Persistent Kidney Injury at Hospital Discharge After Cardiac Surgery With Cardiopulmonary Bypass in Patients With Normal Preoperative Serum Creatinine and Normal Estimated Glomerular Filtration Rate

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Objective: **Acute kidney injury is a serious complication after cardiac surgery. Although it resolves in most cases, a significant portion of patients persistently have raised creatinine values at hospital discharge. These patients are at greater risk for developing chronic kidney disease and mortality. Therefore, the present study aimed to ascertain risk factors of persistent acute kidney injury after cardiac surgery in patients with normal preoperative renal function.**

Design: **Prospective cohort study.**

Setting: **Tertiary heart centers.**

Participants: **2,181 adult cardiac surgical patients, predominantly Asian.**

Interventions: **Cardiac surgery between August 2008 and July 2012.**

Measurements and Main Results: **The incidence of acute kidney injury, as defined by the Acute Kidney Injury Network stage 1 criteria, was 21.7%. At discharge, 10.5% of these patients had persistent kidney injury, which was defined as a $\geq$26.4 μmol/L ($\geq$0.3 mg/dL) difference between preoperative and discharge creatinine levels and/or a 50% rise in serum creatinine. These patients were more likely to be aged $\geq$70 years (relative risk = 2.232, 95% confidence interval = 1.326-3.757, p = 0.003), have a higher peak postoperative creatinine value within 48 hours (relative risk = 1.007, 95% confidence interval = 1.004-1.010, p < 0.001), and have lower hemoglobin on intensive care unit arrival (relative risk = 0.759, 95% confidence interval = 0.577-0.998, p = 0.048).**

Conclusions: **Age $\geq$70 years, higher peak postoperative creatinine within 48 hours, and lower hemoglobin on intensive care unit arrival are associated with persistent acute kidney injury. Strategies to improve hemoglobin on intensive care unit arrival potentially can reduce persistent acute kidney injury. The authors recommend that patients aged $\geq$70 years undergo further renal evaluation for better risk stratification.**

KEY WORDS: acute kidney injury, age groups, cardiac surgical procedures, cardiopulmonary bypass, glomerular filtration rate, hemodilution, anemia

ACUTE KIDNEY INJURY (AKI) is a common and serious complication after cardiac surgery, affecting up to 30% of patients.[1] Typically, patients who survive AKI have resolution of their condition and achieve almost full or full recovery of their renal function within a week.[2–4] However, recently published data showed that in a significant number of patients, the renal function remained impaired and persisted up to the time of hospital discharge.[5] This corroborates other studies that showed that patients with AKI may not have resolution of their AKI.[2] These patients are at greater risk for developing chronic kidney disease (CKD), renal failure, and mortality.[3,4,6]

Perioperative risk factors associated with AKI after cardiac surgery have been studied extensively;[7] however, there is a paucity of studies that look at the perioperative risk factors of persistent AKI at the time of hospital discharge among AKI patients after cardiac surgery. In the absence of efficacious therapy, it is important to identify the patients who survive AKI after cardiac surgery but continue to have renal impairment postoperatively. The aim of this study was to identify risk factors that contribute to persistent AKI after cardiac surgery in patients with normal preoperative renal function.

MATERIALS AND METHODS

With institutional review board approval, data of 2,250 patients who had normal preoperative renal function and underwent cardiac surgery with cardiopulmonary bypass (CPB) between August 2008 and July 2012 at two South-East Asian tertiary heart centers, at which predominantly Chinese patients are seen, were included. Written informed consent was obtained. Only patients who underwent coronary artery bypass graft (CABG), valve, and combined CABG and valve surgery were included. Sixty-nine patients were excluded from the study because they had missing postoperative creatinine values (n = 8) and missing discharge creatinine values (n = 61). The total number of patients who met the inclusion and exclusion criteria was 2,181. The normal creatinine range was considered to be 60 μmol/L to 105 μmol/L (0.7-1.2 mg/dL) for males and 40 μmol/L to 75 μmol/L (0.5-0.8 mg/dL) for females. The normal estimated glomerular filtration rate (eGFR) was considered to be $\geq$60 mL/minute/1.73 m^2 and calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which has been previously validated in the local population.[8]

All perioperative data were collected prospectively and collated in a central database. Full-time personnel who were blinded to the details of the study analyzed the outcomes from the reports. Quality assurance checks of the database showed a missing data rate of <5% and a data entry error of <5%.

