

Reassessment of Acute Kidney Injury after Cardiac Surgery: A Retrospective Study

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Abstract

Objective To evaluate the incidence, risk, or protective factors of acute kidney injury (AKI) in patients after cardiac surgery based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

Methods A retrospective analysis of 2,575 patients undergoing their first documented cardiac surgery with cardiopulmonary bypass (CPB) was conducted. Perioperative variables were collected and analyzed. Univariate and multiple logistic regression models were used for determining the association between the development of AKI and risk factors. Multiple Cox-proportional hazards modeling was performed to evaluate the impact of AKI on the mortality in the intensive care unit and hospital length of stay.

Results Of 2,575 patients, 931 (36%) developed AKI. A total of 30 (1.2%) patients required renal replacement therapy. In the multivariate analysis, mechanical ventilation duration (OR 1.446, 95% CI 1.195-1.749, $p < 0.001$), CPB duration of ≥ 110 min (OR 1.314, 95% CI 1.072-1.611, $p = 0.009$), erythrocytes transfusion (OR 1.078, 95% CI 1.050-1.106, $p < 0.001$), and postoperative body temperature greater than 38°C within 3 days (OR 1.234, 95% CI 1.018-1.496, $p = 0.032$) were independent risk factors for CSA-AKI, while ulinastatin use was associated with a reduced incidence of CSA-AKI (OR 0.694, 95% CI 0.557-0.881, $p = 0.006$). CSA-AKI was significantly associated with in-hospital mortality (adjusted HR: 2.218, 95% CI 1.161-4.238, $p = 0.016$), especially in patients needing renal replacement therapy (adjusted HR: 18.683, 95% CI 8.579-40.684, $p < 0.001$).

Conclusion Mechanical ventilation duration, erythrocytes transfusion, and postoperative body temperature above 38°C within 3 days were considered independent risk factors for CSA-AKI. The use of ulinastatin was associated with a reduced incidence of CSA-AKI.

Key words: cardiac surgery-associated acute kidney injury, risk factors, cardiopulmonary bypass, ulinastatin, cardiac surgery

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Introduction

Acute kidney injury is an abrupt loss of the kidney function characterized by an acute increase in serum creatinine concentration (1). Previous studies (2, 3) revealed that even a mild increase in serum creatinine levels following cardiac surgery is associated with progression of chronic kidney disease and increased mortality. CSA-AKI is a common and

severe complication in patients undergoing cardiac surgery and is associated with poor outcomes (4-6)

At present, there are three widely accepted and used consensus definitions providing uniform criteria for the diagnosis of AKI, comparisons between studies, and the development of quantitative research. In 2004, the risk-injury-failure-loss-end-stage kidney disease (RIFLE) classification was developed by the Acute Dialysis Quality Initiative Group (7) and then improved by the Acute Kidney Injury

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Network (AKIN) in 2005 (8). In 2012, a modified definition, harmonized and not balancing the limitations of the AKIN and RIFLE, was established by the Kidney Disease: Improving Global Outcomes (KDIGO) group (1).

The incidence of AKI as well as management practices differ based on the definition of AKI (9). Furthermore, the definition of AKI also influences the identification of risk variables and independent predictors (10). While post-cardiac surgery AKI had been extensively studied before the establishment of KDIGO criteria (11-13) and has also been touched on recently by several studies using the KDIGO criteria (14, 15), it has not been fully investigated. In addition, the postoperative body temperature and potential protective factors, such as the administration of ulinastatin, statins, and phosphocreatine, remain to be elucidated.

Therefore, the aim of this study was to evaluate the incidence, risk factors, and the presence of any preventive factors in the development of CSA-AKI in Chinese patients according to the KDIGO classification.

Materials and Methods

Data collection

This retrospective cohort study included 2,575 patients ≥ 18 years of age who underwent cardiac surgery with cardiopulmonary bypass and were admitted to the cardiac intensive care unit at Nanjing First Hospital in Nanjing, China, between January 2008 and December 2013. The preoperative baseline serum creatinine (Scr) values were defined as the most recent Scr ($\mu\text{mol/L}$) detected within 7 days before the surgery. The exclusion criterion was end-stage kidney disease requiring renal replacement therapy.

