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Cardiac Surgery-Associated Acute Kidney Injury (CSA-AKI) in Adults and Pediatrics; Prevention is the Optimal Management

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ABSTRACT

Background: Cardiac surgery-associated acute kidney injury (CSA-AKI) is a significant and severe complication that affects morbidity and mortality. We studied both pediatric and adult patients using the Acute Kidney Injury Network (AKIN) definition.

Methods: This was an observational retrospective cohort study done at King Abdulaziz University Hospital in Jeddah, Saudi Arabia, and approved by the ethical committee. The exclusion criteria were baseline serum creatinine (SCr) ≥ 4 mg/dL or preexisting renal failure requiring dialysis, reoperation, death within 24 hours postoperatively, and operative mortality or missing data. We included 941 patients in the analysis using statistical software SPSS, version 15.0.

Results: Of the total number of patients, 28.68% in the adult group and 20.07% in the pediatric group developed CSA-AKI. Adult risk factors included the age group 60-69 years, cardiopulmonary bypass (CPB), number of grafts, and hypertension. In the pediatric group, CPB, aortic cross-clamping (ACX), and the lower preoperative SCr were the main risk factors

Conclusion: Conventional conservative management and preoperative identification of predictor risk factors are essential for preventing CSA-AKI, constituting the primary strategy for optimal management.

INTRODUCTION

Acute kidney injury (AKI) is a rapid deterioration of glomerular filtration rate (GFR) associated with significant renal function impairment. CSA-AKI is reported in up to 30% of patients undergoing cardiac surgery and is considered an independent risk factor for increased morbidity and mortality causing dialysis in up to 4% [Hoste 2008; Wijeysundera 2007; Mehta 2006; Thakar 2005]. A slight increase of (0.3-0.5 mg/dL) in SCr is significantly correlating to an increase in 30-day mortality [Lassnigg 2004]. CSA-AKI is the second cause of AKI in intensive care units (ICU), preceded by sepsis, increasing the death by fourfold, reaching up to 8% [Uchino 2005; Karkouti 2009]. Mortality associated with renal replacement therapy (RRT) reaches up to 63% [Thakar 2005]. It is known that hypertension, advanced age, hyperlipidemia, and peripheral vascular disease are nonmodifiable risk factors for AKI [Lopez-Delgado 2013]. Uniquely among surgeries, cardiac surgery has some properties that increase AKI risks, such as CPB, ACX, high rates, volumes of exogenous blood product transfusion, and high doses of vasopressors [Gomez 2014]. Fortunately, many CSA-AKI risk factors can be modified. Identifying risk factors is one of the essential strategies to prevent or minimize CSA-AKI.

MATERIALS AND METHODS

This was an observational retrospective cohort study done at King Abdulaziz University Hospital (KAUH) Jeddah, SA, approved by KAUH ethical committee. A total of 1265 patients underwent cardiac surgery between January 2016 and December 2020. AKIN defined CSA-AKI for pediatric and adult groups as an increase in SCr of ≥ 0.3 mg/dL above baseline that persisted for more than 48 hours postoperatively. Also, it classifies CSA-AKI into 3 stages [Bellomo 2004]. (Table 1)

The exclusion criteria were baseline SCr ≥ 4 mg/dL or preexisting renal failure requiring dialysis, reoperation, death within 24 hours postoperatively, and operative mortality or missing data. A total of 941 patients were included in the analysis using the statistical software SPSS, version 15.0. Mann-Whitney test was used in univariate analysis of continuous variables, and the Pearson Chi-square test or Fisher's exact test was used to analyzing categorical variables.

Statistical analysis: Continuous variables are presented as medians and 25-75 (25-75 median percentiles) as data were not normally distributed, and categorical variables are expressed as frequencies and percentages. Mann-Whitney test was used in univariate analysis of continuous variables, and the Pearson Chi-square test or Fisher's exact test was used to analyzing categorical variables.