AKI was the primary outcome, defined by an absolute increase in serum creatinine of $\geq$26.4 μmol/L ($\geq$0.3 mg/dL) (ΔCr) and/or a 50% rise in serum creatinine from preoperative to peak postoperative serum creatinine (Acute Kidney Injury Network [AKIN] criteria).[9] AKI patients are said to have persistent AKI when the difference between the discharge and preoperative creatinine is $\geq$26.4 μmol/L ($\geq$0.3 mg/dL) (ΔCr) and/or a 50% rise in serum creatinine. The discharge serum

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This research was supported by a grant from the Khoo Research Grant (Grant number: R-913-200-023-304) from the Duke-NUS Graduate Medical School, Singapore.

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1053-0770/2601-0001$36.00/0

http://dx.doi.org/10.1053/j.jvca.2014.05.007

creatinine value used was that obtained closest to discharge, typically within 48 hours of discharge. If a material change had occurred in the patient's condition, the serum creatinine measurement would be repeated on the day of discharge, and that value would be used as the discharge serum creatinine.

Perioperative surgical management and clinical practices at both institutions were similar and followed international practices. Typically, anesthesia was induced with intravenous induction agents (etomidate or propofol) and maintained with a balanced anesthesia regimen of low-dose fentanyl (10-20 μg/kg) and volatile agents (primarily sevoflurane). Conventional CPB circuits with roller pumps, membrane oxygenators, heat exchangers, venous reservoirs, cardiotomy suction, and arterial blood filters were used. The volume of prime used in the CPB circuits was typically between 1,300 and 1,400 mL. Perfusion targets were mild-to-moderate hypothermia (32°C-35°C), hematocrit levels of ≥22%, activated coagulation times of >400 seconds, glucose levels of <10 mmol/L, non-pulsatile flow rate of 2.2 L/min/m^2 to 2.4 L/min/m^2, and mean arterial pressure of 50 to 70 mmHg. Myocardial protection was achieved with cold blood cardioplegia. Aprotinin was not used in any of the patients.

Population demographic characteristics, medical history, preoperative risk assessment, intraoperative variables, and postoperative outcomes were analyzed descriptively. Univariate analyses were carried out by using two-tailed independent sample *t* test for numerical factors and chi-square test for categoric factors. Variables with a p value <0.1 by univariate analyses were selected and were included in the multivariate analysis. Multivariate analysis was performed using the Poisson regression model with robust estimator to estimate the adjusted relative risk (RR) of developing persistent AKI postoperatively for cardiac patients. Collinearity among the factors was checked. To compare the mean preoperative serum creatinine and eGFR among the non-AKI, transient, and persistent AKI groups of patients, one-way ANOVA was performed. All statistical analyses were performed using IBM SPSS v. 21.0 (Chicago IL).

RESULTS

A total of 2,250 patients with normal serum creatinine and normal eGFR underwent cardiac surgery during the study period. Of these, 2,181 patients met the inclusion and exclusion criteria of the study. A total of 474 (21.7%) patients developed AKI postoperatively, and 50 (10.4%) of these AKI patients developed persistent AKI with raised creatinine values at discharge.

The AKI patients who developed persistent AKI were more likely to be ≥70 years old and to have preoperative anemia. Other risk factors included higher peak postoperative creatinine value, lower hemoglobin value on arrival in the intensive care unit (ICU), and lowest hemoglobin in the first 24 hours in ICU. Patients with persistent AKI also were more likely to have a new need for dialysis (Table 1).

The multivariate analysis identified the risk factors contributing to persistent AKI as aged ≥70 years, higher peak postoperative creatinine values, and lower hemoglobin on arrival in the the ICU (Table 2).

