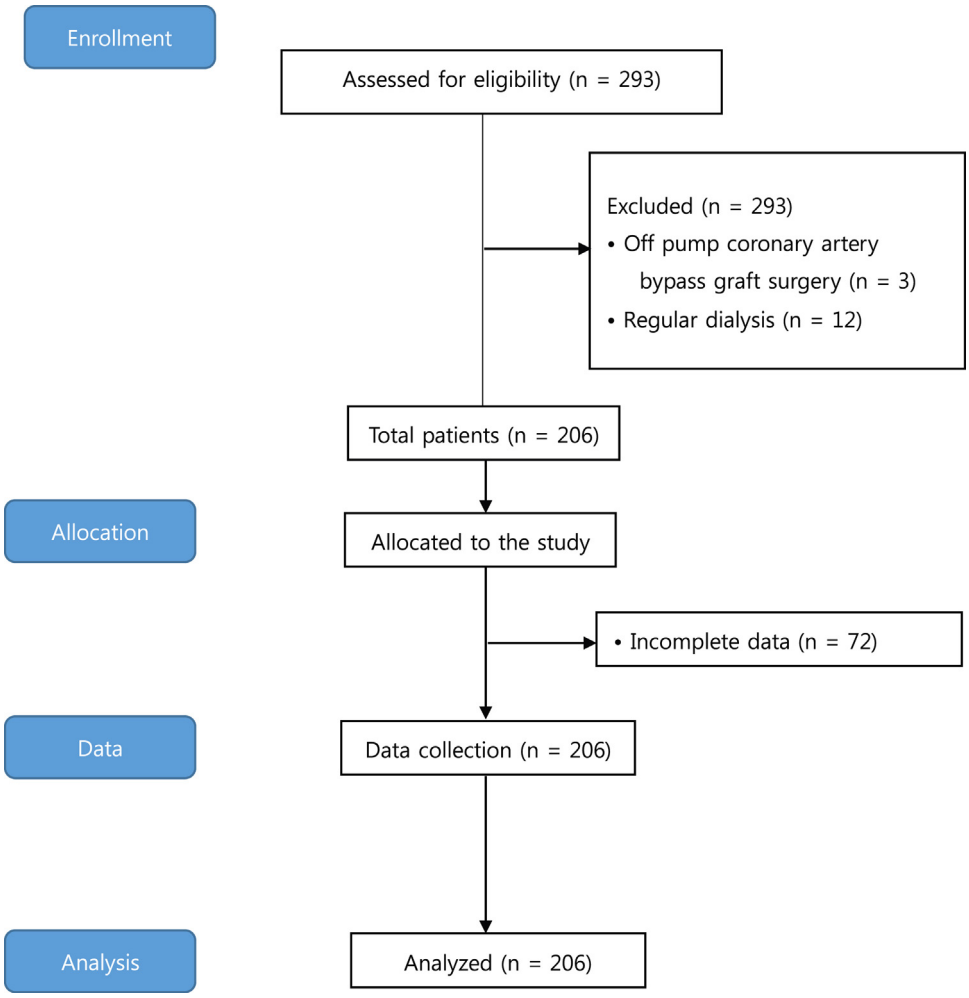

Figure 1 CONSORT flow chart.

associated AKI in terms of the anesthesia time (p = 0.049), total input fluid (p = 0.103), or estimated blood loss (p = 0.029). However, the extracorporeal circulation (ECC) time was higher among patients with cardiac surgery-associated AKI than among those without cardiac surgery-associated AKI (p < 0.0001) (Table 3).

Postoperative creatinine levels were significantly higher among patients with cardiac surgery-associated AKI than among those without cardiac surgery-associated AKI (p < 0.0001) (Table 4). Patients with cardiac surgery-associated AKI had a longer ICU stay than those without cardiac surgery-associated AKI (p = 0.004). (Table 4).

Patients with cardiac surgery-associated AKI had a higher incidence of pulmonary complications and continuous renal replacement therapy (CRRT; p = 0.007 and p = 0.002, respectively).