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Table 1. Acute Kidney Injury Network (AKIN) criteria

Stage	Serum Creatinine	Urine Output
1	Increase ≥0.3 mg/dL, or Increase ≥150-200% (1.5-2-fold) from baseline	<0.5 mL/kg/h for 6 h
2	Increase ≥200-300% (2-3-fold) from baseline	<0.5 mL/kg/h for 12 h
3a Patients receiving renal replacement therapy are included in Stage 3	Increase > 300% (>3-fold) from baseline, or Serum creatinine to ≥4 mg/dL with an acute Increase of ≥0.5 mg/dL	<0.3 mL/kg/h for 24 h, or Anuria for ≥12 h

Table 2. Characteristics of pediatrics patients undergoing cardiac surgery, according to the occurrence of acute kidney injury (AKI).

Variables	All patients (*N* = 568)	AKI (*N* = 114)	No AKI (*N* = 454)	Significance
Age category	-	-	-	0.092
≤ 30 days	69 (12.1%)	18 (15.8%)	51 (11.2%)	
> 30 days- ≤2 years	329 (57.9%)	72 (63.2%)	257 (56.6%)	
> 2- < 13 years	139 (24.5%)	21 (18.4%)	118 (26.0%)	
≥ 13- < 18 years	31 (5.5%)	3 (2.6%)	28 (6.2%)	
Gender	-	-	-	0.600
Male	312 (54.9%)	60 (52.3%)	252 (55.5%)	
Female	256 (45.1%)	54 (47.4%)	202 (44.5%)	
Nationality	-	-	-	0.784
Saudi	100 (17.6%)	21 (18.4%)	79 (17.4%)	
Non-Saudi	468 (82.4%)	93 (81.6%)	375 (82.6%)	
Cardiac pulmonary bypass (min)	68 (49.0-88.5)	79.0 (61.5-97.5)	64.0 (47.0-85.0)	0.0001
Aortic cross-clamp (min)	48 (31.0-64.0)	57.0 (42.0-70.5)	45.0 (29.0-63.0)	0.0001
Case urgency	-	-	-	0.891
Elective	469 (82.6%)	95 (83.3%)	374 (82.6%)	
Emergent	99 (17.4%)	19 (16.7%)	99 (17.4%)	
Preoperative creatinine (mg/dl)	0.33 (0.25-0.44)	0.24 (0.19-0.32)	0.35 (0.27-0.46)	0.0001
Postoperative creatinine (mg/dl)	0.34 (0.24-0.46)	0.49 (0.37-0.67)	0.31 (0.21-0.41)	0.0001
Difference between pre- and postoperative creatinine (mg/dl)	0.00 (-0.10-0.11)	0.24 (0.16-0.36)	-0.04 (-0.12-0.03)	0.0001
Percentage changes of creatinine (%)	100 (71.98-135.25)	195.50 (163.86-259.29)	87.50 (65.63-109.62)	0.0001
Stages of acute kidney injury				
Stage 1	-	62 (54.4%)	-	
Stage 2	-	35 (30.7%)	-	
Stage 3	-	17 (14.9%)	-	
Death within index hospitalization	15 (2.6%)	8 (7.0%)	7 (1.5%)	0.004

RESULTS

Table 2 shows the demographic and clinical characteristics of pediatric patients who were subjected to cardiac surgery. Those patients were divided into two groups, according to the occurrence of acute kidney injury. Most of the pediatric patients were in the age group > 30 days- ≤2 years (*N* = 329, 57.9%), and the least were ≥ 13- < 18 years (*N* = 31, 5.5%). Males were greater in number than females (54.9% vs. 45.1%); non-Saudi patients were more than Saudi (82.4% vs. 17.6%). The same distributions of age, gender, and nationality were found in patients with and without AKI with insignificant differences between them (*P* = 0.092, *P* = 0.600, and *P* = 0.784, respectively). The median of CPB and ACX durations were 68 and 48 min that was significantly prolonged in patients with AKI versus those without AKI (79 versus 64 min and 57 vs. 45, *P* < 0.0001 for both). Case urgency was mostly elective than emergent in all patients (82.6% vs.

Table 3. Characteristics of adult patients undergoing cardiac surgery according to the occurrence of acute kidney injury (AKI).

