Use of minimally invasive surgery and therapies mitigating pulmonary arterial pressure and intraoperative blood loss may offer protection against cardiac surgery-associated acute kidney injury

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Abstract

Background: Cardiac surgery-associated acute kidney injury (CSA-AKI) is associated with increased morbidity and mortality. We aimed to identify potentially modifiable risk factors for CSA-AKI.

Methods: This was a single-center retrospective cohort study of 495 adult patients undergoing cardiac surgery. AKI was diagnosed and staged using full KDIGO criteria incorporating baseline serum creatinine (SC) levels and correction of postoperative SC levels for fluid balance. We examined the association of routinely available clinical and laboratory data with AKI using multivariate logistic regression modeling.

Results: A total of 103 (20.8%) patients developed AKI: 16 (15.5%) patients were diagnosed with AKI upon hospital admission, and 87 (84.5%) patients were diagnosed with CSA-AKI. Correction of SC levels for fluid balance increased the number of AKI cases to 104 (21.0%), with six patients categorized to different AKI stages. Univariate logistic regression analysis identified five preoperative (age, sex, diabetes mellitus, preoperative systolic pulmonary arterial pressure (PSPAP), acute decompensated heart failure) and five intraoperative predictors of AKI (age, sex, red blood cell (RBC) volume transfused, use of minimally invasive surgery, duration of cardiopulmonary bypass). When all preoperative and intraoperative variables were incorporated into one model, six predictors remained significant (age, sex, use of minimally invasive surgery, RBC volume transfused, PSPAP, duration of cardiopulmonary bypass). Model-discrimination performance showed an area under the curve of 0.69 for the model including only preoperative variables, 0.76 for the model including only intraoperative variables, and 0.77 for the model including all preoperative and intraoperative variables.

Conclusions: Use of minimally invasive surgery and therapies mitigating PSPAP and intraoperative blood loss may offer protection against CSA-AKI. Trial Registration: www.ClinicalTrials.gov (NCT03102528)

Introduction

Cardiac surgery-associated acute kidney injury (CSA-AKI) occurs in approximately one-third of patients, and represents one of the most important negative predictors of outcome in this population [1, 2]. CSA-AKI is associated with an increased prevalence of hospitalization and readmission to hospital[3] and risk of short- and long-term mortality [4, 5]. Even if kidney injury is relatively modest, it is associated independently with increased morbidity and mortality, including the long-term risk of end-stage renal disease [1, 6]. Nevertheless, there are few tools to predict CSA-AKI in the early postoperative period.

Recognizing general and center-specific risk factors (especially modifiable risk factors) could help clinicians to mitigate the risk of CSA-AKI and CSA-AKI-associated complications. Novel urinary biomarkers have been favored for early postoperative recognition of CSA-AKI, however, these do not measure risk before exposure and may not be available routinely [7]. Several tools to stratify the risk of AKI have been introduced into clinical practice and have shown good discrimination in most of the populations tested, but have been tested only for severe CSA-AKI necessitating dialysis [8–10]. Thus, the

benefits of using these risk models may be limited due to the small number of patients needing dialysis after surgery [11].

Few research teams have attempted to predict overall CSA-AKI using full Kidney Disease: Improving Global Outcomes (KDIGO) consensus criteria [12]. Two models have been proposed: Jiang and colleagues included variables from the preoperative to early postoperative period to predict CSA-AKI in a Chinese population [13]; Chen and co-workers used preoperative variables only to predict AKI after isolated coronary artery bypass grafting in a Taiwanese population [14]. No research team has utilized full KDIGO consensus criteria for AKI to incorporate a reference value for the serum creatinine (SC) level at baseline and correction of the postoperative SC level for fluid balance. Both factors are important because the AKI diagnosis is reliant on the baseline SC level, which reflects steady-state kidney function most appropriately but is often unavailable upon hospital admission [15]. This is particularly true for patients undergoing emergency or urgent surgical procedures, who often exhibit upstaging of AKI if the reference baseline SC level is taken into account. Also, fluid accumulation seen typically within the first days after cardiac surgery may dilute SC and delay the diagnosis and staging of AKI [16].

We sought to determine the utility of routinely available preoperative and intraoperative clinical and laboratory data for the prediction of CSA-AKI. AKI was diagnosed taking the baseline SC level and correction of the postoperative SC level for fluid balance into account.

Methods

Study design and participants

This was a single-center retrospective cohort study of adult patients undergoing cardiac surgery between November 2014 and October 2015 at San Bortolo Hospital. We analyzed data on 729 adult patients undergoing cardiac surgery (elective, urgent and emergency; coronary artery bypass, valve replacements, combined or other surgery) (Fig. 1). Approval of the study protocol was obtained from the Human Research Ethics Committee of San Bortolo Hospital (Vicenza, Italy; 79/16 D). The study protocol complied with the tenets of the Declaration of Helsinki.