This study complied with the Declaration of Helsinki and was approved by the Regional Human Research Ethics Committee of Nanjing First Hospital without the need for informed consent, on the condition that the subjects' identities be removed before analysis due to this study being a retrospective analysis.

The KDIGO classification was applied to define AKI as either or both an increase in Scr ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/L}$) within 48 hours or an increase in Scr ≥ 1.5 times the baseline value, known or presumed to have occurred within the prior 7 days.

The demographics and intraoperative and postoperative data were collected from an electronic medical record database. The serum creatinine level was recorded each day until the 7th day after surgery. The patients who received a dose of ulinastatin 500,000 KIU intravenously in 50 mL saline for 15 minutes after induction of anesthesia were also identified. The surgery procedures included coronary artery bypass grafting (CABG) with CPB, valve surgery, and combined CABG and valve surgery.

Data analysis

The data were analyzed using the SPSS software package

(ver. 21.0, SPSS, Chicago, USA). Continuous variables following a normal distribution were presented as the mean \pm standard deviation and categorical variables as a percentage. An unpaired t-test was used to compare the means between two groups, and the chi-squared test was used to compare the proportions between two groups of subjects. The Mann-Whitney U test was used to compare medians.

Univariate binary logistic regression was performed to evaluate the potential modifiable risk factors associated with AKI. All of the potential covariates determined in a univariate analysis ($p < 0.05$) were entered in the final model. Multiple binary logistic regression with a backwards stepwise method was used to determine risk or protective factors for AKI (AKI vs. non-AKI). The significance and removal levels for a covariate were set at 0.05 and 0.1, respectively. The data were listed as the odds ratios (ORs) with 95% confidence intervals (CIs). The impact of AKI and the need for renal replacement therapy on the mortality of ICU and hospital length of stay were evaluated using multiple Cox-proportional hazards modeling. The data were expressed as hazard ratios (HRs) with 95% CI and p values. The influence of different KDIGO stages on the probability of 30-day hospital mortality was determined using a Kaplan-Meier survival analysis.

Results

AKI incidence, patient characteristics, and patient outcomes

A total of 2,808 patients who underwent cardiac surgery with cardiopulmonary bypass between January 2008 and December 2014 in our center were selected for our study, and 2,575 of them met the inclusion criteria and were entered into the final analysis. The postoperative CSA-AKI incidence was 36% (931 of 2,575). The demographic data and clinical characteristics of the study population are described in Table 1. The mean age at cardiac surgery was 56.0 ± 13.9 years, with 52.7% men. Patients who developed AKI were more likely to be men, were older, and had higher BMI ($p < 0.01$). Those with AKI more frequently had a history of hypertension ($p < 0.001$) and a history of diabetes mellitus ($p = 0.003$), especially insulin-controlled diabetes ($p < 0.001$), compared with those who did not have AKI.

The patients who experienced AKI had higher creatinine levels ($p < 0.001$), a lower ejection fraction ($p = 0.001$), a longer cardiopulmonary bypass time ($p < 0.001$), a longer mechanical ventilation time ($p < 0.001$), a longer aortic cross-clamp time ($p < 0.001$), more RBC units transfused during surgery ($p < 0.001$), a lower nasopharyngeal temperature during CPB ($p < 0.001$), higher lactic acid levels ($p < 0.001$), a more frequent high body temperature ($> 38^\circ\text{C}$) within 3 days after surgery ($p = 0.006$), a more frequent use of mannitol ($p = 0.048$), and a less frequent use of ulinastatin ($p = 0.003$) than those without AKI. RRT rate was 1.2% (30 of 2,575), and the overall in-hospital mortality rate was 1.5% (38 of

Table 1. Patient Characteristics and Preoperative Variables.

