A SINGLE CENTER RETROSPECTIVE STUDY OF CARDIAC SURGERY ASSOCIATED ACUTE KIDNEY INJURY – INCIDENCE AND OUTCOMES

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Introduction: Cardiac surgery associated acute kidney injury (CSA-AKI) is an important complication. It is recognized as the second cause of AKI in the intensive care patients after sepsis. *Methods:* We conducted a single center retrospective three-year cohort study to reveal the incidence of the postoperative AKI genesis and severity, as well as the use of continuous renal replacement therapy in patients with normal preoperative renal function submitted to cardiac surgery. Our study included 1000 patients. Secondary outcomes were length of intensive care and hospital stay, major postoperative complications, and in-hospital mortality rate. Statistical analysis was applied to correlate CSA-AKI development and patient perioperative variables. *Results:* The overall CSA-AKI incidence was 15.1% (n=151). The incidence of CSA-AKI was 12.8% (n=128) in stage 1; 1.9% (n=19) in stage 2; and 0.4% (n=4) in stage 3 according to the KDIGO AKI (RIFLE/AKIN) criteria. The incidence of continuous renal replacement therapy in the AKI group was 2.65% or 0.4% of the total cohort (n=4). The CSA-AKI in-hospital mortality rate was 2.65% (n=4), while AKI patients that required dialysis survived. *Conclusion:* Once again, our study revealed the importance of timely recognizing CSA-AKI. It also reaffirmed CSA-AKI as a serious complication with a high incidence rate. We also confirmed the usefulness of preoperative AKI risk prediction models such as Cleveland Clinic Score in everyday clinical practice.

Key words: acute kidney injury; cardiac surgery; dialysis; mortality

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INTRODUCTION

Cardiac surgery associated acute kidney injury (CSA-AKI) is a considerable complication with the incidence of 8.9%-39% according to current studies (1-10). It is the second cause of acute kidney injury (AKI) development in the intensive care patients after sepsis, as well as an independent risk factor for mortality (11-13). Although the incidence of postoperative AKI development is higher in patients with preoperative chronic kidney disease, patients with normal preoperative renal function submitted to cardiac surgery are under major risk as well. Remarkable characteristics of cardiac surgery procedures are the use of cardiopulmonary bypass, aorta cross-clamping, high transfusion rates, and use of vasopressors and inotropes, which all contribute to the risk of AKI development. Also, specific risk factors associated with anesthetic, surgical and intensive care management, as well as unmodifiable risk factors such as age, hypertension and peripheral vascular disease, contribute to the greater risk of postoperative AKI emergence (14). Current studies propose that CSA-AKI is a consequence of complex and different pathophysiological mechanisms. These mechanisms include altered renal perfusion, alternating cycles of ischemia and reperfusion, increased oxidative stress reaction, and increased renal and systemic inflammatory response (15). We conducted a single center retrospective three-year cohort study to reveal the incidence of the postoperative AKI genesis, AKI severity, and continuous renal replacement therapy (RRT) use in patients with normal preoperative renal function submitted to cardiac surgery procedures. We also validated the association between preoperative and intraoperative risk factors and AKI development. We also compared the incidence of major postoperative complications between the group of patients who developed CSA-AKI and those who did not.

PATIENTS AND METHODS

Patient selection and study design

We conducted a retrospective cohort study from January 2014 until December 2016 at the Department of Cardiovascular Surgery and cardiac Intensive Care Unit (ICU). All necessary patient data were collected from medical records and hospital electronic medical database. Our study included 1000 patients older than 18 years submitted to urgent or scheduled cardiac surgery (coronary artery bypass grafting, valve replacement, combined coronary artery bypass grafting and valve replacement, Bentall procedure, supracoronary replacement of the ascending aorta and aortic valve replacement) with preoperative estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m² calculated on baseline serum creatinine values within the period of 7 days before the surgery according to the Cockcroft-Gault equation. All patients had signed a written informed consent and postoperatively were submitted to cardiac ICU. Excluded from the study were patients with incomplete data, patients submitted to other type of cardiac surgery (transcatheter aortic valve implantation, re-do operations, cardiac pacemaker and implantable cardioverter defibrillator insertion, revision surgery, subxiphoid pericardial drainage, and other procedures that did not require use of extracorporeal circulation) beyond those mentioned in inclusion criteria, who died intraoperatively or within 48 hours postoperatively, and those on chronic renal hemodialysis program. The research protocol was approved by the institution Human Research Ethics Committee for cardiovascular disease.