Cardiac surgery was performed as conventional sternotomic or minimally invasive cardiac surgery. Conventional sternotomic approach was the standard of care for a) isolated coronary artery bypass graft; b) coronary artery bypass graft combined with other surgeries (valvular surgery, maze procedure, replacement of the ascending aorta or surgery of atrial septal defects and cardiac tumors); and c) replacement of the ascending aorta with or without valve surgery. Minimally invasive surgery included both mini-sternotomic and endoscopic surgical approaches. The endoscopic surgical approach was the standard of care for mitral valve and tricuspid valve surgeries, and surgery of atrial septal defects and cardiac tumors with no patient selection and without additional preoperative examinations. 60% of aortic valve surgeries were performed with endoscopic surgical approach; the other 40% were performed with a mini-sternotomic approach. Regardless the surgery, the standard setup for the minimally invasive group

included one 3 cm working port (periareolar incision for mitral and tricuspid valve surgery, and atrial septum defect surgery; prepectoral incision for isolated aortic valve or combined aortic and other valve surgery) and two 5 mm miniports for the introduction of the 30° thoracoscope and the left ventricle vent-line. In all patients undergoing minimally invasive surgery, cardiopulmonary bypass (CPB) was achieved from femoral vessels with retrograde perfusion.

Patients were excluded if (I) the baseline SC level or SC level within 3 days before hospital discharge were not available; (II) they had stage-5 chronic kidney disease (CKD) [17]; (III) they were recipients of dialysis before surgery or solid-organ transplantation.

Laboratory methods

SC levels were obtained from the Department of Clinical Chemistry and Hematology Laboratory within San Bortolo Hospital to avoid inter-laboratory variations. The SC level was measured by an enzymatic method (IL test™; Instrumentation® Laboratory, Milan, Italy) on an ILab650 analyzer (Werfen, Barcelona, Spain). The glomerular filtration rate (GFR) was estimated using the CKD Epidemiology Collaboration equation [18].

Data collection

We abstracted clinical variables from the medical records of patients. Use of renal replacement therapy (RRT) was undertaken according to the discretion of the treating physician. Complications were recorded, and postoperative myocardial infarction and stroke were defined as described previously [19]. The SC level at baseline was considered to be the value within 90 days before surgery, which reflects steady-state kidney function most appropriately [12]. Positive fluid balance and hemodilution were considered in the diagnosis and staging of AKI using the following formula [16]:

Adjusted SC level = SC × correction factor

where the correction factor = (weight (kg) upon hospital admission × 0.6 + Σ (daily cumulative fluid balance (L)))/hospital admission weight × 0.6

Use of potentially nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides, vancomycin, intravenous contrast media) during the study period was recorded.

Endpoints

The primary endpoint was to determine the predictive variables of AKI using multivariate logistic regression models. AKI development was diagnosed within 7 days after cardiac surgery as determined by a Clinical Adjudication Committee using full consensus criteria from KDIGO [12]. The secondary endpoint was the prevalence of renal recovery upon hospital discharge. “Renal recovery” was defined as the absence of any stage of AKI according to the SC level or urine output upon hospital discharge, as described previously [20]. We considered death before hospital discharge to be “non- recovery” because

renal recovery without survival is rare and not patient-centered, as suggested by international consensus recommendations [21, 22].

Statistical analyses

Descriptive statistics are expressed as the mean ± standard deviation or median [interquartile range (IQR)] for continuous variables and analysed by an independent Student's t-test. Shapiro-Wilk test was used to test the Gaussian distribution of the continuous variables. Categorical variables are reported as absolute frequencies and percentages, and were analyzed by the chi-square test or Fisher's exact test, as appropriate. The Student's t-test or chi-square test (or equivalent non-parametric test) were used to compare the two groups: AKI and non-AKI. Successively, we conducted univariate logistic regression for each variable. Variables with $p < 0.05$ were considered to be significant. Then, statistically significant or clinically relevant variables were gathered into three groups and used in three stepwise backward multivariate logistic regression analyses: preoperative, intraoperative, and intensive care unit (ICU) stay. The selected models were finally combined in an unitary logistic regression model, which after postestimation analysis included only preoperative and intraoperative variables. All the models were verified with respect to collinearity and the interactions between variables to guard against confounding. The goodness of fit was calculated by the Hosmer–Lemeshow test. The accuracy of the classification was assessed by analyses of receiver operating characteristic (ROC) curves and the Akaike information criterion. The Bonferroni correction was applied to adjust for multiple testing. Analyses were conducted using STATA 14 (Stata Corporation, College Station, TX, USA).