Variable	All patients (n=2,575)	AKI (n=931)	Non AKI (n=1,644)	p
Age (y)	56.0±13.9	57.6±13.3	55.1±14.1	<0.001
Male, n (%)	1,356(52.7)	555(59.6)	801(48.7)	<0.001
BMI(kg/m ²)	23.6±3.6	24.1±3.8	23.3±3.5	<0.001
Baseline				
History of hypertension,n(%)	847(32.3)	396(42.5)	451(27.4)	<0.001
History of diabetes,n(%)	265(10.3)	118(12.7)	147(10.0)	0.003
Insulin-controlled diabetes,n(%)	156(6.1)	77(8.3)	79(4.8)	<0.001
COPD, n (%)	47(1.8)	21(2.3)	26(1.6)	0.220
Acute myocardial infarction,n(%)	86(3.3)	29(3.1)	57(3.5)	0.633
Chronic kidney disease, n (%)	41(1.6)	18(1.9)	23(2.0)	0.298
Cerebrovascular disease, n (%)	123(4.8)	53(5.7)	70(4.3)	0.101
Coronaryangiography, n (%)	977(34.1)	325(34.9)	552(33.6)	0.493
Ejection fraction (%)	59.3±8.8	58.6±9.1	59.8±8.2	0.001
Urgent surgery, n(%)	19(0.7)	10(1.1)	9(0.55)	0.207
Creatinine (μmol/L)	76.6±32.3	80.4±39.9	74.6±27.2	<0.001
Administration of statins, n (%)	631(24.5)	238(25.6)	393(23.9)	0.347
Phosphocreatine, n (%)	2,345(91.1)	854(91.7)	1,491(91.7)	0.376
Intraoperative				
CPB duration (min)	110.0±48.4	121.5±57.7	102.±40.5	<0.001
Aortic cross-clamp time (min)	73.3±36.2	80.0±38.9	69.4±33.9	<0.001
MAP (mmHg)	62.3±7.1	62.2±7.2	62.2±7.3	0.696
Red blood cells transfused,(U)	4.6±4.6	5.9±5.9	3.9±3.5	<0.001
Need for cardioversion, n (%)	771(29.9)	298(32.0)	473(28.8)	0.085
Mannitol, n (%)	2,273(88.3)	837(89.9)	1,435(87.3)	0.048
Ulinastatin, n (%)	2,045(80.0)	710(76.3)	1,335(81.2)	0.003
Hydroxyethyl starch, n (%)	1,977(76.8)	728(78.2)	1,249(76.0)	0.199
Nasopharyngeal temperature during the lowest flow of CPB (°C)	28.4±0.2	28.2±0.2	28.7±0.3	<0.001
Hematocrit	23.7±6.1	23.8±5.2	23.5±4.6	0.179
Postoperative				
Mechanical ventilation (h),median(IQR)	7.8(5.5to 10.7)	8.8(6.0to 12.7)	7.3(5.2to 9.7)	<0.001
Lactic acid(mmol/L)	2.26 ±1.79	2.47± 2.13	2.14 ±1.55	<0.001
Body temperature within 3 days after surgery (>38°C), n (%)	1,003(39.0)	395(42.4)	608(37.0)	0.006
NSAIDs, n(%)	855(33.2)	298(32.0)	557(33.9)	0.332
Outcomes				
RRT, n (%)	30(1.2)	30(3.2)	-	<0.001
In-hospital mortality, n (%)	38(1.5)	24(2.6)	14(0.9)	0.001
ICU LOS, days [median (range)]	2(1to2)	2(1to3)	2(1to2)	<0.001
Hospital LOS, days [median (range)]	20(17to24)	21(17to26)	20(17to24)	<0.001

2,575). Patients who developed CSA-AKI had higher chances of in-hospital mortality rate than those who did not have AKI (2.6% vs. 0.9%, $p=0.001$). AKI was more likely to occur in men than in women (52.0% vs. 48.7, $p<0.001$). The subgroup analysis of the subjects who developed AKI revealed higher frequencies of coronary heart disease (42.34% vs. 29.26% $p<0.01$), hypertension (52.79% vs. 32.71%, $p<0.001$), and diabetes mellitus (14.77% vs. 12.77%, $p=0.386$) in men than in women.

Patients with CSA-AKI had a longer length of hospital stay than patients without AKI (median 21 vs. 20 days, $p<0.001$). Despite having a similar median length of stay in the ICU, a statistically significant difference was noted in the value between the AKI and non-AKI group [median (range), 2 (1-3) vs. 2 (1-2) days, $p<0.001$].