The results of univariate analysis to identify the risk and protective factors for AKI are presented in Table 5. The following variables were associated with the development of cardiac surgery-associated AKI: age, anesthesia time, ECC time, aortic cross-clamping time, and transfusion of red blood cells. Preoperative hemoglobin and albumin levels were inversely associated with the development of cardiac surgery-associated AKI (Table 5).

Covariates with p < 0.1 in univariate analysis were entered in a multivariate logistic analysis. The independent risk factors for cardiac surgery-associated AKI included preoperative myoglobin levels and ECC time (OR = 1.001, 95% CI, 1.000–1.002; p = 0.034; and OR = 1.009, 95% CI = 1.000–1.019, p = 0.048, respectively) (Table 5).

Discussion

We identified the potential of higher preoperative myoglobin levels as a predictive factor for cardiac surgery-associated AKI. Our main finding was that high preoperative myoglobin level was an independent risk factor for the development of cardiac surgery-associated AKI. Myoglobin is a low molecular weight heme protein that is abundantly found in skeletal muscles and cardiac muscle, and it is released from necrotic muscle.[15] Valvular heart disease and coronary artery disease are associated with myocardial infarction. A group with mitral insufficiency in an animal study had an increased amount of myoglobin.[16] It has also been reported that coronary artery disease, valve insufficiency (such as ischemic mitral regurgitation), and papillary muscle dysfunction are associated with myocardial infarction.[17–19] The large quan-

Table 1 Demographic data.

Variable	Non-AKI group (n = 129)	AKI group (n = 77)	*p*-value
Age (years)	58.02 ± 13.22	62.94 ± 13.03	0.003[a]
Height (cm)	163.83 ± 9.44	161.76 ± 8.38	0.115[b]
Weight (kg)	65.61 ± 12.89	62.70 ± 12.04	0.110[b]
BMI ($kg.m^{-2}$)	24.35 ± 3.81	23.86 ± 3.73	0.365[b]
Sex			0.690[c]
Male, n (%)	82 (63.6)	46 (59.7)	
Female, n (%)	47 (36.4)	31 (40.3)	
Underlying disease			
Hypertension, n (%)	61 (47.3)	53 (68.8)	0.004[c]
Diabetes mellitus, n (%)	47 (36.4)	28 (36.4)	1.000[c]
COPD, n (%)	4 (3.1)	3 (3.9)	1.000[c]
CVA, n (%)	29 (22.5)	24 (31.2)	0.224[c]
OHS Hx, n (%)	8 (6.2)	5 (6.5)	1.000[c]
CAD, n (%)	69 (53.5)	43 (55.8)	0.854[c]
IHD, n (%)	34 (26.4)	25 (32.5)	0.436[c]
CHF, n (%)	35 (27.1)	19 (24.7)	0.823[c]
Type of surgery			
Valve	73 (56.6)	40 (51.9)	0.615[c]
CABG	55 (42.6)	32 (41.6)	0.995[c]
Valve + CABG	1 (0.8)	5 (6.5)	0.028[c]

AKI, acute kidney injury; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; OHS Hx, open heart surgery history; CAD, coronary artery disease; IHD, ischemic heart disease; CHF, chronic heart failure; CABG, coronary artery bypass graft.
Data are displayed as mean ± standard deviation or number of patients (%).
[a] *p*-value indicates comparisons between two groups using the Mann-Whitney U test. Values < 0.0125 were considered significant following post-hoc Bonferroni correction.
[b] *p*-value indicates comparisons between two groups using the t-test. Values < 0.0125. were considered significant following post-hoc Bonferroni corrections.
[c] *p*-value indicates comparisons between two groups using the chi-square test.

Table 2 Laboratory findings during the preoperative period.