Results

A total of 495 patients were enrolled in our study (Fig. 1). Patient characteristics at baseline as well as clinical data on the surgical procedure and ICU stay are shown in Table 1. Overall, 103 (20.8%) had an episode of AKI during hospitalization: 76 (15.4%) had stage-1, 18 (3.6%) had stage-2, and 9 (1.8%) had stage-3 AKI (Table 2). All patients with stage-3 AKI required RRT and were diagnosed according to both SC and urine output criteria. Of the 103 patients who experienced AKI, 16 (15.5%) patients were diagnosed with AKI upon hospital admission – all had emergency or urgent cardiac surgery – whereas the remaining 87 (84.5%) patients were diagnosed with CSA-AKI within 48 h after surgery. In addition, 73.8% of patients were diagnosed and staged according to positive SC criteria for AKI.

Table 1
Patient characteristics

	Total (n = 495)	Non-AKI group (n = 392)	AKI group (n = 103)	p-value*
Demographics				
Age (years)	64 ± 13	63 ± 13	68 ± 12	0.0001
Sex (males)	335 (67.7%)	273 (69.1%)	62 (60.2%)	0.034
Body mass index (kg/m^2)	24.5 ± 4.6	24.4 ± 4.9	24.8 ± 4.2	0.456
Comorbidities				
Hypertension [yes]	394 (79.6%)	306 (78.1%)	88 (85.4%)	0.098
Atrial fibrillation [yes]	95 (19.2%)	70 (17.9%)	25 (24.3%)	0.141
Diabetes mellitus [yes]	61 (12.3%)	37 (9.4%)	24 (23.3%)	< 0.0001
Heart failure [yes]	16 (12.3%)	7 (1.8%)	9 (8.7%)	< 0.0001
Chronic obstructive pulmonary disease [yes]	35 (7.1%)	23 (5.9%)	12 (11.7%)	0.0421
Coronary heart disease [yes]	141 (28.5%)	95 (23.2%)	46 (44.7%)	< 0.0001
Peripheral vasculopathy [yes]	82 (16.6%)	51 (13.0%)	31 (30.1%)	< 0.0001
Dyslipidemia [yes]	226 (45.7%)	162 (41.3%)	64 (62.1%)	< 0.0001
Previous myocardial infarction [yes]	54 (11.9%)	33 (8.4%)	21 (20.4%)	0.0012
Previous cardiac surgery [yes]	22 (4.4%)	16 (4.1%)	6 (5.8%)	0.234
Medication				
Antiplatelet [yes]	145 (29.3%)	105 (26.8%)	40 (87.4%)	0.0173
Beta-blocker [yes]	252 (50.9%)	190 (48.5%)	62 (60.2%)	0.0342
ACEi or ARB [yes]	268 (54.1%)	212 (54.1%)	56 (54.4%)	0.958
Statin [yes]	184 (37.2%)	130 (33.2%)	54 (52.4%)	< 0.0001
Diuretic [yes][a]	486 (98.2%)	385 (98.2%)	101 (98.1%)	0.140

	Total (n = 495)	Non-AKI group (n = 392)	AKI group (n = 103)	p-value*
Aldosterone antagonist [yes]	42 (8.5%)	32 (8.2%)	10 (9.7%)	0.616
Preoperative intravenous contrast media [yes][b]	63 (13.1%)	39 (9.9%)	24 (23.3%)	< 0.0001
Baseline clinical data				
Leucocytes (× 10^9/L)	6.4 ± 1.9	6.4 ± 1.9	6.4 ± 1.8	0.9408
Hemoglobin (g/dL)	13.8 ± 1.7	14.0 ± 1.7	13.3 ± 1.8	0.001
Platelets (× 10^9/L)	213 ± 50	211.4 ± 48.9	217.63 ± 52.9	0.259
Albumin (g/dL)	4.0 ± 1.1	4.0 ± 1.2	3.9 ± 0.2	0.344
Urea (mg/dL)[c]	37.6 ± 10.5	36.7 ± 9.4	41 ± 13.3	0.0017
NYHA classification				
1	134 (27.1%)	114 (29.1%)	20 (19.4%)	0.0024
2	301 (60.8%)	241 (61.5%)	60 (58.3%)	
3	50 (10.1%)	32 (8.2%)	18 (17.5%)	
4	10 (2.0%)	5 (1.3%)	5 (4.9%)	
Left ventricular ejection fraction (%)	60.5 ± 9.6	60.83 ± 9.32	59.19 ± 10.49	0.1229
Systolic pulmonary arterial pressure (mm Hg)	33.2 ± 10.2	33.03 ± 10.48	33.86 ± 9.28	0.4656
EuroSCORE II for operative risk (%)[d]	2.86±-4.21	2.26 ± 2.84	5.16 ± 6.96	< 0.0001
Surgical clinical data				
Aortic cross-clamp (min)	81.6 ± 32.1	80.2 ± 31.19	86.8 ± 34.9	0.064
Cardiopulmonary bypass time (min)	120.5 ± 43.3	116.58 ± 38.7	135.51 ± 55.3	0.0034
Procedure				
Conventional surgery [yes]				
Coronary artery bypass graft only	52 (10.5%)	46 (11.7%)	6 (5.8%)	0.384