The primary endpoint was observation of AKI development and AKI staging after cardiac surgery, incidence of AKI that required continuous RRT during the postoperative period, length of ICU and hospital stay, and in-hospital mortality rate. Secondary outcomes included correlation of preoperative variables, intraoperative variables and major postoperative complications with AKI development. Postoperative AKI was defined by a modified definition of the Kidney Disease: Improving Global Outcomes (KDIGO) AKI Workgroup, harmonizing differences between the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) and the Acute Kidney Injury Network (AKIN) definitions based on changes in serum creatinine alone (16). The postoperative serum creatinine levels were obtained from the highest serum creatinine values measured on each postoperative day during patient stay in ICU and on surgical ward, or the highest value on the last day of hospital stay. We observed a rise in postoperative serum creatinine by ≥26.5 μmoL within 48 hours, or a rise of postoperative serum creatinine by ≥1.5 baseline preoperative serum creatinine levels during hospital stay. We did not use urine output as a criterion for determining AKI after cardiac surgery because postoperative output is a consequence of the variables other than renal function, such as achieving optimal fluid balance, diuretic use and perioperative surgery and anesthesia stress reaction with hormonal and metabolic imbalance. All patients were followed-up until discharge from the hospital. AKI group was determined as AKI stage 1, 2 or 3 according to the KDIGO AKI (RIFLE/AKIN) guidelines. It means that AKI was defined by the RIFLE criteria using maximal change in serum creatinine until release from the hospital compared with baseline serum creatinine values before surgery. Patients were stratified according to the highest RIFLE class (Risk, Injury, or Failure) attained by serum creatinine. At the same time, AKIN criteria were also used in determining AKI using the strict definition for increments of serum creatinine within a 48-hour interval (16). It means that we compared daily serum creatinine value with subsequent levels for the next 2 days until discharge from the hospital. The most severe degree of AKI was recorded as final AKIN stage. Control no-AKI group included patients with normal postoperative renal function according to the KDIGO AKI (RIFLE/AKIN) criteria during clinical observation. The indications for continuous RRT in the AKI group included uremia, volume overload, biochemical abnormalities, or AKI with diuretic resistance, and were based on clinical judgment (17). Other indications for continuous RRT in the cohort group were severe hemodynamic instability, severe systemic inflammatory response, cardiac decompensation, and presence of any other organ failure accompanied by AKI (17).

Patient preoperative characteristics and postoperative outcomes

We collected data on the following preoperative variables as the possible predictors of AKI development: age, gender, weight, height, left ventricular ejection fraction, preoperative insertion and perioperative use of intra-aortic balloon pump (IABP), hemoglobin and hematocrit levels measured within 7 days prior to surgery, urgency of surgery (defined as scheduled or urgent (within 24 hours after initial diagnosis)), and Euroscore II (18). Patient preoperative comorbidities were bundled into prior myocardial infarction, neurologic disease (history of prior transient ischemic attack or stroke), preexisting chronic obstructive pulmonary disease (COPD), arterial hypertension, and diabetes treated with oral agents or insulin. Surgery duration (from skin incision to closure) was recorded in the intraoperative period. Pump time and cross clamp time were recorded in the perfusion record. Major complications were defined as the number of transfused packed red blood cell (PRBC) units, duration of the postoperative mechanical ventilation, length of ICU

stay, length of hospital stay, in-hospital infection rate, and in-hospital mortality rate.