Variables	Adult (≥ 18 years) (*N* = 373)	AKI (*N* = 107)	No AKI (*N* = 266)	Significance
Age category	-	-	-	0.004
< 50 years	114 (30.6%)	21 (19.6%)	93 (35.0%)	
50-59 years	115 (30.8%)	33 (30.8%)	82 (30.8%)	
60-69 years	106 (28.4%)	35 (32.7%)	71 (26.7%)	
≥ 70 years	38 (10.2%)	18 (16.8%)	20 (7.5%)	
Gender				
Male	301 (80.7%)	83 (77.6%)	218 (82.0%)	0.384
Female	72 (19.3%)	24 (22.4%)	48 (18.0%)	
Nationality	-	-	-	0.143
Saudi	41 (11.0%)	16 (15.0%)	25 (9.4%)	
Non-Saudi	332 (89.0%)	91 (85.0%)	241 (90.6%)	
Type of surgery	-	-	-	0.235
Adult congenital	92 (24.7%)	18 (16.8%)	74 (27.8%)	
Valve repair	16 (4.3%)	5 (4.7%)	11 (4.1%)	
Valve replacement	57 (15.3%)	15 (14.0%)	42 (15.8%)	
Coronary artery bypass graft	205 (55.0%)	68 (63.6%)	137 (51.5%)	
Combined (CABG+Valve repair)	1 (0.3%)	-	1 (0.4%)	
Combined (CABG+Valve replacement)	2 (0.5%)	1 (0.9%)	1 (0.4%)	
Valve type	-	-	-	0.588
Mechanical	49 (13.1%)	12 (11.2%)	37 (13.9%)	
Biologic	10 (2.7%)	4 (3.7%)	6 (2.3%)	
Cardiac pulmonary bypass (min)	112.00 (89.50-138.00)	122.0 (96.0-158.0)	108.5 (87.0-130.25)	0.003
Aortic cross-clamp (min)	67.50 (54.00-92.00)	72.0 (58.5-100.0)	66.0 (53.0-89.0)	0.051
Case urgency	-	-	-	0.384
Elective	307 (82.3%)	92 (86.0%)	215 (80.8%)	
Emergent	64 (17.2%)	15 (14.0%)	49 (18.4%)	
Urgent	2 (0.5%)	-	2 (0.8%)	
Smoking	93 (24.9%)	25 (23.4%)	68 (25.6%)	0.693
Pre-existing hypertension	175 (46.9%)	62 (57.9%)	113 (42.5%)	0.008
Pre-existing diabetes mellitus	147 (39.4%)	48 (44.9%)	99 (37.2%)	0.196
Preoperative creatinine (mg/dl)	0.97 (0.80-1.17)	1.11 (0.81-1.29)	0.95 (0.79-1.10)	0.0001
Postoperative creatinine (mg/dl)	1.01 (0.78-1.40)	1.84 (1.42-2.62)	0.90 (0.72-1.08)	0.0001
Difference between pre- and postoperative creatinine (mg/dl)	0.06 (-0.11-0.40)	0.67 (0.47-1.18)	-0.04 (-0.15-0.09)	0.0001
Percentage changes creatinine (%)	106.17 (87.17-141.50)	162.71 (147.91-223.58)	95.70 (82.67-109.03)	0.0001
Death within index hospitalization	21 (5.6%)	14 (13.1%)	7 (2.6%)	0.0001
Stages of AKI				
Stage 1	-	73 (68.2%)		
Stage 2	-	20 (18.7%)		
Stage 3	-	14 (13.1%)		

17.4%) and the same distribution in patients with and without AKI. Regarding creatinine levels, preoperative SCr was significantly higher in patients without AKI versus those with AKI ($P < 0.0001$). Meanwhile, postoperative creatinine levels, the difference between post- and preoperative creatinine, and percentage changes of creatinine were significantly lower in patients without AKI versus patients with AKI ($P < 0.0001$ for all). Stages of AKI were stage I (54.4%), then stage II (30.7%), and lastly, stage III (14.9%). Death within index hospitalization was significantly higher in patients with AKI versus those without (7% vs. 1.5%, $P = 0.004$). (Table 2)

Data were expressed as Median (25-75 median percentiles) or frequency (%) as appropriate. Stage I of AKI: Increase ≥0.3 mg/dL (≥26.4 mmol/L), or Increase ≥150-200% (1.5-2-fold) from baseline. Stage II of AKI: Increase >200-300% (2-3-fold) from baseline. Stage III of AKI: Increase > 300% (>3-fold) from baseline, or SCr to ≥4 mg/dL (≥354 mmol/L) with an acute increase ≥0.5 mg/dL (≥44 mmol/L).