Variable	Non-AKI group (n = 129)	AKI group (n = 77)	*p*-value
Hemoglobin ($g.dL^{-1}$)	13.10 (12.84 ± 2.00)	12.00 (11.98 ± 2.06)	0.002[a]
Platelets ($\times 10^3/\mu L$)	209.00 (229.45 ± 95.95)	227.00 (228.81 ± 66.11)	0.378
PT (INR)	1.03 (1.08 ± 0.25)	1.03 (1.10 ± 0.24)	0.463
Albumin ($g.dL^{-1}$)	4.00 (4.04 ± 0.49)	3.80 (3.87 ± 0.47)	0.021
Sodium ($mmol.L^{-1}$)	141.00 (140.46 ± 2.85)	141.00 (140.23 ± 3.08)	0.742
Potassium ($mmol.L^{-1}$)	4.20 (4.17 ± 0.44)	4.20 (4.18 ± 0.50)	0.793
Myoglobin ($ng.mL^{-1}$)	31.23 (81.58 ± 171.69)	45.14 (210.65 ± 575.92)	0.001[a]
Creatinine	0.93 (0.94 ± 0.25)	1.04 (1.03 ± 0.31)	0.019
Ejection fraction	57.50 (52.83 ± 11.84)	57.50 (52.30 ± 13.55)	0.996
eGFR	79.93 (80.38 ± 22.33)	68.73 (73.90 ± 31.27)	0.0052

AKI, acute kidney injury; PT, prothrombin time; INR, international normalized ratio; eGFR, estimated glomerular filtration rate.
Data are displayed as median (mean ± standard deviation).
[a] *p*-value indicates comparisons between two groups using the Mann-Whitney U test. Values < 0.005 were considered significant following post-hoc Bonferroni correction.

tities of myoglobin released into the circulation precipitate in the renal glomerulus, causing kidney injury.[15]

The basic mechanisms underlying the development of cardiac surgery-associated AKI are as follows: First, renal vasoconstriction, a consequence of intravascular volume depletion and altered expression of vasoactive compounds, markedly reduces renal blood flow.[20] Nitric oxide is involved in maintaining renal blood flow, and myoglobin acts as a potent nitric oxide scavenger, thereby contributing to vasoconstriction.[21,22] Myoglobin induces the formation of F2-isoprostanes, which are potent renal vasoconstrictors formed during lipid peroxidation.[23] Moreover, the released myoglobin leads to selective reduction in outer medullary blood flow and oxygenation.[24] Myoglobin may adversely affect medullary oxygen balance, both by reducing oxygen supply and increasing oxygen demand and workload for distal tubular reabsorption, and it may cause ischemic tubular damage.[20,25,26] Second, the precipitation of myo-

Table 3 Clinical variables during the intraoperative period.

Variables	Non-AKI group (n = 129)	AKI group (n = 77)	*p*-value
Anesthetic time (min)	515.00 (530.98 ± 123.08)	550.00 (572.92 ± 145.72)	0.049
Operative time (min)	420.00 (434.51 ± 117.19)	450.00 (478.03 ± 143.74)	0.037
ECC time (min)	170.50 (181.95 ± 60.78)	200.00 (223.30 ± 99.53)	< 0.0001[a]
ACC time (min)	121.00 (127.93 ± 41.42)	135.00 (152.81 ± 80.09)	0.032
MAP	80.42 (78.87 ± 7.32)	79.43 (77.55 ± 6.08)	0.184
MAP(pump)	65.31 (65.00 ± 5.43)	64.26 (63.95 ± 5.68)	0.188
Input			
Total (mL)	3873.50 (4208.78 ± 2831.02)	4090.00 (4689.83 ± 2317.56)	0.103
Fluid (mL)	2400.00 (2585.00 ± 1964.47)	2300.00 (2704.81 ± 1640.61)	0.903
Albumin (mL)	0.00 (27.34 ± 123.76)	0.00 (38.18 ± 136.71)	0.610
Colloid (mL)	400.00 (333.44 ± 311.56)	400.00 (335.06 ± 378.37)	0.928
RBC (mL)	600.00 (732.41 ± 644.01)	800.00 (938.57 ± 650.65)	0.007
Output			
EBL (mL)	1200 (1492.97 ± 2166.67)	1300 (1691.56 ± 1290.44)	0.029
Urine output (mL)	1272.50 (1441.04 ± 750.05)	1020.00 (1264.48 ± 819.32)	0.028

