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Predictors of Early Deterioration of Renal Function in Patients Older Than 70 Years Undergoing Valvular Surgery

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ABSTRACT

Background: Cardiac surgery-associated acute kidney injury (CSA-AKI) is the most common clinically important complication in adult patients undergoing open-heart surgery, with an incidence between 8.9% and 39%. Studies have shown that even a slight increase in serum creatinine levels after cardiac surgery significantly affects the mortality and morbidity of these patients.

Aim: This study sought to determine the predictors and incidence of acute kidney injury (AKI) in patients older than 70 years undergoing elective valvular surgery.

Methods: Prospective study included 156 patients scheduled for elective cardiac surgery requiring cardiopulmonary bypass (CPB) at Dedinje Cardiovascular Institute between January and September 2019. Isolated valvular surgery was performed in 87 patients, while the remaining 69 patients underwent combined coronary and valvular surgery. The development and stage of CSA-AKI were diagnosed, according to Kidney Disease Improving Global Outcome (KDIGO) criteria. Predictors and incidence of CSA-AKI development were assessed using univariate binary logistic regression analysis.

Results: The incidence of CSA-AKI was 17.3%. CSA-AKI stage 1 was diagnosed in 25 patients (16.02%). CSA-AKI stage 2 was noted in one patient (0.64%), as well as stage 3 (0.64%). In six patients (3.85%), renal replacement therapy (RRT) was required. Using univariate binary logistic analysis, the following parameters were identified as predictors for CSA-AKI development: duration of cardiopulmonary bypass (OR 1.01; CI 95% (1.01-1.02); P = .002), duration of aortic clamping (OR 1.02; CI 95% (1.01-1.03); P = .002), lactate levels during the intensive care unit (ICU) stay (OR 1.33; CI 95% (1.04-1.70); P = .026), duration of mechanical ventilation (MV) (OR 1.03; CI 95% (1.1-1.07); P = .014), the use of inotropic drugs (adrenaline, dobutamine) (OR 0.38: CI 95% (0.16-0.9); P = .026; and OR 0.23; CI 95% (0.1-0.56); P = .0019, respectively), and the use of diuretics (OR 0.24; CI95% (0.06-095); P = .041). Using Mann-Whitney U test for independent samples show that the group of patients who developed CSA-AKI had significantly longer duration of hospitalization (Z = -2.751); P = .006), prolonged ICU stay (Z = -4.160; P < .001), and need for prolonged mechanical ventilation (Z = -4.411; P < .001).

Conclusion: Independent predictors for AKI development after valvular surgery in patients older than 70 years are prolonged mechanical ventilation and increased lactate values, while the use of diuretics after surgery reduces the incidence of AKI. Also, the development of CSA-AKI is associated with prolonged ICU stay and a longer duration of hospitalization.

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INTRODUCTION

Cardiac surgery is the second most common cause of acute kidney injury (AKI) in the intensive care unit (ICU), after septic shock [Wang 2017]. Cardiac surgery-associated acute kidney injury (CSA-AKI) is the most common clinically important complication in adult patients undergoing open-heart surgery with an incidence between 8.9% and 39% and significantly contributes to the increase in mortality, morbidity, and length of hospitalization in these patients [Wang 2017; Mao 2013]. Studies have shown that even a slight increase in serum creatinine levels after cardiac surgery significantly affects mortality [Lassnigg 2004; Kolli 2010]. An increase in serum creatinine levels for 0.5mg/dl triples the risk of a lethal outcome, while an increase for more than 0.5mg/dl eighteen times enhances the risk [Lassnigg 2004; Kolli 2010]. After cardiac surgery, due to the development of AKI renal replacement therapy (RRT) is used in 2-5% of patients [Jason 2016].