Potential risk or protective factors for CSA-AKI in univariate analysis

A univariate analysis for identifying the risk or protective factors of AKI and the results are listed in Table 2. The results showed that the following variables were associated with the development of AKI: age, male gender, BMI, history of hypertension, history of diabetes mellitus, insulin-controlled diabetes, creatinine >88.4 μmol/L, cardiopulmonary bypass time, aortic cross-clamp time, RBC transfusion during surgery, nasopharyngeal temperature during the lowest flow of CPB, mechanical ventilation duration, lactic acid ≥ 2 mmol/L, body temperature ($>38^{\circ}\text{C}$) within 3 days after surgery. The administration of ulinastatin during surgery had an inverse association with CSA-AKI.

In a multivariate logistic regression analysis (Table 3), the

Table 2. The Results of a Univariate Analysis for Determining the Risk Factors for AKI.

Variable	Odds ratio	95% CI	p
Age (≥ 65 vs. < 65 years)	1.367	1.145-1.632	0.001
Male gender	1.553	1.320-1.828	< 0.001
BMI	1.335	1.184-1.504	< 0.001
Baseline			
History of hypertension	1.958	1.653-2.319	< 0.001
History of diabetes mellitus	1.478	1.143-1.911	0.003
Insulin-controlled diabetes	1.786	1.291-2.472	< 0.001
COPD	1.436	0.083-2.567	0.222
AMI	1.108	0.720-1.703	0.641
History of chronic kidney disease	1.389	0.746-2.588	0.300
Cerebrovascular disease	1.357	0.941-1.958	0.102
Coronaryangiography	1.061	0.896-1.257	0.493
Ejection fraction ($\geq 35\%$ vs. $< 35\%$)	1.875	0.995-3.532	0.052
Creatinine ($> 88.4 \mu\text{mol/L}$)	3.429	1.926-6.107	< 0.001
Statins	1.091	0.906-1.314	0.356
Phosphocreatine	1.138	0.855-1.516	0.376
Intraoperative			
CPB duration (≥ 110 vs. < 110 min)	1.646	1.388-1.952	< 0.001
Aortic cross-clamp time (≥ 60 vs. < 60 min)	1.305	1.095-1.556	0.003
MAP (≤ 60 vs. > 60 mmHg)	1.182	0.966-1.446	0.104
RBCs transfused	1.009	1.077-1.121	< 0.001
Need for cardioversion	0.839	0.702-1.003	0.054
Mannitol	0.194	0.020-1.872	0.156
Ulinastatin	0.712	0.578-0.877	0.001
Hydroxyethyl starch	0.973	0.757-1.251	0.832
Nasopharyngeal temperature during lowest flow of CPB	1.660	1.391-1.980	< 0.001
Haematocrit (≤ 20 vs. > 20 min)	1.011	0.993-1.029	0.233
Postoperative			
Mechanical ventilation (≥ 9 vs. < 9 h)	1.869	1.585-2.205	< 0.001
Lactic acid (≥ 2 vs. < 2 mmol/L)	1.198	1.017-1.412	0.030
Body temperature ($> 38^\circ\text{C}$) within 3 days after surgery	1.252	1.063-1.475	0.007
Administration of NSAIDs	0.919	0.774-1.091	0.332

Table 3. The Results of a Multivariable Analysis Examining the Covariate Factors Associated with AKI Development.

Variable	Odds ratio	95% CI	p
Male gender	1.41	1.17-1.71	< 0.001
BMI	1.29	1.11-1.49	0.001
History of hypertension	1.49	1.21-1.84	< 0.001
Insulin-controlled diabetes	1.56	1.06-2.30	0.025
Creatinine ($> 88.4 \mu\text{mol/L}$)	1.87	0.94-3.72	0.074
Nasopharyngeal temperature during CPB	1.22	0.97-1.53	0.090
Red blood cells transfused	1.08	1.05-1.11	< 0.001
CPB duration ≥ 110 min	1.31	1.07-1.61	0.009
Mechanical ventilation ≥ 9 h	1.45	1.20-1.75	< 0.001
Ulinastatin administration	0.69	0.56-0.88	0.006
Body temperature ($> 38^\circ\text{C}$) within 3 days after surgery	1.23	1.02-1.50	0.032