ACC, aortic cross clamping; AKI, acute kidney injury; EBL, estimated blood loss; ECC, extracorporeal circulation; MAP, mean arterial pressure; RBC, red blood cell.
Data are displayed as median (mean ± standard deviation).
[a] *p*-value indicates comparisons between two groups using the Mann-Whitney U test. Values < 0.0045 were considered significant following post-hoc Bonferroni correction.

Table 4 Laboratory findings and clinical variables during the postoperative period.

Variables	Non-AKI group (n = 129)	AKI group (n = 77)	*p*-value
Hb ($g.dL^{-1}$)	10.30 (10.57 ± 1.47)	10.10 (10.32 ± 1.64)	[a]0.311
Platelet count ($\times 10^3/\mu L$)	129.00 (139.37 ± 46.54)	121.00 (125.84 ± 40.12)	[a]0.090
Albumin ($g.dL^{-1}$)	3.60 (3.59 ± 0.44)	3.50 (3.42 ± 0.48)	[b]0.009
Sodium ($mmol.L^{-1}$)	144.00 (143.61 ± 3.00)	144.00 (144.30 ± 3.76)	[a]0.136
Potassium ($mmol.L^{-1}$)	3.90 (3.94 ± 0.43)	4.10 (4.10 ± 0.51)	[b]0.017
Creatinine	0.96 (0.98 ± 0.24)	1.40 (1.58 ± 0.68)	[a]<0.0001
ICU stay (days)	2.00 (3.62 ± 5.67)	3.00 (6.25 ± 9.09)	[a]0.004
POD (days)	16.00 (22.08 ± 22.72)	18.00 (26.66 ± 23.28)	[a]0.016

AKI, acute kidney injury; Hb, hemoglobin; ICU, intensive care unit; POD, postoperative date to discharge.
Data are displayed as median (mean ± standard deviation).
[a] *p* values indicate comparisons between two groups using Mann-Whitney U test. Values < 0.00625 were considered significant following post-hoc Bonferroni correction.
[b] *p* values indicate comparisons between two groups using the t-test. Values < 0.00625 were considered significant following post-hoc Bonferroni correction.

globin within the distal tubules results in cast formation and possibly, intratubular obstruction.[27] In the tubular lumen, myoglobin may precipitate in combination with the Tamm-Horsfall protein, forming tubular casts.[22] Heyman et al. showed that myoglobin cast formation with marked dilation of the collecting ducts and focal tubular necrosis as well as rupture at the outer medullary region likely play a major role in the deterioration of kidney function.[24] Third, myoglobin has the potential to be directly cytotoxic.[28] Many studies suggest that the cytotoxic effects of myoglobin stem from iron-driven hydroxyl radical generation via the Haber Weiss reaction.[29,30] If tubular cell death occurs, the necrotic debris provides additional substrates for cast formation, worsening tubular obstruction and leading to filtration failure.[31] By this mechanism, the function of a vulnerable kidney exposed to myoglobin before cardiac surgery could deteriorate due to hypoperfusion, hypovolemia, and metabolic acidosis caused by cardiac surgery with cardiopulmonary bypass. According to Umberto et al., coexisting hypovolemia and acidic urine pH due to metabolic acidosis are regulating factors that intensify the nephrotoxic action of myoglobin.[32]

Patients who developed cardiac surgery-associated AKI were generally older, had a history of hypertension, had undergone valve surgery with concomitant CABG, had lower levels of hemoglobin, had prolonged ECC time, and had severe left ventricular dysfunction.[33–35] Our findings align with the current data which show correlations between cardiac surgery-associated AKI and advanced age, history of hypertension, valve surgery with concomitant CABG, as well as lower hemoglobin levels. However, in this study, the ejection fraction was not significantly associated with the development of cardiac surgery-associated AKI. Christian et al. demonstrated that patients who developed AKI demonstrated a lower ejection fraction (< 30%) than those who did not.[33] A possible explanation for the discrepancy in this finding is that in the present study, we did not classify

Table 5 Univariate and multivariate logistic regression analyses for AKI.