CSA-AKI is characterized by an abrupt deterioration in renal function, which occurs under the influence of various factors, either related to the patients' characteristics or to operative and postoperative procedures [Moss 2012]. Preoperative risk factors include emergency surgery, reoperation, valvular surgery, intra-aortic balloon pump administration, elderly population, female gender, decreased

Table 1. Preoperative data

Patient characteristics	Sample (N = 156), Mean ± SD/N (%)	AKI (no) (N = 129), Mean ± SD/N (%)	AKI (yes) (N = 27), Mean ± SD/N (%)	*P*
Age (years)	75.25 ± 4.16	75.1 ± 4.24	76.15 ± 3.68	NS†
Gender (male)	82 (52.9%)	66 (51.2%)	16 (59.3%)	NS†
BMI (kg/m2)	27.27 ± 3.97	27.08 ± 4.0	28.22 ± 3.78	NS†
Euroscore (%)	4.71 ± 4.96	4.48 ± 4.88	5.83 ± 5.29	.034‡
GFR (ml/min/1.73m2)	67.19 ± 22.75	67.51 ± 20.47	65.95±31.64	NS‡
Preoperative Hgb (g/l)	127.01 ± 16.19	127.15 ± 15.94	126.33 ± 17.65	NS†
Preoperative urea (mmol/l)	8.53 ± 3.60	8.3 ± 3.52	9.64 ± 3.88	NS†
Preoperative creatinine (mmol/l)	98.37 ± 38.38	96.14 ± 36.05	109.04 ± 47.33	NS‡
RVSP (mmHg)	35.79 ± 23.66			
LVEF (%)	48.29 ± 12.24	48.43 ± 12.42	47.59 ± 11.51	NS†
Hypertension (yes)	146 (93.6%)	121 (93.8%)	25 (92.6%)	NS*
Diabetes mellitus (yes)	116 (74.4%)	31 (24.0%)	9 (33.3%)	NS*
Hyperlipoproteinemia (yes)	65 (41.7%)	53 (41.1%)	12 (44.4%)	NS*
COPD (yes)	21 (13.5%)	17 (13.2%)	4 (14.8%)	NS*
Atrial fibrillation (yes)	38 (24.4%)	30 (23.3%)	9 (33.3%)	NS*
Thyroid disease (yes)	9 (5.8%)	7 (5.4%)	2 (7.4%)	NS*
History of cancer (yes)	17 (10.9%)	15 (11.6%)	2 (7.4%)	NS*
BPH (yes)	16 (10.3%)	15 (11.6%)	1 (3.7%)	NA
Gastrointestinal diseases (yes)	7 (4.5%)	7 (5.4%)	0	NA
Previous myocardial infarction (yes)	28 (17.9%)	24 (18.6%)	4 (14.8%)	NS*
Previous cerebrovascular accident (yes)	7 (4.5%)	6 (4.7%)	1 (3.7%)	NA
Significant stenosis of carotid artery (yes)	26 (16.7%)	17 (13.2%)	9 (33.3%)	.011*
Peripheral vascular disease (yes)	11 (7.1%)	7 (5.4%)	4 (14.8%)	NS*
Procedures requiring contrast application				
MSCT (yes)	19 (12.1%)	15 (11.6%)	4 (14.8%)	NS†
PTA of carotid artery (yes)	5 (3.2%)	4 (3.1%)	1 (3.7%)	NA
Coronary angiography (yes)	100 (64.1%)	86 (66.7%)	14 (51.9%)	NS†
FFR (yes)	1 (1.5%)			
Type of operation				
AVR	59 (37.8%)	52 (40.3%)	7 (25.9%)	
MVR	5 (3.2%)	5 (3.9%)	0	
MVP	4 (2.6%)	4 (3.1%)	0	
Combined valve surgery	19 (12.2%)	5 (10.1%)	3 (22.2%)	
Valve + ACB surgery	69 (44.2%)	55 (42.6%)	14 (51.9%)	

BMI, body mass index; GFR, glomerular filtration rate; Hgb, hemoglobin; RVSP, right ventricle systolic pressure; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; BPH, benign prostatic hyperplasia; MSCT, multi-slice computed tomography; PTA, percutaneous transluminal angioplasty; FFR, fractional flow reserve; AVR, aortic valve replacement; MVR, mitral valve replacement; MVP, mitral valve repair; ACB, aortocoronary bypass, *CHi square test; †t-test; ‡Mann-Whitney test; NS, not significant, NA, not applicable

left ventricular function or congestive heart failure, diabetes mellitus, presence of peripheral vascular disease, chronic obstructive pulmonary disease, and increased serum creatinine values [Moss 2012]. Attention should also be drawn to the preoperative diagnostic procedures that include contrast application since they have been identified as a