	Total (n = 495)	Non-AKI group (n = 392)	AKI group (n = 103)	p-value*
Combined coronary artery bypass graft and other surgery[e]	46 (9.3%)	36 (9.2%)	10 (9.7%)	0.67
Replacement of the ascending aorta with or without valve surgery	56 (11.3%)	45 (11.5%)	11 (10.7%)	0.344
Minimally invasive surgery [yes]				
Aortic valve surgery	25 (5.0%)	10 (2.6%)	5 (4.9%)	0.034
Mitral valve surgery	122 (24.7%)	88 (22.4%)	34 (33.0%)	0.0002
Tricuspid valve surgery	2 (0.4%)	1 (0.3%)	1 (1.0%)	0.689
Combined valve surgery and other surgery [f]	192 (38.8%)	166 (42.3%)	36 (35.0%)	0.234
Valve procedure				
Valve reconstruction	245 (49.5%)	220 (49.5%)	25 (56.3%)	0.157
Valve replacement	191 (38.6%)	129 (32.9%)	62 (60.1%)	< 0.0001
Bioprosthetic valve	186 (37.6%)	126 (32.1%)	60 (58.3%)	
Mechanical valve	5 (1.0%)	3 (0.8%)	2 (1.9%)	
Urgency				
Elective	399 (80.6%)	315 (80.4%)	84 (81.6%)	0.76
Urgent	56 (11.3%)	45 (11.5%)	11 (10.7%)	0.76
Emergency	40 (8.1%)	32 (8.2%)	8 (7.8%)	0.76
Surgery fluid balance (mL)	3662 ± 1295	3652 ± 1199	3700 ± 1303	0.741
Base excess at end of surgery (mmol/L)[g]	−1.9 ± 2.9	−2.01 ± 2.81	−1.31 ± 3.1	0.0292
HCO_3^- at end of surgery (mmol/L)[g]	22.6 ± 2.5	22.4 ± 2.3	23.1 ± 2.9	0.0113
Serum lactate at end of surgery (mmol/L)[g]	1.8 ± 0.8	1.8 ± 0.7	1.9 ± 1.1	0.0874
Red blood cell volume transfused (mL)	66.1 ± 194.2	42.9 ± 157.7	154.4 ± 278.2	< 0.0001

	Total (n = 495)	Non-AKI group (n = 392)	AKI group (n = 103)	p-value*
ICU clinical data				
Mechanical ventilation (days)	1.5 ± 2.2	1.1 ± 0.6	2.8 ± 4.5	< 0.0001
Intra-aortic balloon pump (days)	0.2 ± 1.0	0.05 ± 0.4	0.6 ± 1.9	< 0.0001
Extra-corporeal membrane oxygenation (days)	0.04 ± 0.5	0 ± 0	0.2 ± 1.0	< 0.0001
Pneumonia [yes]	10 (2.0%)	3 (0.8%)	7 (6.8%)	< 0.0001
Sepsis [yes]	11 (2.2%)	3 (0.8%)	8 (7.8%)	< 0.0001
Re-intervention [yes]	23 (4.7%)	11 (2.8%)	12 (11.7%)	< 0.0001
Fluid balance at day-1 (mL)	−599 ± 847	−709 ± 823	−177 ± 810	< 0.0001
Fluid balance day 2 (mL)	−230 ± 859	−346 ± 815	218 ± 882	< 0.0001
Cumulative fluid balance in the ICU (mL)	−1618 ± 1912	−1679 ± 1662	−1389 ± 2657	0.066
Weight difference (kg)[h]	−0.9 ± 5.4	−1.3 ± 4.9	0.6 ± 7	0.002
Furosemide dose per day (mg)	32.5 ± 58.7	19.7 ± 16	81.4 ± 112.7	< 0.0001
Cumulative colloids (mL)	159.4 ± 293.1	134.4 ± 245.8	254.4 ± 416.1	0.018
Transfusion of red blood cells (mL)	251.3 ± 769.4	116.2 ± 320	764 ± 1461	< 0.0001
ICU stay (h)	78.7 ± 74.2	65.3 ± 37.2	129.8 ± 134.4	< 0.0001
Hospital stay (days)	8.2 ± 7.0	7.3 ± 4.9	11.6 ± 11.5	< 0.0001
In-hospital mortality	4 (0.8%)	0 (0%)	4 (3.9%)	< 0.0001