Statistical analysis

Descriptive statistics for categorical variables were reported as frequency and percentage while continuous variables were reported as mean ± standard deviation. Categorical variables were analyzed using Pearson χ^2-test. Continuous variables were analyzed using unpaired T-test. Univariate analysis was applied to evaluate the potential preoperative and intraoperative risk factors and major postoperative complications associated with CSA-AKI. The values of p<0.05 were considered statistically significant. The SPSS statistical software version 24 was used in all analyses.

RESULTS

In our study, cardiac surgery was performed on 1441 patients between January 2014 and December 2016. Eighty patients were excluded from the study due to incomplete data, 3 patients were on chronic hemodialysis program, 19 patients were disqualified due to submission to cardiac surgery type other than requested in inclusion criteria, and 339 patients had preoperative eGFR <60 mL/min/1.73 m^2. The final study cohort consisted of 1000 patients; 151 patients developed postoperative AKI. The overall AKI incidence was 15.1%. The incidence of AKI was 12.8% (n=128) in stage 1; 1.9% (n=19) in stage 2; and 0.4% (n=4) in stage 3 according to the KDIGO AKI (RIFLE/AKIN) criteria. In the entire cohort, 11 (1.1%) patients required postoperative continuous RRT. Continuous veno-venous hemodiafiltration (CVVHDF) was the modality applied (19). The incidence of continuous RRT in the AKI group was 2.65% or 0.4% of the total cohort (n=4). The indications for initiating CVVHDF were volume overload, biochemical abnormalities, uremia or AKI with diuretic resistance (17). Moreover, indications for applying continuous RRT in 7 patients without AKI in the cohort (0.7% of the total cohort) were significant hemodynamic instability, cardiogenic shock, and severe systemic inflammatory response (17). Control no-AKI group consisted of 849 (84.9%) patients who did not develop AKI during clinical observation. We did not observe any significant differences between AKI and no-AKI groups in the following preoperative variables: gender, height, left ventricular ejection fraction, preoperative hemoglobin and hematocrit levels (Table 1). However, the AKI group was significantly older and had greater body mass than no-AKI group (Table 1). Also, perioperative use of IABP was significantly associated with AKI development (Table 1). AKI group had a significant-

ly higher Euroscore II and was more often submitted to urgent cardiac surgery in comparison to no-AKI group (Table 1). We found no differences between AKI and no-AKI group in preoperative comorbidities such as history of prior myocardial infarction and neurologic disease (Table 1). Besides, although the history of COPD had a higher incidence in the AKI group in comparison to no-AKI, we did not find significant correlation between postoperative AKI genesis and preexisting COPD (Table 1). Interestingly, arterial hypertension was present in more than 80% of patients in both groups but there was no significant correlation between CSA-AKI and preoperative arterial hypertension (Table 1). However, we showed that the history of diabetes treated with oral agents was associated with postoperative AKI development (Table 1). Also, longer duration of surgery, pump time and aortic cross-clamp time were significantly longer in the AKI group in comparison to no-AKI group and associated with postoperative AKI development (Table 2). Thus, AKI patients had significantly higher transfusion of PRBC units during clinical observation in comparison to no-AKI group (Table 3). Other major complications associated with AKI development were longer length of ICU stay, longer duration of postoperative mechanical ventilation, and greater in-hospital mortality rate (Table 3). According to the studies, prolonged intubation was defined as mechanical ventilation for >24 hours postoperatively (5). Our study revealed that AKI group did not only have longer duration of postoperative mechanical ventilation than no-AKI group, but also had a significantly prolonged intubation (mean ± SD: 32.39±53.9 hours) (Table 3). Interestingly, we did not find significant difference in the length of hospital stay between AKI and no-AKI groups (Table 3). The CSA-AKI in-hospital mortality rate was 2.65% (n=4). Moreover, the overall mortality rate in patients who had continuous RRT during the study was 27.27% (n=3), while all AKI patients who required continuous RRT survived. At discharge from the hospital, according to RIFLE classification, 2 AKI patients who had continuous RRT recovered their renal function to Risk class, 1 patient recovered renal function to Injury class, and 1 patient had loss of kidney function. We did not find significant difference in in-hospital infection rate between AKI and no-AKI groups (Table 3).