Table 2. Operative and postoperative data

Operation	Sample (N = 156), Mean ± SD/N (%)	AKI (no) (N = 129), Mean ± SD/N (%)	AKI (yes) (N = 27), Mean ± SD/N (%)	*P*
CPB duration (min)	110.17 ± 44.96	104.57 ± 41.66	136.89 ± 51.07	.001‡
Clamp duration (min)	79.18 ± 32.54	75.03 ± 30.01	99.0 ± 37.22	.002‡
Duration of operation (h)	4.57 ± 7.99	4.6 ± 8.78	4.39 ± 1.05	.013‡
Duration of MV (h)	19.11 ± 26.46	15.12 ± 9.89	38.17 ± 56.892	<.001‡
Lactate at the beginning of anesthesia (mmol/l)	1.43 ± 0.48	1.44 ± 0.47	1.35 ± 0.52	NS‡
Lactate values during the CPB (mmol/l)	2.51 ± 0.67	2.52 ± 0.69	2.44 ± 0.53	NS†
Drainage (ml)	619.03 ± 765.50	578.13 ± 742.04	812.96 ± 856.71	NS‡
Postoperative period Mean±SD/N (%)				
Lactate upon arrival to ICU (mmol/l)	2.82 ± 1.32	2.67 ± 1.19	3.54 ± 1.66	.004‡
Peak lactate value in ICU (mmol/l)	3.38 ± 2.13	3.03 ± 1.58	5.07 ± 3.33	<.001‡
Peak Na value in ICU (mmol/l)	140.85 ± 3.38	140.64 ± 3.29	141.89 ± 3.42	NS†
Albumin value on first day (g/l)	29.30 ± 3.11	29.43 ± 3.11	28.67 ± 3.10	NS†
Albumin value on second day (g/l)	28.20 ± 2.72	28.12 ± 2.58	28.56 ± 3.35	NS†
Hgb value on first day (g/l)	110.42 ± 15.82	111.16 ± 15.64	106.93 ± 16.51	NS†
Hgb value on second day (g/l)	99.04 ± 15.48	99.28 ± 16.12	97.89 ± 12.21	NS†
Adrenaline (yes)	62 (39.7%)	46 (35.7%)	16 (59.3%)	.023*
Adrenaline (mcg/min)	2.41 ± 1.01	2.26 ± 0.76	2.29 ± 1.39	NS‡
Dobutamine (yes)	40 (25.6%)	26 (20.2%)	14 (51.9%)	.001*
Dobutamine (mcg/kg/min)	7.20 ± 4.75	6.27 ± 4.0	8.91 ± 5.66	NS‡
Noradrenaline (yes)	88 (56.4%)	70 (54.3%)	18 (66.7%)	NS*
Noradrenaline (mcg/min)	9.38 ± 12.76	6.54 ± 4.86	20.43 ± 23.98	.005‡

CPB, cardiopulmonary bypass; MV, mechanical ventilation; ICU, intensive care unit; Na, sodium; Hgb, hemoglobin, *CHi square test; †t-test; ‡Mann-Whitney test; NS, not significant

significant contributing factor in AKI development [Mao 2013]. Important operative and postoperative risk factors include on-pump versus off-pump technique, pulsatile versus non-pulsatile flow, normothermic versus hypothermic cardiopulmonary bypass (CPB), hemodilution, and CPB duration [Rosner 2008].

Changes in serum creatinine often occur late in the development of CSA-AKI, typically 24-48 h after cardiac surgery [Mao 2013]. This may be attributed to hemodilution related to the CPB pump, fluid administration, and blood loss [Mao 2013]. Due to the delay in diagnosis, treatment of CSA-AKI is usually initiated too late, after acute tubular necrosis already has been established, which can reduce treatment efficiency [Mao 2013]. Identification of risk factors and early diagnosis of subclinical and clinical forms of CSA-AKI is crucial for preventing or reducing kidney damage and improving outcomes in these patients [Wang 2017; Brown 2010]. Therefore, this study sought to determine the predictors and incidence of acute kidney injury (AKI) in patients older than 70 years undergoing elective valvular surgery.