	Total (n = 495)	Non-AKI group (n = 392)	AKI group (n = 103)	p-value*
Summaries of quantitative variables are the mean ± standard deviation. For categorical variables, the absolute and relative frequencies (as %, in parentheses) for the categories are presented. For dichotomous variables, the respective category is presented in square brackets. Additional data are provided in Additional file 1: Table S1.				
*After application of the Bonferroni correction, $p < 0.0008$ was considered significant.				
[a]Diuretics include loop diuretics and thiazides.				
[b]Intravenous contrast media within 7 days before surgery.				
[c]To convert the value for urea to blood urea nitrogen, multiply by 0.467.				
[d]The European System for Cardiac Operative Risk Evaluation (EuroSCORE) score is calculated by means of a logistic-regression equation and ranges from 0–100%, with higher scores indicating greater risk.				
[e]Other surgery includes valvular surgery, maze procedure, replacement of the ascending aorta, surgery of atrial septal defects, and surgery of cardiac tumors.				
[f]Other surgery includes maze procedure, surgery of atrial septal defects, and surgery of cardiac tumors.				
[g]Sampling of arterial blood gas.				
[h]ICU discharge − hospital admission.				
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; HCO_3^- = bicarbonate; ICU = intensive care unit; NYHA = New York Heart Association.				

Table 2
Outcomes

	Non-AKI group (n = 392)	AKI group (n = 103)	p-value*
Serum creatinine (mg/dL)[a]			
Hospital admission	0.91 ± 0.60	0.99 ± 0.62	0.0005
Postoperative day 1	0.91 ± 0.85	0.83 ± 0.25	0.9839
Postoperative day 2	0.95 ± 0.55	0.99 ± 0.35	0.0152
Hospital discharge	0.82 ± 0.22	1.06 ± 0.50	< 0.0001
Estimated GFR (mL/min/1.73 m^2)[b]			
Hospital admission	86.95 ± 16.71	73.17 ± 20.21	< 0.0001
Hospital discharge	90.6 ± 16.46	71.18 ± 24.50	< 0.0001
AKI at hospital admission	–	16 (15.5%)	N/A
AKI within 48 h after surgery	–	87 (84.5%)	N/A
AKI stage			N/A
1	–	76 (73.8%)	
2	–	18 (17.5%)	
3	–	9 (8.7%)	
Postoperative renal replacement therapy [yes]	–	9 (8.7%)	N/A
Positive AKI criterion			N/A
Serum creatinine	–	76 (73.8%)	
Urine output	–	14 (13.6%)	
Serum creatinine and urine output	–	13 (12.6%)	
Renal recovery state at upon hospital discharge[c]			N/A
Recovery	–	86 (83.5%)	
Non-recovery	–	17 (16.5%)	

Summaries of quantitative variables are the mean ± standard deviation. For categorical variables, the absolute and relative frequencies (as %, in parentheses) are presented for the categories. For dichotomous variables, the respective category is presented in square brackets.

*After application of the Bonferroni correction, $p < 0.008$ was considered significant.

	Non-AKI group (n = 392)	AKI group (n = 103)	p-value*
[a]To convert the values for serum creatinine to μmol/L, multiply by 88.4.			
[b]The estimated GFR was calculated using the Chronic Kidney Disease–Epidemiology			
Collaboration equation [18].			
[c]AKI reversal was defined as the absence of any stage of AKI based on the serum			
creatinine or urine output [20].			
AKI = acute kidney injury; GFR = glomerular filtration rate.			

By correcting the SC level for fluid balance, the total number of AKI cases increased to 104 patients (21.0%) (Table 3). Two patients who previously had stage-1 AKI were now classified as having not developed AKI; three patients with previously did not have AKI were now staged as having stage-1 AKI; and one patient who previously had stage-2 AKI was now classified as having stage-3 AKI (Table 3).

Table 3
Comparison of staging of acute kidney injury with and without correction of serum creatinine for fluid balance

	AKI stages with serum creatinine corrected for fluid balance				
AKI stages	0	1	2	3	Total
0	389	3	0	0	392
1	2	74	0	0	76
2	0	0	17	1	18
3	0	0	0	9	9
Total	391	77	17	10	495
AKI = acute kidney injury.					

The mean estimated GFR upon hospital admission for patients who were found to have AKI subsequently was 73.2 ± 20.2 mL/min/1.73 m^2, and this value was significantly lower than that for people who did not have AKI (86.95 ± 16.71 ml/min/1.73 m^2; $p < 0.0001$). There was no detectable variability in the proportion of patients who developed AKI among the different types of surgical procedure. However, patients with AKI were older (68 ± 12 versus 63 ± 13 years; $p < 0.001$) and more likely to have associated comorbidity (e.g., heart failure, coronary heart disease, peripheral vasculopathy, diabetes mellitus (DM),

chronic obstructive pulmonary disease; Table 1). Overall, patients with AKI were more likely to develop postoperative complications and experience surgical re-interventions. Also, patients with AKI were more likely to require mechanical ventilation, intra-aortic balloon pump and extracorporeal membrane oxygenation for a longer duration in the postoperative period. Furthermore, patients in the AKI group had an increased length of stay in the ICU (129.8 ± 134.4 versus 65.3 ± 37.2 h; $p < 0.0001$) and hospital (11.6 ± 11.5 versus 7.3 ± 4.9 days; $p < 0.0001$).