Table 1
Selected patient preoperative characteristics and comorbidities expressed as mean ± SD and percentage after applying t-test (p value <0.05 was considered significant)

Characteristic N=1000	AKI n=151 (15.1%)	No AKI n=849 (84.9%)	p
Age (yrs)	65.95±9.40	64.19±9.66	0.04
Gender			
Female	31 (21%)	174 (20%)	0.95
Male	120 (79%)	675 (80%)	
Height (cm)	172.38±9.26	172.15±8.89	0.77
Weight (kg)	93.06±15.08	87.67±13.87	<0.001
Left ventricle ejection fraction (%)	59±9	58±11	0.47
Hemoglobin (g/L)	139.05±16.11	140.01±17.62	0.54
Hematocrit (%)	41.67±5.10	41.71±6.12	0.93
Preoperative IABP	14 (9.27%)	38 (4.48%)	0.015
Euroscore II (%)	5.22±8.89	3.25±6.46	<0.001
Comorbidity			
Prior myocardial infarction	31 (20.53%)	132 (15.55%)	0.13
Arterial hypertension	123 (81.46%)	720 (84.81%)	0.29
Diabetes controlled with oral agents/insulin	53 (35%)	121 (14%)	<0.001
Chronic obstructive pulmonary disease	20 (13.25%)	131 (86.75%)	0.25
Neurologic disease	10 (6.62%)	50 (5.89%)	0.73
Surgery urgency			
Urgent	56 (37.09%)	232 (27.33%)	0.003
Scheduled	95 (62.91%)	617 (72.67%)	

AKI – acute kidney injury; IABP – intra-aortic balloon pump

Table 2
Association between intraoperative variables and cardiac surgery associated acute kidney injury

Intraoperative variable	AKI	No AKI	p
Surgery duration (min)	273.58±75.58	258.55±60.35	0.007
Pump time (min)	94.70±52.24	83.14±33.26	0.001
Cross clamp time (min)	58.83±25.53	49.03±16.30	<0.001

AKI – acute kidney injury; values are expressed as mean ± SD; p value <0.05 was considered significant

Table 3
Patient outcomes after cardiac surgery expressed as mean ± SD and percentage

	AKI	No AKI	p
Total transfusion of PRBC (units)	4.35±5.73	2.78±3.43	<0.001
Patients transfused with PRBC n (%)	108 (71.52%)	545 (64.19%)	0.08
Duration of mechanical ventilation (hours)	32.39±53.92	14.2±29.52	<0.001
ICU length of stay (hours)	133.47±146.03	73.54±76.99	<0.001
Overall length of hospital stay (days)	15.14±9.93	13.79±7.62	0.068
In-hospital infection rate, n (%)	1 (0.66%)	2 (0.24%)	0.377
In-hospital mortality rate, n (%)	4 (2.65%)	7 (0.82%)	0.048

AKI – acute kidney injury; PRBC – packed red blood cells: ICU – intensive care unit; p value <0.05 was considered significant

DISCUSSION

Cardiac surgery associated acute kidney injury is not only an independent risk factor for mortality, but also a serious complication with long-term consequences in every aspect of human life in the patients who develop it regardless of its severity. There are many preoperative renal risk stratification models and new renal biomarkers in the process of clinical and experimental research validation of the prognostic ability to timely identify AKI development. The most popular is the Cleveland Clinic Score (CCS) (also called the Thakar score) (20). It is the best validated and most predictive tool, but only for serious CSA-AKI that requires RRT (21-24). The CCS is a predictive risk model based on preoperative risk factors for CSA-AKI (20,22-26). The weakness of this model is that it does not include intraoperative parameters that could increase its prognostic power and AKI severity stratification. As opposed to CCS in our study we included patients with normal preoperative renal function defined as eGFR >60 mL/min/1.73 m^2 calculated by Cockcroft-Gault equation and retrospectively validated correlation of almost all preoperative risk factors of the CCS, except for previous cardiac surgery, with CSA-AKI development. We also wanted to investigate a three-year review of the AKI incidence, AKI severity and use of continuous RRT (CVVHDF) in our hospital, and compare it with current literature. Thereby, the incidence of CSA-AKI in our centre was 15.1%, which is in the CSA-AKI reported range of 8.9% to 39%, depending on AKI definition (1-10). Our study acknowledged that AKI requiring continuous RRT occurred in 2.65% of AKI patients and 0.40% of the total cohort. According to the literature, AKI that requires RRT occurs in 2%-5% of patients following cardiac surgery and is associated with a mortality rate of up to