Variables	Univariate		Multivariate	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.030 (1.007 to 1.054)	0.012	1.022 (0.997 to 1.048)	0.087
BMI	0.966 (0.895 to 1.041)	0.363		
Pre Hb	0.811 (0.703 to 0.936)	0.004	0.848 (0.698 to 1.029)	0.095
Pre PT	1.532 (0.497 to 4.717)	0.458		
Pre albumin	0.470 (0.254 to 0.870)	0.016	0.832 (0.378 to 1.832)	0.648
Anes. time	1.002 (1.000 to 1.005)	0.034	1.001 (0.997 to 1.005)	0.595
ECC time	1.008 (1.003 to 1.012)	0.001	1.009 (1.000 to 1.019)	0.048
ACC time	1.007 (1.002 to 1.013)	0.007	0.995 (0.983 to 1.007)	0.381
Input				
Total	1.000 (1.000 to 1.000)	0.274		
Fluid	1.000 (1.000 to 1.000)	0.688		
RBC	1.001 (1.000 to 1.000)	0.039	1.000 (1.000 to 1.001)	0.740
Output				
EBL	1.000 (1.000 to 1.000)	0.478		
Urine output	1.000 (0.999 to 1.000)	0.096	1.000 (0.999 to 1.000)	0.139
Pre EF	0.997 (0.974 to 1.019)	0.767		
Pre eGFR	0.990 (0.978 to 1.002)	0.089		
OHS Hx	1.050 (0.331 to 3.333)	0.934		
Pre myoglobin	1.001 (1.000 to 1.002)	0.058	1.001 (1.000 to 1.002)	0.037

AKI, acute kidney injury; BMI, body mass index; Pre, preoperative; Hb, hemoglobin; PT, prothrombin time; Anes., anesthesia; ECC, extracorporeal circulation; ACC, aortic cross clamping; RBC, red blood cell; EBL, estimated blood loss; EF, ejection fraction; eGFR, estimated glomerular filtration rate; OHS Hx, open heart surgery history.
Data presented with *p* values and odds ratio's (OR) with 95% CI.
Statistically significant *p* value for univariate analysis: $p < 0.1$ and for myltivariate analysis: $p < 0.05$.

ejection fraction based on severity but rather analyzed it as a continuous variable.

This study had some limitations. It has been reported that perioperative myocardial infarction occurs infrequently in patients with valvular heart disease.[36] However, this issue is controversial because the patients in the study were not limited to those with advanced valvular heart disease that required cardiac surgery. Another limitation of this study is that it was a retrospective single-center study. Nevertheless, our study provides the possibility that preoperative myoglobin level is a predictive factor for cardiac surgery-associated AKI. Controlled studies are needed to establish a clear association between preoperative myoglobin level and cardiac surgery-associated AKI.

Although it is difficult to verify an early diagnosis of cardiac surgery-associated AKI due to its complex and multifactorial pathogenesis,[37] early identification is critical for optimizing perioperative management and improving outcomes. First, it may help in identifying the patients eligible for referral to nephrology; second, it could allow for timely interventions, such as CRRT, that could prevent complications and improve outcomes.[38] Therefore, it is important to identify the patients who are at risk of developing AKI following cardiac surgery.

In summary, we found that preoperative myoglobin levels may be a predictor of cardiac surgery-associated AKI. Based on our findings, patients scheduled to undergo valve surgery or CABG who have high myoglobin levels should be managed appropriately to prevent the development of cardiac surgery-associated AKI.

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Conflicts of interest

The authors declare no conflicts of interest.

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