Table 3 shows the demographic and clinical characteristics of adult patients subjected to cardiac surgery. The patients were divided into two groups, according to the occurrence of acute kidney injury. Adult patients who developed AKI were found in the age group 60-69 years; while those who did not develop AKI were in age group <50 years with a significant difference in age group distribution of patients ($P = 0.004$). The number of males was higher than females in both adult patients with AKI and without AKI ($P = 0.384$); non-Saudi were higher than Saudi in both adult patients with AKI and without AKI ($P = 0.143$). Surgery type was mostly coronary artery bypass graft (CABG) in both adult patients with AKI and without AKI ($P = 0.235$); valve replacement was mostly mechanical than biologic in both adult patients with AKI and without AKI ($P = 0.588$). Adult patients with AKI were significantly higher than adult patients without AKI in median of CPB ($P = 0.003$), pre-existing hypertension (57.9% vs. 42.5%, $P = 0.008$), preoperative creatinine level ($P < 0.0001$), postoperative creatinine level ($P < 0.0001$), difference between pre-and postoperative creatinine level ($P < 0.0001$), percentage changes creatinine level ($P < 0.0001$), and death within index hospitalization (13.1% vs. 2.6%, $P < 0.0001$). Stages of AKI were mostly stage I (68.2%), then stage II (18.7%), and lastly, stage III (13.1%). (Table 3)

Data were expressed as Median (25-75 median percentiles) or frequency (%) as appropriate. Stage I of AKI: Increase ≥0.3 mg/dL (≥26.4 mmol/L), or Increase ≥150-200% (1.5-2-fold) from baseline. Stage II of AKI: Increase >200-300% (2-3-fold) from baseline. Stage III of AKI: Increase > 300% (>3-fold) from baseline, or SCr to ≥4 mg/dL (≥354 mmol/L) with an acute increase ≥0.5 mg/dL (≥44 mmol/L).

DISCUSSION

This study uniquely focuses on pediatrics and adults to identify CSA-AKI risk factors to help prevent it. GFR is the best measure of kidney function, but it lacks specificity and sensitivity as a biomarker, and SCr has been the primary method to detect AKI. The main CSA-AKI predictive risk factors include age, perioperative GFR, lactate dehydrogenase (LDH), prothrombin time (PT), history of surgery, transfusion, cardiac arrhythmia, coronary heart disease (CHD), or chronic kidney disease (CKD), calcium channel blocker (CCB), proton pump inhibitors (PPI), non-steroidal anti-inflammatory drugs (NSAID), antibiotic or statin before surgery [Harky 2020]. Obesity is an independent risk factor, and oxidative stress may partially mediate this association [Moon 2018]. Our study showed that younger age is a protective factor against CSA-AKI. The incidence in the pediatric patients was 20.07%, compared with 28.68% in adults.

The reported incidence varies, according to AKI definition, between 1%-30%. We chose strict criteria that define AKI by increasing SCr ≥ 0.3 mg/dL above baseline, thus justifying the high incidence in our study 28.68% compared with others. CSA-AKI pathophysiology is not fully understood. It can be related to impaired renal reserve or decreased renal perfusion, reperfusion, inflammation, oxidative stress, toxins, and hemolysis. Hemoglobin-induced pigment nephropathy is another factor. Prophylactic sodium bicarbonate might help in prevention [Haase 2007]. Many studies showed that CSA-AKI is significantly related to the female gender, presence of chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), peripheral vascular disease, renal impairment and congestive heart failure (CHF), valve surgery, case urgency, cardiogenic shock requiring intra-aortic balloon, left coronary insufficiency, length of ACX and CPB, off-pump versus on-pump surgery, non-pulsatile flow, hemolysis, and hemodilution [Harky 2020; Wang 2017; Guan 2019; O'Neal