63% (20,27-30). It is important to emphasize that all AKI patients who required RRT in our study survived. There are several explanations. First is careful preoperative renal risk prediction and stratification, as well as implementation of measures that best optimize preoperative renal function such as withholding nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and metformin for at least 24 hours before surgery (31,32). Although studies about preoperative use of ACE inhibitors or ARBs and incidence of CSA-AKI are controversial and recommend risk/benefit clinical analysis, the practice in our hospital is that they are stopped a day before surgery (17,33,34). Intraoperative factors such as less invasive surgical techniques, shorter duration and optimal cardiopulmonary bypass techniques, shorter aortic cross-clamp time and avoiding aortic clamping during coronary artery bypass grafting are also important factors that contribute to renal protection. Significantly, current studies have shown that early and judicious RRT initiation in patients with postoperative AKI evolution, which is diuretic resistance and has preserved hourly urine output produces better survival rate (17,35,36). Moreover, the use of CVVHDF modality in postcardiac patients offers better survival due to better inflammatory mediator removal, less hemodynamic instability, as well as superiority in mortality rate and recovery of renal function (19,37). So, we confirmed that our results were consistent with the current literature. Moreover, consistently with Thakar *et al.*, our study verified that preoperative variables such as perioperative use of IABP, diabetes and urgent surgery were significant predictors of AKI emergence (9). As opposed to Thakar *et al.*, we did not prove female gender, history of COPD and arterial hypertension as significant AKI risk factors. Interestingly, we revealed that age and weight as anthropometric measures were significant risk factors for CSA-AKI development. Patients with CSA-AKI were older and had greater weight. In accordance with Wong *et al.*, our results also recognized longer surgery duration, longer pump time and longer cross-clamp time as intraoperative risk factors for AKI development (24). However, we must emphasize that although AKI patients in our study had pump time 3-fold and cross-clamp time 1.5-fold shorter than AKI patients in the study by Wong *et al.*, they still had a significant risk of AKI development (24). We did not detect differences in the frequency of transfusion between AKI and no-AKI groups. However, when transfused, patients in the AKI group received a considerably larger number of PRBC units in comparison to no-AKI group. Since transfusion of PRBC is potentially a modifiable AKI risk factor, we should always try in clinical practice to delay it as long as possible and apply perioperative measures and procedures for reducing the transfusion rate and triggers. Acknowledgment to the recognition of AKI as a serious postoperative complication was emergence of significant major complications in AKI patients, such as prolonged postoperative mechanical ventilation, longer ICU length of stay and higher in-hospital mortality rate. These results were in accordance with current studies (5). However, we did not find difference in the length of hospital stay between AKI and no-AKI groups. Other studies indicate opposite (5). In addition, we did not confirm significant difference in the infection rate as a major complication between AKI and no-AKI groups. Our results showed some potential clinical and research implications. Firstly, although age-associated loss of kidney function has been recognized for a while, our study once again confirmed it as a significant risk factor for CSA-AKI genesis. Another novelty of our research was validation of weight as a strong preoperative risk factor in the CSA-AKI genesis. Since we are aware of obesity and overweight as a growing population problem worldwide, especially in younger population, this simple anthropometric measure deserves further clinical research in the field of CSA-AKI. Therefore, we believe that further researches are necessary to validate age and weight as preoperative risk factors for CSA-AKI development and maybe incorporate these variables in the current preoperative risk factor tools. Interestingly, we did not find difference in the length of hospital stay between AKI and no-AKI groups. One explanation is that in cardiac surgery, there are many more major complications such as revision surgery, hemorrhage, postoperative delirium and neurologic sequels that we did not investigate but which influence the patient postoperative course. So, our study should be broadened in these aspects. We also validated pump time, cross-clamp time and transfusion rate as strong modifiable intraoperative CSA-AKI risk factors. Every center should be directed in improving these factors. It means that by improving and developing surgical technique, the pump time and cross-clamp time should be shorter. Also, transfusion rates should be lower. Other study results were mostly consistent with the current literature.