MATERIAL AND METHODS

Patients

The study included 156 consecutive, clinically stable patients, older than 70 years, who were scheduled for elective cardiac surgery at Dedinje Cardiovascular Institute between January and September 2019. Isolated valvular surgery was performed in 87 patients, while the remaining 69 patients underwent combined coronary and valvular surgery. Patients were excluded if they had met any of the following criteria: 1. emergency surgery, 2. reoperation, 3. patients with end-stage renal disease who were already on a chronic dialysis program.

Definition of acute kidney injury

Acute kidney injury after the operation was defined according to Kidney Disease Improving Global Outcome (KDIGO) criteria and includes one of the following: 1. an increase in serum creatinine for ≥0.3 mg/dl (≥26.5 µmol/l) within 48 h; 2. an increase in serum creatinine to ≥1.5 times compared with baseline values within the previous 7 days; and 3. urine volume ≤0.5 ml/kg/h for 6 h [Khwaja 2012].

Table 3. Univariate binary logistic analysis with impaired renal function as a dependent variable

Predictors	B	OR	CI 95%	Significance (*P*)
Length of MV	0.05	1.05	(1.01, 1.09)	.014*
Peak lactate value in ICU	0.44	1.55	(1.21, 1.99)	.001†
Lactate upon arrival to ICU	0.45	1.57	(1.17, 2.12)	.003†
Length of clamp	0.02	1.02	(1.01, 1.03)	.002†
Length of CPB	0.01	1.01	(1.01, 1.02)	.002*
Postoperative diuretic	-1.59	0.20	(0.06, 0.71)	.013*
Procalcitonin	-2.18	0.11	(0.03, 0.43)	.002†
Dobutamine	-1.45	0.23	(0.1, 0.56)	.001†
Adrenaline	-0.97	0.38	(0.16, 0.9)	.026*
Preoperative infection	-2.4	0.10	(0.02, 0.52)	.007†

*statistical significance <.05; †statistical significance <.01; MV, mechanical ventilation; ICU, intensive care unit; CPB, cardiopulmonary bypass

Table 4. The most important predictors separated by a multi-step method#

Predictors	b	OR	CI 95%	*Significance (*P*)
Duration of MV	0.03	1.03	(1-1.07)	.060
Postoperative diuretic administration	-1.42	0.24	(0.06-0.95)	.041†
Peak lactate value in ICU	0.28	1.33	(1.04-1.70)	.026†

*Backward Wald method; †statistical significance <.05; MV, mechanical ventilation; ICU, intensive care unit

Furthermore, the KDIGO Clinical Practice Guideline for Acute Kidney Injury Guide provides a classification of AKI into three stages, based on an increase in serum creatinine levels or duration of oliguria/anuria. KDIGO AKI stage 1 includes patients with an increase in serum creatinine to 1.5-1.9 times baseline values or creatinine increase to ≥0.3 mg/dl (≥26.5 μmol/l), as well as urine output <0.5 ml/kg/h during the 6-12 h. Patients with AKI stage 2 have an increase in serum creatinine to 2.0-2.9 times baseline and urine output <0.5 mg/kg/h for ≥12 h. Stage 3 AKI includes an increase in serum creatinine to 3 times baseline or ≥4 mg/dl/kg (≥353.6 μmol/l), as well as the need for initiation of RRT. Patients with stage 3 AKI also have urine output <0.3 ml/kg/h for ≥24 h or anuria for ≥12 h.

Preoperative, intraoperative, and postoperative data: Anamnestic data, risk factors, and comorbidities have been assessed preoperatively in all patients. Demographic and anthropometric data were noted, as well as a smoking habit. Left ventricular ejection fraction (LVEF) and valvular heart disease (stenosis/insufficiency) were assessed using transthoracic and transesophageal echocardiography. In each patient, it was noted whether and when a preoperative diagnostic procedure requiring iodine contrast application (such as multi-slice computed tomography scan, coronary angiography, fractional flow reserve, etc.) was performed. Preoperative values of urea, creatinine, hemoglobin, and potassium were verified from the medical documentation in all patients. The surgery and anesthesia were performed, according to the standard protocol. During the operation, the need to return to the extracorporeal circulation, duration of the operation, the length of the CPB, length of the clamp as well as the use of blood and colloidal solutions (albumins, hydroxyethyl starch) and their quantity were noted. The length of mechanical ventilation (MV) was verified, as well as the use of inotropic (adrenaline, dobutamine) and vasopressor drugs (noradrenaline) and their maximum doses. Lactate values before, during, and after CPB, were recorded from blood gas analyses. Also, the immediate postoperative values of lactate and sodium, as well as peak values during the first 48 h were collected from the blood gas analyses.