variables found to be statistically significant in the univariate analysis were all entered as determinants of AKI. The independent risk factors for CSA-AKI were male gender (OR, 1.41, 95% CI, 1.17-1.71 $p < 0.001$), BMI (OR, 1.29, 95% CI, 1.11-1.49, $p = 0.001$), history of hypertension (OR, 1.49, 95% CI, 1.21-1.84, $p < 0.001$), insulin-controlled diabetes (OR, 1.56, 95% CI, 1.06-2.30, $p = 0.025$), RBC units transfused (OR, 1.08, 95% CI, 1.05-1.11, $p < 0.001$), CPB duration ≥ 110

minutes (OR 1.31, 95% CI, 1.07-1.61, $p = 0.009$), mechanical ventilation time ≥ 9 hours (OR, 1.45, 95% CI, 1.20-1.75, $p < 0.001$), and body temperature ($> 38^\circ\text{C}$) within 3 days after surgery (OR, 1.23, 95% CI, 1.02-1.50, $p = 0.032$). Notably, the administration of ulinastatin was found to be beneficial for protecting against CSA-AKI development (OR, 0.69, 95% CI, 0.56-0.88, $p = 0.006$) after adjustment for age, gender, BMI, history of hypertension, insulin-controlled diabetes, blood units transfused, CPB duration, and mechanical ventilation time.

AKI and the need for RRT are risk factors for mortality

Kaplan-Meier survival curves (Figure) showed that KIDGO stage 2-3 AKI was associated with an increased 30-day mortality risk compared with stage 0 (chi-square: 12.28, $p < 0.001$; 242.05, $p < 0.001$, respectively), while no significant association was found with stage 1 (chi-square: 0.762, $p = 0.383$).

The multivariable Cox proportional hazards model analysis revealed that AKI was an independent predictor of in-hospital mortality (unadjusted and adjusted HR: HR 2.14, 95% CI, 1.13-4.08, $p = 0.02$; HR 3.16, 95% CI, 1.38-7.20, $p = 0.006$, respectively), not of ICU mortality. The need for

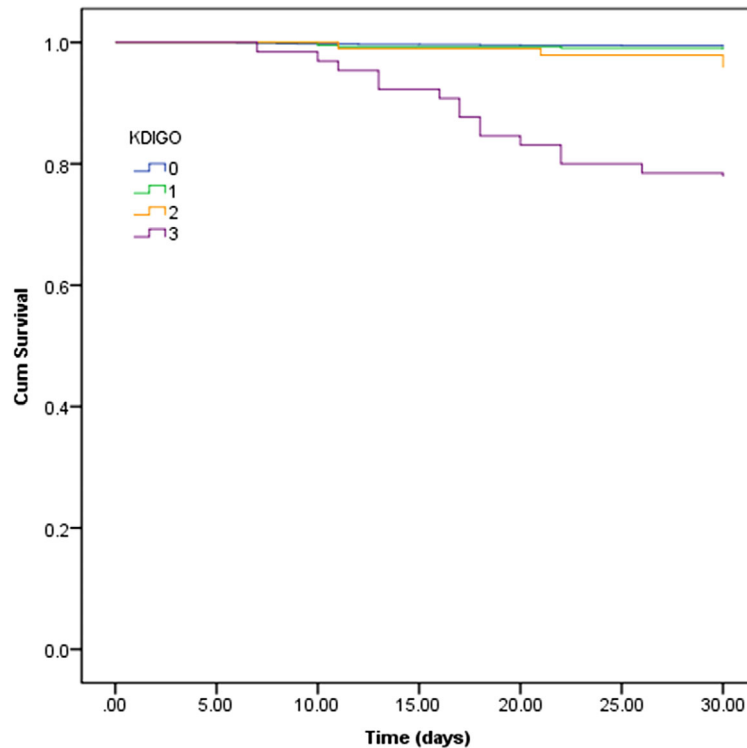


Figure. A Kaplan-Meier curve of the overall survival for the patients divided into four groups according to the KDIGO classification.

Table 4. The Influence of AKI and RRT on the Length of the ICU Stay and the Length of the Hospital Stay.