Table 4. Prevention and Recommendations

Preoperatively	Intraoperatively	Postoperatively
Avoiding or minimizing contrast media	Avoid prolonged CPB, ACX	Maintain hemodynamics (dobutamine)
Nephrotoxic drugs	Avoid hypotension	Avoid vasopressors
Optimize renal function	Maintain sufficient perfusion pressure	Balanced fluid and salt administration
Optimize hemodynamics'	-	Early diagnosis and institution of RRT when indicated
Rehydration	-	Discontinuing angiotensin converting enzyme inhibitors and receptor blockers
Delay surgery if needed, Tight glycemic control	Tight glycemic control	Tight glycemic control

2016]. Park and colleagues showed that off-pump surgery has a similar incidence of CSA-AKI to on-pump [Vaschetto 2007]. Hybrid coronary revascularization minimizes cardiopulmonary bypass and aortic cross clamping but has the risk of contrast exposure [Elassal 2021]. Prevention of major complications like sternal wound infection and postoperative bleeding requiring re-exploration greatly affect the risk of CSA-AKI [Al-Ebrahim 2020; Elassal 2021].

The urge was not a significant risk factor in our study. Some CSA-AKI risk factors have an insignificant P-value because of the small study number. Our study showed an insignificant female gender, DM, type of surgery, and case urgency. Age and hypertension were significant risk factors in our adults. In our study, the age group 60-69 years was the high-risk group.

In addition to morbidity burden, 30 days mortality or death within indexed hospitalization is significantly associated with CSA-AKI. In our study, this was 13.1%, slightly lower than the reported literature between 15%-30% [Karim 2017]. CSA-AKI is the most expensive complication, especially when using RRT [Ronco 2008; Jiang 2019]. Our study, like others, showed that stage 1 was the most common type (68.2%). Jiang and colleagues reported high mortality of CSA-AKI-RRT and recommended adjustment of the modifiable predictors to help in prevention [Jiang 2019].

The incidence was 20.07% in the pediatric group as per AKIN criteria. Considering that, especially when it comes to pediatric patients, average serum creatinine values vary based on age. Krawczeski and colleagues reported an incidence of 42% using the same criteria [Li 2011]. Most of our pediatric cases that developed CSA-AKI (63.2%) were in the age group > 30 days-≤2 years. This age group is at greater risk of renal failure because of their limited physiological GFR before two years of age [Li 2011; Cardoso 2016]. Our study showed that lower preoperative SCr in pediatric patients is a predictive risk factor. This might be due to age, lousy nutrition, and smaller body weight.

Prevention: The available and approved management is confined to hemodynamic manipulations, intravenous resuscitation, balanced-salt fluid administration. Perioperative administration of sodium bicarbonate for the prevention of CSA-AKI is debated [Kim 2015]. Identification of high-risk groups and prevention is the best and optimal strategy [Harky 2020; Moon 2018; Haase 2007; Wang 2017; Guan 2019; O'Neal 2016; Vaschetto 2007; Schetz 2008; Meersch 2017].

Post-cardiac surgery hyperglycemia is a common complication reported in 33.7-74% of non-diabetic patients after cardiac surgery [Meersch 2017]. Novel biomarkers of kidney injury, such as neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), and cystatin C (CysC), have the potential to facilitate the early diagnosis of CSA-AKI [Sandokji 2020]. Fenoldopam, a short-acting dopamine A1 receptor agonist, may reduce RRT and mortality in critically ill patients and patients undergoing cardiovascular surgery [Zangrillo 2012].

We adopted a simple protocol for all our cardiac surgery patients to help in prevention. (Table 4)

Limitation of study: The main limitation of this study is its retrospective, small number, and single-center nature. Another limitation was not considering other criteria for AKI, especially in pediatrics, because of the controversiality of choosing the definitive criteria for this group.

CONCLUSIONS

CSA-AKI is a common and significant complication that affects cardiac surgery results both in adults and pediatrics. Prevention by preoperative identification of predictor risk factors and modification is the best strategy for management.

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