On the first and second postoperative day hemoglobin, leukocytes, albumin, procalcitonin, urea, and creatinine values were collected. The glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula. The occurrence of postoperative complications, such as postoperative infection, atrial fibrillation, psychomotor disturbance, need for permanent pacemaker implantation, pericardial and pleural effusion, as well as respiratory and neurological complications, were verified. The need for renal replacement therapy (RRT) and the type of RTT used were noted. Also, data regarding

Table 5. Correlation between the occurrence of acute kidney injury and postoperative complications

	Postoperative complication, n (%)	Acute kidney injury	*Significance (*P*)
	No	Yes	
Pleural effusion	5 (3.9%)	4 (14.8%)	.049†
Respiratory problems	8 (6.2%)	7 (25.9%)	.002*
Infection	21 (16.3%)	12 (44.4%)	.001*
Neurology complication	2 (1.6%)	3 (11.1%)	.037†
Lethal outcome	3 (2.3%)	3 (11.1%)	.065†

*CHi-square test; †Fisher's Exact test

the length of ICU stay and duration of hospitalization were collected.

Statistical analysis

Collected data were statistically analyzed, using descriptive and inferential statistical methods. In descriptive statistics, the arithmetic mean was used as a measure of central tendency for numerical variables, while the standard deviation was used as a measure of variability. Absolute frequency and percentage were used to describe the categorical variables. For two independent samples, t-test or Mann-Whitney U test was used to determine the difference between numerical variables depending of normality of distribution and homogeneity of data. The difference between dependent variables was examined using the paired samples t-test or Wilcoxon Signed Ranks test, and Freidman test for more than two related samples. Analysis of contingency tables with chi-square test were used to examine the different frequencies of matching the variable AKI (the group that developed versus the group that did not develop AKI) with other nominal characteristics. Differences in parameter change during time between the two groups (with and without AKI) were examined by Mixed analysis of variance (ANOVA) with one repeated and one non-repeated factor. The significance of individual traits determining the impact of multiple independent variables in the prediction of the occurrence of AKI was examined by binary logistic regression analysis. The level of statistical significance was defined by the value of $P < .05$. Data analysis was performed using the IBM SPSS 25.0 software package (IBM, USA).

RESULTS

Our study included a total of 156 patients, of whom 87 (55.8%) patients underwent isolated valvular surgery, while 69 (44.2%) patients underwent combined coronary and valvular surgery. The study group included 82 (52.9%) male patients and 74 (47.1%) female patients. An observed sample average age was 75.25 ± 4.16 years. Other baseline patient characteristics and data, regarding preoperative procedures with comparison between groups defined by presence of CSA-AKI development, are listed in Table 1.

Table 2 shows intraoperative factors and their association with CSA-AKI development (Table 2). Cardiopulmonary bypass duration and clamp duration were significantly longer in patients who developed CSA-AKI (Mann-Whitney test, $P = .001$, $P = .002$, respectively). Also, significant postoperative factors, including laboratory values and data regarding the use of inotropes and vasopressors, are listed in Table 2. Duration of mechanical ventilation also was significantly longer in patients who developed CSA-AKI. Association between administration of inotropic drugs (adrenaline, dobutamine) and development of CSA-AKI has shown statistical significance (Chi-square, $P = .023$, $P = .001$, respectively). It also was found that higher doses of vasopressor drug (Noradrenaline) were used in patients with CSA-AKI developed (Mann-Whitney test, $P = .005$).