Variable	Unadjusted hazard ratio (95% CI)		Adjusted hazard ratio(95% CI)	
	ICU LOS	Hospital LOS	ICU LOS	Hospital LOS
AKI	1.28(0.64-2.54)	2.14(1.13-4.08) *	2.10 (0.842-5.224)	3.16(1.38-7.1984) *
RRT	5.97(2.59-13.76) #	18.74(8.66-40.55) #	8.31 (2.98-23.18)	23.86(9.31-60.15) #

*p<0.05, #p<0.001; Adjusted for age, gender, BMI, mechanical ventilation time, and CPB duration.

RRT was an independent risk factor for both ICU and in-hospital mortality (unadjusted and adjusted HR: HR 5.97, 95%CI 2.59-13.76, p<0.001; HR 8.31, 95%CI, 2.98-23.18, p<0.001, respectively) and in-hospital length of stay mortality (unadjusted and adjusted HR: 18.74, 95%CI, 8.66-40.55, p<0.001; HR 23.86, 95%CI 9.31-60.15, p<0.001) (Table 4).

Discussion

In the present study we investigated the incidence of AKI, as defined by the KDIGO classifications, in patients after cardiac surgery and evaluated the impact of AKI on 30-day mortality rates. We also identified the potential risk factors and preventive factors for AKI. In contrast to previous studies, our main findings were that a body temperature greater than 38°C within 3 days after cardiac surgery was an independent risk factor, while the administration of ulinastatin played a beneficial role in the development of AKI.

Our results demonstrated that the postoperative AKI incidence of cardiac surgery was 36%, conflicting with a previous finding of 8.9% (13), and 39% (16) based on AKIN criteria, 31% (17) according to RIFLE criteria, and 14% (18)

based on the KDIGO criteria. The 1.2% rate of requiring renal replacement therapy is consistent with the 1-5% previously reported (19). The mortality rate was 1.5%, which is similar to the reported 1.4% (17). We found that patients with CSA-AKI had a higher hospital mortality rate, longer length of ICU stay and longer length of hospital of stay than patients who did not have CSA-AKI.

Our data demonstrated that KDIGO stages 2 and 3 were associated with a significant increase in the overall 30-day mortality compared with stage 0, while no significance was found between stages 1 and 0. Furthermore, the patients needing RRT had a significantly higher risk of mortality than those who did not need RRT. Liotta (20) reported that even a minimal elevation in the postoperative serum creatinine values of <0.3 mg/dL was associated with increased long-term mortality over 6 years of follow-up, but not with mortality within 30 days of surgery. In his study, AKI groups 2 (creatinine 0.3 to 0.5 mg/dL) and 3 (creatinine >0.5 mg/dL) were strongly associated with increased mortality in both the short and long term. The slight discrepancy with our results is probably due to their use of different methods of classification from our own study.

Our study showed that men were more likely to experience AKI than women, which differs from the findings of Rosner's study (21) but concurs with the findings of other studies (22, 23). We observed a higher frequency of coronary heart disease, hypertension, and diabetes mellitus among men, suggesting that these factors may contribute to some extent to men being more likely than women to experience AKI. Our data revealed that RBC transfusion during surgery was an independent risk factor for AKI, which was in agreement with the findings of previous studies (24). However, although RBC transfusion was found to be associated with a high risk of AKI, the "ideal" transfusion thresholds in cardiac patients remain largely unknown (25). The mechanisms by which intraoperative RBC transfusions contribute to CSA-AKI have not been fully clarified, although one suggested mechanism involves the changes that occur to RBCs during storage, such as decreased deformability, depletion of ATP and 2,3-diphosphoglycerate, an inability to generate nitric oxide, increased adhesiveness to vascular endothelium, and an increase in the levels of potassium cytokines, iron, and free hemoglobin. These factors may lead to the impairment of oxygen delivery, the activation of oxidative stress, and the exacerbation of the inflammatory response, which eventually result in the kidney dysfunction (26).

Our results demonstrated that a CPB time longer than 110 minutes was an independent risk factor for CSA-AKI. The pathogenesis mechanism of CPB may cause an immunoreactive state where neutrophils are activated and recruited in tissues, resulting in tissue edema and necrosis and subsequently causing the organ's dysfunction (27).