Seventeen (16.5%) patients in the AKI group did not recover their renal function at the time of hospital discharge, whereas 3 (33.3%) cases remained RRT-dependent. Four patients died; all were in the AKI group.

All variables were brought into an univariate analysis to predict CSA-AKI. Multivariate logistic analysis was conducted at three time periods: preoperative, intraoperative, and during ICU stay, then finally combined in a conclusive model to predict CSA-AKI (Table 4). Significant preoperative variables were age (odds ratio [OR] 1.36, 95% confidence interval [CI] 1.10–1.68), male sex (OR 0.63, 95% CI 0.39–1.02), DM (OR 2.68, 95% CI 1.47–4.90), diagnosis of acute decompensated heart failure (OR 4.69, 95% CI 1.60–13.74), and estimated preoperative systolic pulmonary arterial pressure (PSPAP; OR 3.32, 95% CI 1.15–9.58). Significant intraoperative variables were age (OR 1.24, 95% CI 0.99–1.55), male sex (OR 0.75, 95% CI 0.46–1.25), transfusion volume of red blood cells (RBCs; OR 2.28, 95% CI 1.23–4.23), use of minimally invasive surgery (OR 0.26, 95% CI 0.15–0.43), and duration of CPB (OR 1.24, 95% CI 0.01–1.24). Finally, when all preoperative and intraoperative variables were included into a model, six predictors of AKI remained significant: age (OR 1.24, 95%CI 0.99–1.55), male sex (OR 0.75, 95% CI 0.46–1.25), use of minimally invasive surgery (OR 0.26, 95% CI 0.15–0.43), PSPAP (OR 3.17, 95% CI 1.08–9.29), RBC volume transfused (OR 2.28, 95% CI 1.23–4.23), and duration of CPB (OR 1.24, 95% CI 1.01–1.54).

Analyses of ROC curves for prediction of CSA-AKI are reported in Table 4. Overall, the three risk models had an moderate-to-good discriminatory power for CSA-AKI, with a C-statistic of 0.69 for the model including only preoperative variables, 0.76 for the model including only intraoperative variables, and 0.77 for the model including preoperative and intraoperative variables. All three models exhibited a good negative predictive value but poor positive predictive value.

Multivariate logistic analysis did not reveal significant predictors of renal recovery upon hospital discharge.

Discussion

Key findings

In this retrospective single-center study, we evaluated the preoperative, intraoperative, and ICU risk factors associated with CSA-AKI development. Overall, 20.8% of patients undergoing cardiac surgery were diagnosed with AKI. Of these, 15.5% were diagnosed upon hospital admission when the SC level at

baseline was incorporated – all these patients were admitted for emergency or urgent cardiac surgery. Correction of the SC level for fluid balance increased the total number of AKI cases only marginally, and changed AKI staging in only six patients. In addition, we identified various factors associated with CSA-AKI development, whereas use of minimally invasive surgery, preoperative PASP, and volume of RBC transfusion were identified as potentially modifiable risk factors. Analyses of ROC curves had moderate-to-good discriminatory power for CSA-AKI, with a C-statistic ranging from 0.69 (preoperative variable) to 0.77 (preoperative and intraoperative variables). Finally, none of the collected variables were associated with renal recovery upon hospital discharge.

Relationship with previous studies

The prevalence of AKI in the total cohort and according to stage was similar to that in a meta-analysis involving > 320,000 patients undergoing cardiac surgery published recently [23]. Interestingly, correction of the SC level for fluid balance did not impact the diagnosis or staging of AKI significantly. This finding is in contrast with the work of Moore and colleagues, which showed an increase in AKI occurrence of ~ 12% when adjustment of fluid balance was made [24], and may reflect inter-hospital differences in intraoperative and postoperative standards of care of adult patients undergoing cardiac surgery. Although we detected significant differences in the total amount net fluid balance on postoperative day (POD)1 and POD2 between the AKI group and non-AKI group, these differences were markedly lower compared with those detailed by Moore and colleagues [24], and may explain the differences in AKI occurrence after adjustment of fluid balance.