CONCLUSION

Once again, our study revealed the importance of timely recognizing AKI. Also, we reaffirmed CSA-AKI as a serious complication with a high incidence of 15.1% in healthy patients submitted to cardiac surgery. We also verified the utility of preoperative risk prediction models in AKI prediction. We also demonstrated that some intraoperative CSA-AKI risk factors were modifiable, and we should make efforts to improve them and decrease their influence on CSA-AKI emergence as much as possible.

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S A Ž E T A K

RETROSPEKTIVNA STUDIJA INCIDENCIJE I POSLIJEOPERACIJSKIH KOMPLIKACIJA AKUTNOG BUBREŽNOG OŠTEĆENJA NAKON KARDIJALNIH ZAHVATA

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Uvod: Akutno bubrežno oštećenje (ABO) je ozbiljna komplikacija kardijalne kirurgije. Istraživanja su pokazala da je kardijalna kirurgija po učestalosti drugi uzrok ABO u jedinicama intenzivnog liječenja. *Metode:* Provedeno je retrospektivno istraživanje za razdoblje od tri godine kako bi se utvrdila incidencija ABO, odredio stupanj ozbiljnosti ABO te incidencija kontinuirane bubrežne nadomjesne terapije u bolesnika s urednom prijeoperacijskom bubrežnom funkcijom podvrgnutih kardijalnom zahvatu. U istraživanje je bilo uključeno 1000 ispitanika. Ovim istraživanjem htjeli smo potvrditi povezanost između prijeoperacijskih čimbenika rizika iz prediktivnog modela *Cleveland Clinic Score* i intraoperacijskih rizičnih varijabla kardijalne kirurgije i anestezije s nastankom poslijeoperacijskog ABO. Sekundarni ishod je pokazao incidenciju velikih poslijeoperacijskh komplikacija u bolesnika s ABO povezanim s kardijalnim zahvatom. *Rezultati:* Ukupna incidencija ABO bila je 15,1 % (n=151). Učestalost ispitanika sa stadijem 1 ABO bila je 12,8 % (n=128), sa stadijem 2 1,9 % (n=19) te sa stadijem 3 0,4 % (n=4) klasificiranima prema kriteriju KDIGO AKI (RIFLE/AKIN). Učestalost primjene kontinuirane bubrežne nadomjesne terapije u ispitanika s ABO iznosila je 2,65 %, odnosno 0,4 % cijele kohorte ispitanika (n=4). Bolnička stopa smrtnosti bolesnika s ABO bila je 2,65 % (n=4). Zanimljivo je da su svi bolesnici podvrgnuti kontinuiranoj bubrežnoj nadomjesnoj terapiji zbog ABO preživjeli. *Zaključak:* Ovim smo istraživanjem još jednom potvrdili važnost pravodobnog prepoznavanja poslijeoperacijskog ABO kao ozbiljne komplikacije kardijalnih zahvata. Potvrdili smo da uporaba prijeoperacijskh prediktivnih modela rizika za nastanak ABO nakon kardijalnih zahvata olakšava prepoznavanje rizičnih bolesnika i pravodobnu primjenu mjera prevencije i liječenja ABO. Najpoznatiji prediktivni model je *Cleveland Clinic Score.*

Ključne riječi: akutno bubrežno oštećenje; kardijalna kirurgija; dijaliza