The mean age of the present cohort was 57.8 ± 9.7 years. The mean age of patients who developed AKI was 61.3 ± 9.7 years (range, 21-84 years old). The number of AKI patients who were aged ≥70 years was 97 (20.5% of the AKI population). These patients had an incidence of 18.6% for persistent AKI compared with an incidence of 8.5% in those who were aged <70 years (p = 0.008). After adjusting for other statistically significant factors, age ≥70 years was found to be independently associated with persistent AKI (RR = 2.232, 95% confidence interval [CI] = 1.326-3.757, p = 0.003) (Fig 1).

There was no significant difference in the mean preoperative serum creatinine of the non-AKI, transient AKI, and persistent AKI patients for those aged ≥70 years old and <70 years old. However, the mean preoperative eGFR was significantly higher in the group that did not develop AKI for patients aged <70 years. The mean preoperative eGFR for patients aged ≥70 years was similar among the 3 groups of patients (Table 3).

A higher peak postoperative creatinine value within 48 hours was independently associated with persistent AKI

Table 1. Univariate Analysis of Perioperative Risk Factors and Outcomes Associated With Persistent AKI

Perioperative Risk Factors and Outcomes	Persistent AKI (n = 50)	Transient AKI (n = 424)	p Value
Preoperative			
Age (≥70 years old)	18 (36.0)	79 (18.6)	0.008
Age (years)	63.4 (10.0)	61.1 (9.7)	0.110
Gender: male	40 (80.0)	344 (81.1)	0.849
Race: Chinese	27 (54.0)	268 (63.2)	0.213
Race: Malay	15 (30.0)	75 (17.7)	
Race: Indian	5 (10.0)	55 (13.0)	
Race: Other	3 (6.0)	26 (6.1)	
Weight (kg)	68.5 (11.6†)	67.8 (13.7†)	0.752
Height (cm)	163.0 (7.2†)	163.3 (8.2†)	0.777
Preoperative anemia	25 (50.0)	140 (33.0)	0.027
History of hypertension	41 (82.0)	331 (78.1)	0.590
History of diabetes mellitus	27 (54.0)	200 (47.2)	0.373
History of myocardial infarction	31 (62.0)	252 (59.4)	0.763
History of congestive heart failure	14 (28.0)	75 (17.7)	0.086
Medication: ACE inhibitor	32 (64.0)	215 (50.7)	0.099
EuroSCORE logistic	5.89 (9.66†)	4.60 (6.95†)	0.236
Intraoperative			
Surgery: CABG only	36 (70.0)	307 (72.4)	0.078
Surgery: CABG with valve	5 (10.0)	37 (8.7)	
Surgery: Valve only	9 (18.0)	80 (18.9)	
Surgery status (urgent/emergent)	11 (22.0)	59 (13.9)	0.140
Lowest hematocrit during CPB (%)	22.7 (3.1†)	23.7 (3.9†)	0.089
RBC transfusion	25 (49.0)	159 (37.0)	0.093
IABP	13 (26.0)	86 (20.3)	0.347
Aortic cross-clamp time	81.4 (50.7†)	80.9 (47.9†)	0.950
CPB time (min)	145.5 (77.7)	134.8 (62.9)	0.271
Postoperative			
Highest creatinine in ICU (μmol/L)	190.4 (79.7†)	143.2 (53.3†)	<0.001
First Hb in ICU (g/dL)	9.4 (1.5†)	10.0 (2.2†)	0.041
Lowest Hb in first 24 hours (g/dL)	8.8 (1.2†)	9.2 (1.5†)	0.033
Outcome			
New need for dialysis	9 (18.0)	16 (3.8)	<0.001
Length of hospitalization	18.0 (21.2†)	14.7 (13.9†)	0.284

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; EuroSCORE, European System for Cardiac Operative Risk Evaluation; Hb, hemoglobin; IABP, intra-aortic balloon pump; ICU, intensive care unit; RBC, red blood cell.

†Data are presented as number (percent) or mean (standard deviation).