Table 3 lists all predictors identified as individually significant for CSA-AKI development that were used for the univariate binary logistic analysis. Immediate postoperative lactate values, as well as the peak lactate values during the ICU stay, have been pointed out as the most significant predictors for CSA-AKI.

Table 4 shows the results of the last step of binary logistic regression that includes the stepwise method (Backward Wald). This method pointed out following three predictors as most significant for AKI development: duration of MV (OR 1.03; CI 95% (1.1-1.07); $P = .060$), postoperative use of diuretics (OR 0.24, CI 95% (0.06-0.95); $P = .041$), and peak lactate values during the ICU stay (OR 1.33; CI 95% (1.04-1.70); $P = .026$). It is shown that prolonged MV and higher lactate values correlated with development of AKI. Contrary to this, the use of diuretics after surgery reduces the chance of AKI development.

According to KDIGO criteria, 27 patients (17.3%) developed CSA-AKI. The CSA-AKI stage 1 was diagnosed in 25 patients (16.02%), while CSA-AKI stage 2 was noted in one patient (0.64%) as well as stage 3 (0.64%). Of the 27 patients who developed AKI during the first 48 hours, six patients (22.2%) required initiation of RRT. Intermittent hemodialysis was performed in four patients, while two patients during the first 72 hours underwent continuous veno-venous hemodiafiltration, followed by intermittent hemodialysis

Table 6. Duration of ICU stay, duration of MV and duration of hospitalization in the group with and without AKI

Variable	AKI (no) (N = 129), Mean ± SD	AKI (yes) (N = 27), Mean ± SD	Sample (N = 156), Mean ± SD	*P*
Duration of hospitalization	17.77 ± 11.61	24.26 ± 15.16	18.89 ± 12.49	.006*
Duration of ICU stay, first postoperative day	3.29 ± 6.56	10.48 ± 16.77	4.54 ± 9.5	<.001*
Duration of MV	15.12 ± 9.89	38.17 ± 56.893	19.11 ± 26.46	<.001*

ICU, intensive care unit; MV, mechanical ventilation; AKI, acute kidney injury; *Mann-Whitney test

according to the indication (acidosis, hypervolemia, increase in urea and creatinine levels, hyperkalemia).

Analysis of variance showed that the change in lactate values, depending on the time of measurement, differs in these two study groups (Freidman test, 236.14, df=3, $P < .001$). Also, there is a significant difference between the lactate values depending on the time of measurement (Freidman, within subject effects, AKI (no), 183.38, df=3, $P < .001$, AKI (yes), 61.33, df=3, $P < .001$). As shown in the Figure, more significant variations in lactate values are noted in the group of patients who developed acute kidney injury.

Table 5 lists the most significant postoperative complications. As shown, respiratory problems (8/129 patients (6.2%), 7/27 patients (25.9%), Chi-square, 10.0, df=1, $P = .002$) and infections (21/129 patients (16.3%, 12/27 (44.4%), Chi-square, 10.62, df=1, $P = .001$) after surgery more frequently occurred in the group of patients who developed AKI. Also, percentage of lethal outcome was higher in this group (3/129 (2.3%), 3/27 (11.1%), Fisher's Exact test, 4.66, df=1, $P = .065$). On the other hand, the incidence of atrial fibrillation, psychomotor agitation, and pericardial effusion did not differ significantly between these two groups.

Table 6 shows difference in duration of hospitalization, duration of ICU stay, and duration of MV between the two study groups. As shown, patients who developed CSA-AKI had prolonged hospitalization, longer ICU stay, and need for prolonged MV (Mann-Whitney test, $P < .006$, $P < .001$, and $P < .001$, respectively).