As expected, we identified various preoperative and intraoperative variables associated with CSA-AKI development. Patients with increased susceptibility to kidney injury (e.g., those with long-term hypertension, DM, or higher age) have a substantially greater risk of developing AKI [25]. Similar to a recent study [26], we identified PSPAP as a risk factor for CSA-AKI. PSPAP has also been independently linked to increased mortality after valve surgery [27]. Increased PSPAP may be due to pulmonary hypertension secondary to left-heart disease but our ability to identify the prevalence and etiology of pulmonary hypertension in this study is limited. Also, the sensitivity and specificity of echocardiography to diagnose pulmonary hypertension are modest [28, 29]. Nevertheless, pulmonary hypertension and right-heart failure have emerged important risk factors for CSA-AKI, with venous congestion as the common cause [30, 31]. Hence, future mechanistic studies investigating therapies mitigating preoperative PSPAP may offer protection against CSA-AKI.

Also, we identified the use of minimally invasive surgery, which was the predominant surgical technique in our study population, to be associated with a low prevalence of AKI; this is likely because of the low risk of postoperative complications and blood transfusion requirement, lower risk of postoperative systemic immune inflammatory syndrome, accelerated recovery, and low use of potential nephrotoxic medications (e.g., non-steroidal anti-inflammatory drugs) [32]. Reports have indicated the noninferiority of this approach to conventional surgery [33], and recent guidelines recommend minimally invasive surgical procedures where expertise is available with an IIa class of recommendation (33). Studies in respect to

renal outcome after minimally invasive surgery have focused on patients undergoing mitral valve or aortic valve surgery [32, 34, 35]. Murzi et al. [35] showed a 1% incidence of CSA-AKI after mitral valve surgery using video-assisted mini-thoracotomy, although in general CPB and cross-clamping times are longer in the port-access procedures [36]. The present study confirms the reported renoprotective benefits of minimally invasive surgery, and this approach may be considered as an alternative to standard median sternotomy valve surgery in patients at high risk for CSA-AKI.

In accordance with the literature [37, 38], we identified perioperative transfusion of packed RBCs to be associated with a high OR of developing CSA-AKI. Changes in intraoperative levels of hemoglobin can cause a proportional decrease in the oxygen-carrying capacity of the blood, which leads to impaired oxygen delivery and hypoxia in renal tissue, particularly if anemia is acute or severe [39]. RBC transfusion, however, has also been associated with increased morbidity and mortality, presumably due to infectious and non-infectious risks [40, 41]. Therefore, it is plausible that, by decreasing the incidence of blood transfusions and bleeding complications (e.g., with minimally invasive valve surgery), CSA-AKI and its associated complications may be reduced. Of note, both variables transfusion of packed RBCs and minimally invasive surgery were not collinear in our analysis emphasizing their independent role in the development of CSA-AKI.

The ability of the model to predict CSA-AKI was worse when compared with previously published and externally validated risk-prediction scores, with the C-statistic ranging from 0.81 to 0.85 [42, 43]. However, those studies also included postoperative variables, which may explain their better performance. Unexpectedly, we did not detect variables that influenced renal recovery.

Study implications

In line with other studies, our study implied that the pathophysiology of CSA-AKI is complex and current risk-prediction tools show only moderate-to-good calibration, suggesting significant heterogeneity in the underlying populations. However, among potentially modifiable risk factors, use of minimally invasive surgery and therapies mitigating preoperative pulmonary arterial pressure and intraoperative blood loss may offer protection against CSA-AKI.

Strengths and limitations of our study

No other research teams have utilized full KDIGO consensus criteria for AKI to incorporate the SC level at baseline and correction of the SC level after surgery for fluid balance for the diagnosis and staging of AKI. The other strength of our study was the assessment of multiple variables at baseline, intraoperatively, and in the ICU. In addition, only few studies evaluated the impact of minimally invasive surgery on CSA-AKI.

Study limitations were its retrospective design, relatively small number of patients, and its single-center location. Thus, our results cannot be extrapolated directly to other patient populations. Also, due to the retrospective nature of the study, complete elimination of selection bias is unlikely. Multivariate logistic

regression analyses verified with respect to collinearity and the interactions between variables were performed to minimize the differences in measured confounders; however, unmeasured confounders cannot be accounted for.

Conclusions

The pathophysiology of CSA-AKI appears to be complex and associated with various risk factors, suggesting significant heterogeneity in the underlying population. However, among potentially modifiable risk factors, use of minimally invasive surgery and therapies mitigating PSPAP and intraoperative blood loss may offer protection against CSA-AKI.