Our data showed that mechanical ventilation duration greater than 9 hours was an independent risk factor in the development of AKI. Recently, van den Akker et al. (28) found that mechanical ventilation exceeding 24 hours is related to a 3-fold risk of developing AKI in critically ill patients. Heringlake (29) analyzed the incidence of AKI in 584 subjects with different times to extubation, suggesting that the length of postoperative positive pressure ventilation is a significant risk factor for the development of CSA-AKI.

One of our main findings was that a body temperature greater than 38°C within 3 days after cardiac surgery was significantly associated with the development of AKI. To our knowledge, this is the first study to identify the postoperative body temperature as a risk factor of CSA-AKI. Body temperature is a basic vital sign; both hyperthermia and hypothermia can lead to an imbalance in the metabolism. A postoperative fever is a common complication of cardiac operations using cardiopulmonary bypass (30). Our data showed that the post-operative fever (body temperature greater than 38°C) rate was 38.5% and an independent risk factor for CSA-AKI. Early postoperative fever (>38°C in the first 72 hours) is a common phenomenon and rarely caused by an infection (31). Systemic inflammatory responses commonly occur as postoperative complications in patients undergoing cardiac surgery with cardiopulmonary bypass (32),

and one manifestation of such a response is an elevated body temperature, usually greater than 38°C. Inflammatory responses play a key role in the development of AKI after cardiac operations (33). Therefore, a postoperative fever should be properly managed in order to reduce the risk of CSA-AKI.

In a newly published review, Thiele (34) found that there are currently no effective prophylactic pharmacologic agents for preventing the development or reducing the risk of CSA-AKI. We tried to determine the influence of perioperative medications such as statins, phosphocreatine, ulinastatin, and NSAIDs on the development of AKI. The results showed no obvious protective effect of phosphocreatines on reducing the risk of AKI. Statins have been shown to have anti-inflammatory effects by reducing the levels of inflammatory cytokines as well as circulating microparticles, which are involved in inflammatory cell activation (35). However, whether or not the use of statins preoperatively can decrease the incidence of CSA-AKI remains controversial (36-38); further studies are therefore needed.

Of note, our data showed that the administration of ulinastatin during CPB played a protective role in reducing the risk of AKI after cardiac surgery by approximately 30%. Ulinastatin, a powerful protease inhibitor derived from human urine, has been proven to possess anti-inflammatory properties and protective effects in many organs such as lung, liver, and kidney (39). Nakanishi et al. (40) found that prepump administration of ulinastatin was effective in suppressing the elevation of interleukin-6 and interleukin-8 soon after coronary artery bypass grafting surgery with cardiopulmonary bypass in a prospective, randomized, double-blind, placebo-controlled study. A meta-analysis of randomized controlled trials also suggested the ulinastatin could significantly reduce the cytokine concentrations in patients undergoing cardiac surgery compared with those who received placebo (32). Compared with ulinastatin, aprotinin, a serine protease inhibitor derived from bovine lung tissue which has antifibrinolytic and anti-inflammatory effects (41), was mainly used to reduce perioperative bleeding and transfusion in cardiac surgery (42), but its renoprotective role is still controversial (43-45). In addition, the protective role of ulinastatin was also confirmed by a propensity score matched study (46). Further prospective, randomized, controlled trials are warranted to confirm the protective role of ulinastatin in the development of CSA-AKI.

Limitations

Several limitations associated with the present study warrant mention. First, our study is a retrospective, single-center study, making it prone to bias. Second, due to the lack of urine output values, only creatinine was employed to determine whether or not a patient met the AKI criteria. In addition, determining the presence of AKI based on the urine output is not very practical, due to the urinary catheters being usually removed around two days after surgery.

Conclusion

Our study showed that, when the KDIGO definition was applied, CSA-AKI commonly occurred in adult patients who underwent cardiac surgery with CPB and was associated with in-hospital mortality and a longer length of ICU and hospital stay. Mechanical ventilation duration, RBC transfusions during surgery, and a postoperative body temperature greater than 38°C within 3 days after surgery were found to be independent risk factors for CSA-AKI. Our findings suggest that effective and proper management of these modifiable risk factors may decrease the risk of developing AKI in this setting. Furthermore, the administration of ulinastatin may be beneficial for patients undergoing cardiac surgery.

The authors state that they have no Conflict of Interest (COI).

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