DISCUSSION

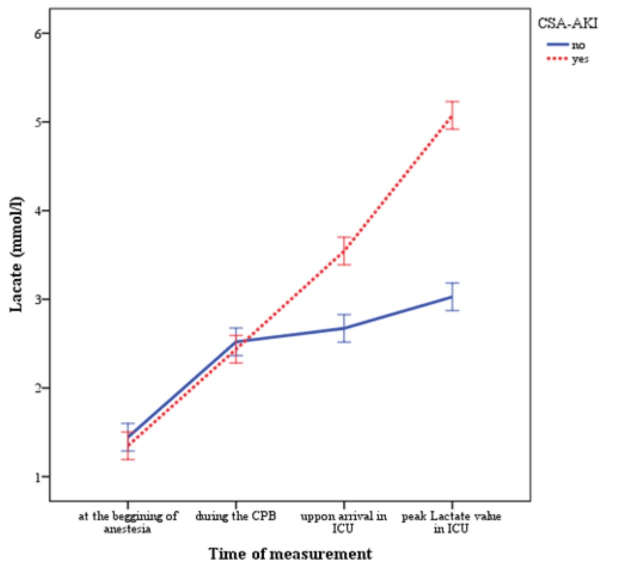
Results of our study have shown that 27 of 156 patients (17.3%) developed acute kidney injury during the first 48 h after cardiac operation. Our results are comparable with the results from previous studies that showed the incidence of CSA-AKI varies between 8.9% and 39% [Mao 2013]. Data from two meta-analyses indicate the incidence of AKI following cardiac surgery is about 22% [Hu 2016; Vandenberghe 2016]. Most patients who developed AKI had mild acute deterioration in renal function, classified as AKI stage 1 (14-18% of patients), while stage 2 was diagnosed in 4% of patients, and stage 3 was noted in 3% of patients. Between 2.3% and 3.1% of patients needed initiation of RRT. Compared to this, in our study group, CSA-AKI stage 1 was diagnosed in 25 patients (16.02%), while CSA-AKI stage 2 was noted in one patient (0.64%) as well as stage 3 (0.64%). In six patients (3.8%), RRT was initiated.

Results of the study by Jason et al showed that 2-5% of patients have AKI requiring RRT, which is associated with a high mortality rate, up to 50% [Jason 2016]. In our study group, six patients (3.8%) died during hospitalization, of whom three patients developed acute renal deterioration with the initiation of RRT during the first 48 h after surgery.

Previous studies pointed out comorbidities, such as heart failure, diabetes mellitus, chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD), as important preoperative risk factors for AKI development [Coleman 2011]. Contrary to this, our results did not indicate that any of the listed comorbidities influenced the development of AKI. The reason behind this difference can be the fact that our study group included elective patients, with low-risk stratification. The majority of patients had mild preoperative renal dysfunction (with estimated GFR (67.19 ± 22.75), mildly reduced LVEF (48.29 ± 12.24), and a low incidence of COPD (13.5%).

The association between the administration of vasopressor and inotropic drugs and the occurrence of AKI is well established [Cartin-Ceba 2012]. In our study, a significant number of patients received inotropic and vasopressor drugs, including adrenaline in 62 (39.7%) patients, dobutamine in 40 (25.6%) patients, and noradrenaline in 88 (56.4%) patients. Similar to previous studies, our results also shown the use of vasopressors and inotropes is a significant factor for the development of early postoperative kidney damage. Some studies have shown that adrenaline and noradrenaline decrease renal blood flow, due to their vasoconstrictor α-adrenoceptor activity. On the other hand, the use of dobutamine, which has mixed β-adrenoceptor effects, does not affect renal blood flow significantly [Bangash 2012]. However, the use of vasopressors and inotropes is associated with hemodynamic impairment, most commonly due to cardiogenic and septic shock, which is a significant cause of the decrease in renal perfusion and consequently leads to acute kidney injury [Cartin-Ceba 2012; Chandiraseharan 2020].

Results of our study indicate that increased lactate values are independent predictors for the development of AKI after cardiac surgery. The peak lactate value during the first 48 h after surgery was identified as the most significant predictor for acute kidney injury. Our results are similar to those of previous studies, such as the study by Hajjar et al, which showed that hyperlactatemia during the first 6 hours



Changes in lactate values during time in the group with and without acute kidney injury. CPB, cardiopulmonary bypass; ICU, intensive care unit.

after ICU admission is an independent risk factor for worse outcomes in adult patients undergoing cardiac surgery [Hajjar 2013]. Similarly, to this, the results of Zhongheng and co-workers showed that lactate values in the first 24 h after cardiac surgery are an independent predictor of CSA-AKI [Zhongheng 2015]. Cardiac surgery may result in an imbalance between oxygen demand and supply, leading to tissue hypoxia and ultimately to organ failure, which can be monitored by measuring lactate values. On the other hand, transient hyperlactatemia can occur even in the absence of tissue hypoperfusion, caused by the anesthetics-related reduced liver clearance of lactate, or due to the effect of the low temperatures during CPB on the cellular metabolism [Hajjar 2013]. However, prolonged high lactate levels after cardiac surgery indicate tissue hypoperfusion [Hajjar 2013], which is consistent with our results that peak lactate values during the first 48 h after surgery are the most significant predictor for acute kidney injury.