Abbreviations

AKI
acute kidney injury
CKD
chronic kidney disease
CPB
cardiopulmonary bypass
CSA-AKI
cardiac surgery-associated acute kidney injury
DM
diabetes mellitus
GFR
glomerular filtration rate
ICU
intensive care unit
KDIGO
Kidney Disease:Improving Global Outcomes
POD
postoperative day
PSPAP
preoperative systolic pulmonary arterial pressure
RBC
red blood cell
ROC
receiver operating characteristic
RRT
renal replacement therapy
SC

serum creatinine

Declarations

Competing interests
None of the authors declare any competing interests.
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Author contributions
Study concept and design: FH-S, FF, PB, SL-G, THD, SS, MdC, LS, CR. CR conceived the concept underlying the study and is the senior author of the study.
Literature research and clinical advice
FF, GY, BY, H-WB, WS, H-DW, LS.
Acquisition, analysis, or interpretation of data
FH-S, MGQ, FF, PB, SL-G, THD, SS, MdC, LS, GY, BY, H-WB, WS, H-DW, LS, CR.
Adjudication of renal function
S-LG, SS, H-WB.
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Critical revision of the manuscript for important intellectual content
FH-S, MGQ, FF, CR.
Statistical analyses
MGQ, FF.
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Figures

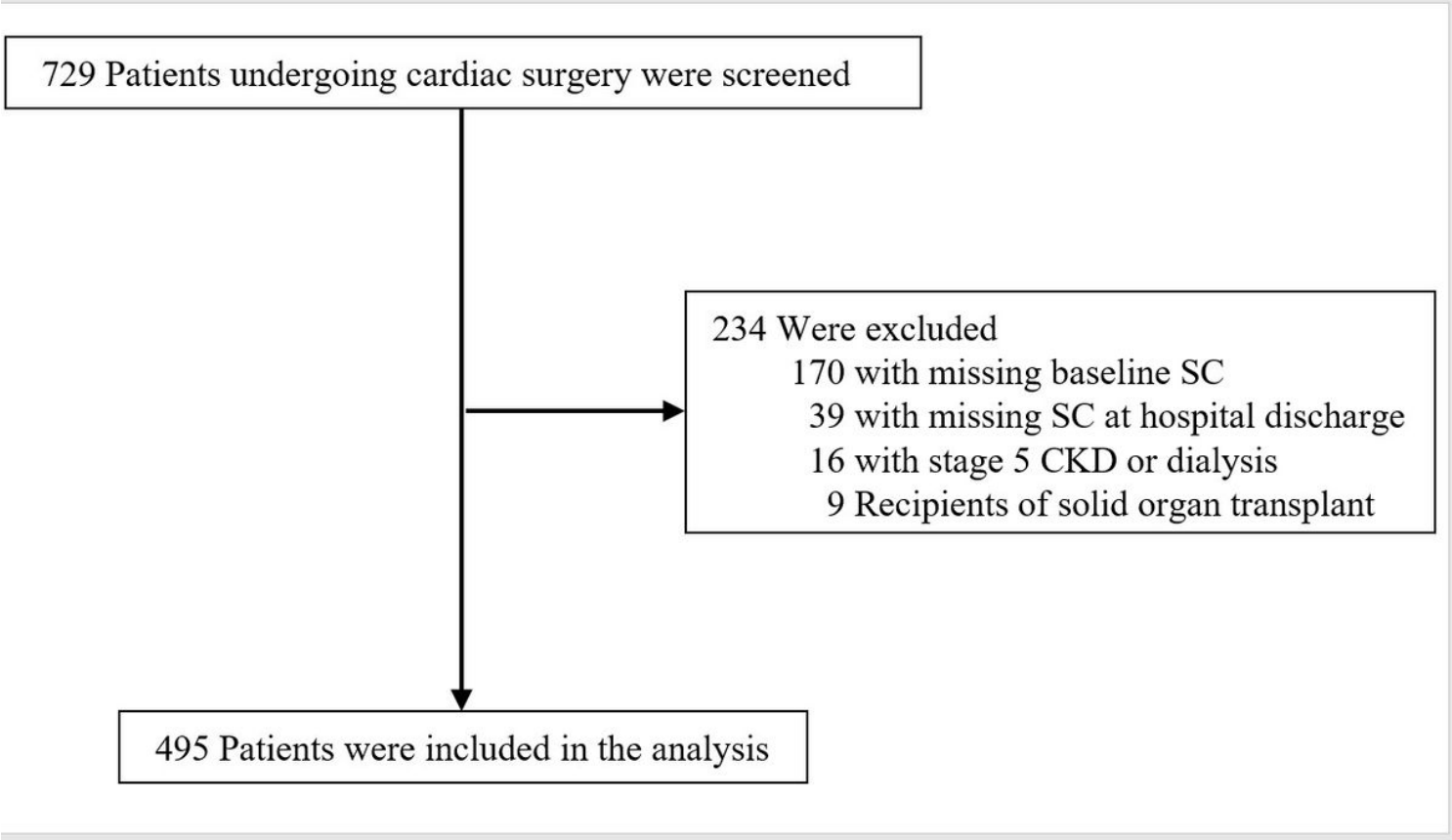

Figure 1

Study flowchart Source population included all adult patients undergoing cardiac surgery. CKD = chronic kidney disease; SC = serum creatinine.

Supplementary Files

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