Our results also pointed out prolonged MV as another independent predictor for the development of AKI after cardiac surgery. A meta-analysis conducted by Akker et al showed that acute kidney injury appears to develop more often in patients in whom invasive MV is used [Akker 2013]. Neither tidal volume nor positive end-expiratory pressure settings affected AKI development, which argues in favor of hemodynamics as a major factor causing AKI during MV [Akker 2013]. Among operative predictors for AKI development, the univariate binary logistic analysis pointed out CPB duration and aortic clamping as most significant. Our results are comparable to the results of previous studies, which showed that not only administration of CPB itself, but also the duration of CPB significantly correlates with AKI [Akker 2013]. Boldt and co-workers showed that patients with prolonged pump administration, longer than 90 minutes, more often have impairment of renal function than those with the administration of CPB less than 70 minutes [Boldt 2003]. This can be explained by the role of CPB in inducing the systemic inflammatory response syndrome with a consequential impact on multiple organs. A study by Tuttle et al also showed the role of aortic clamping as a risk factor for AKI development, pointing out the increased incidence of AKI in patients who underwent valve surgery in comparison with other cardiac surgical procedures [Tuttle 2003]. Jarnberg and co-workers showed that the use of diuretics during the early postoperative period can reduce the severity of renal impairment by preventing tubular obstruction and reducing oxygen consumption [Jarnberg 2004], which coincides with our results. A study by Grams and co-workers also confirmed reduced mortality after 60 days of admission to the intensive care unit in patients with AKI who received a higher cumulative dose of furosemide [Grams 2011]. Contrary to these findings, in a double-blind randomized controlled trial continuous infusion of furosemide was shown to be associated with a higher rate of renal impairment compared with the placebo or dopamine group [Lassnigg 2000]. Possible explanation for this is furosemide-induced maldistribution of renal blood flow with diversion of medullary perfusion by a decrease in cortical vascular resistance, which might promote tubular dysfunction [Lassnigg 2004]. However, these data remain controversial and need further investigation.

As previously mentioned, numerous studies showed that cardiac surgery-associated acute kidney injury is the most common clinically important complication in adult patients undergoing cardiac surgery [Wang 2017; Mao 2013]. Moreover, our results showed that patients who develop CSA-AKI also have a higher incidence of other postoperative complications, as well as prolonged ICU and hospital stay. This is the reason why identification of risk factors and early diagnosis of clinical and subclinical forms of acute kidney injury is crucial for preventing or reducing kidney damage and, therefore, improving outcomes in these patients.

Although there are many studies focusing on risk factors for AKI following cardiac surgery, most focus on coronary artery bypass surgery rather than valvular surgery. Furthermore, most investigators excluded fragile groups, including older patients. As a result, there is a paucity of evidence whether older age correlates with a higher incidence of CSA-AKI and poorer prognosis. The aim of our study was to advance the knowledge on this topic by focusing on patients older than 70 years who underwent valvular surgery, either isolated or combined with coronary surgery. Our results are in correspondence with previous results, showing that the most common risk factors for CSA-AKI are mutual for all patients undergoing cardiac surgery requiring CPB, regardless of age and type of surgery.

CONCLUSION

Our results indicate that prolonged mechanical ventilation and increased lactate levels are independent predictors for acute kidney injury after elective valvular surgery in patients older than 70 years, while the use of diuretics after surgery significantly reduces the incidence of AKI development. Our study also showed that CSA-AKI is associated with prolonged ICU stay and a longer duration of hospitalization. Despite the rapid development of novel diagnostic and treatment methods for acute kidney injury after cardiac surgery, its incidence and associated morbidity and mortality remain high.

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