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 an important and serious complication that affects morbidity and mortality. We studied both pediatric and adults using the definition of the Acute Kidney Injury Network (AKIN). **Methods** This is an observational retrospective cohort study done at King Abdulaziz University Hospital in Jeddah, Saudi Arabia approved by 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. 941 patients were included in the analysis using the statistical software *SPSS*, version 15.0. **Results** 28.68% in the adult group and 20.07% in the pediatric group developed CSA-AKI. Adult risk factors included age group of 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 are the main risk factors **Conclusion** Conventional conservative management and preoperative Identification of predictor risk factors are essential for prevention of CSA-AKI which constitute the main strategy for optimal management.

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Abstract

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Methods

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ConclusionConventional conservative management and preoperative Identification of predictor risk factors are essential for prevention of CSA-AKI which constitute the main strategy for optimal management.

Introduction

Acute kidney injury (AKI) is a rapid deterioration of glomerular filtration rate (GFR) that is associated with significant impairment of renal function. CSA-AKI is reported in up to 30% and considered an independent risk factor for increased morbidity and mortality causing dialysis in up to 4%[1-4]. Slight increase of (0.3-0.5 mg/dL) in SCr is significantly correlated to an increase in 30-days mortality[5]. 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%[6-7]. Mortality associated with renal replacement therapy (RRT) reaches up to 63%[8]. It is known that hypertension, advanced age, hyperlipidemia, and peripheral vascular disease are nonmodifiable risk factors for AKI[9]. Uniquely among surgeries, cardiac surgery has some properties that increase the risk of AKI such as CPB, ACX, high rates, and volumes of exogenous blood product transfusion and high doses of vasopressors [10]. Fortunately, many CSA-AKI risk factors can be modified. Identifying risk factors is one of the most important strategies to prevent or minimize CSA-AKI.

Methodology

This is an observational retrospective cohort study done at KAUH Jeddah, SA approved by KAUH ethical committee. 1265 patients underwent cardiac surgery between January 2016 and December 2020. CSA-AKI was defined for pediatric and adult groups by AKIN 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[11]. (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. 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 Person Chi-square test or Fisher's exact test was used to analyze categorical variables.

(Table 1): Acute Kidney Injury Network (AKIN) criteria.

Acute Kidney Injury Network (AKIN) criteria. Stage	Acute Kidney Injury Network (AKIN) criteria. Serum Creatinine	Acute Kidney Injury Network (AKIN) criteria. 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 a 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

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 Person Chi-square test or Fisher's exact test was used to analyze categorical variables.

Results

Table 2 showed the demographic and clinical characteristics of pediatric patients who were subjected to cardiac surgery. Those were divided into 2 groups according to the occurrence of acute kidney injury, most of all pediatric patients were in age group > 30 days- [?]2 years (n=329, 57.9%), and least was [?] 13- < 18 years (n= 31, 5.5%). The males were greater than females (54.9% versus 45.1%); Non-Saudi patients were more than Saudi (82.4% versus 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 versus 45, P < 0.0001 for both). Case urgency was mostly elective than emergent in all patients (82.6% versus 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, post-operative creatinine levels, the difference between post- and pre-operative 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% versus 1.5%, P =0.004).

Table 3 showed the demographic and clinical characteristics of adult patients who were subjected to cardiac surgery. The patients were divided into 2 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 male was higher than female 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). The number of grafts in adult patients with AKI was 1 in 12.1% (n= 13), 2 in 28.0% (n= 30), 3 in 17.8% (n= 19) and 4 in 6.5% (n= 7); while graft numbers in patients without AKI were 1 in 7.5% (n= 20), 2 in 19.2% (n= 51), 3 in 22.2% (n= 59) and 4 in 4.3% (n= 16) with significant difference between them (P =0.046). Adult patients with AKI were significantly higher than adult patients without AKI in median of CPB (P =0.003), pre-existing hypertension (57.9% versus 42.5%, P =0.008), pre-operative creatinine level (P <0.0001), postoperative creatinine level (P <0.0001), difference between pre-and post-operative creatinine level (P <0.0001), percentage changes creatinine level (P <0.0001) and death within index hospitalization (13.1% versus 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).

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%)	
Pre-operative creatinine (mg/dl)	0.33 (0.25-0.44)	0.24 (0.19-0.32)	0.35 (0.27-0.46)	0.0001
Post-operative 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 Post- operative 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 I	-	62 (54.4%)	-	
Stage II	-	35 (30.7%)	-	
Stage III	-	17 (14.9%)	-	
Death within index hospitalization	15 (2.6%)	8 (7.0%)	7 (1.5%)	0.004

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): 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%)	
Number of grafts				0.046
1	33 (8.8%)	13 (12.1%)	20 (7.5%)	
2	81 (21.7%)	30 (28.0%)	51 (19.2%)	
3	78 (20.9%)	19 (17.8%)	59 (22.2%)	
4	16 (4.3%)	7 (6.5%)	9 (3.4%)	
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

Pre-operative creatinine (mg/dl)	0.97 (0.80-1.17)	1.11 (0.81-1.29)	0.95 (0.79-1.10)	0.0001
Post-operative 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 Post- operative 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 I		73 (68.2%)		
Stage II		20 (18.7%)		
Stage III		14 (13.1%)		

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 both pediatrics and adults to identify CSA-AKI risk factors to help in prevention. GFR is the best measure of kidney function, but it lacks specificity and sensitivity as a biomarker and SCr had been the main 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[12]. Obesity is an independent risk factor and oxidative stress may partially mediate this association[13]. Our study showed that younger age is a protective factor against CSA-AKI. The incidence in the pediatric patients was (20.07%) compared to 28.68% in adults.

The reported incidence varies, according to AKI definition, between 1%-30%. We chose strict criteria that define AKI by increasing in SCr [?] 0.3 mg/dL above baseline, thus justifying the high incidence in our study 28.68% compared to others. CSA-AKI pathophysiology is not fully understood. it can be related to impaired renal reserve or decrease renal perfusion, reperfusion, inflammation, oxidative stress, toxins and hemolysis. Hemoglobin induced pigment nephropathy is another factor. Prophylactic sodium bicarbonate might help in prevention[14]. 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[12,15-17]. Park and colleagues showed that off pump surgery has similar incidence of CSA-AKI to on pump[18].

Urgency was not an important risk factor in our study.

Our study showed insignificant relation to 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%[18,19]. CSA-AKI is the most expensive complication especially when using RRT[20,21]. Our study like others showed that stage 1 is the most common type (68.2%). Jiang and colleagues reported high mortality of CSA-AKI-RRT and recommend adjustment of the modifiable predictors to help in prevention[21].

In pediatric group the incidence was 20.07% as per AKIN criteria. Krawczeski and colleagues reported an incidence of 42% using the same criteria[22]. The majority 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 2 years of age[22,23]. Our study showed that lower preoperative SCr in pediatric patients is a predictive risk factor. This might be due to age, bad nutrition, and smaller body weight.

Prevention

Nowadays, there is no pharmacological or nonpharmacological treatment of CSA-AKI. 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[25]. Identification of high-risk group and prevention is the best and optimal strategy[12-18,26,27.]

Post cardiac surgery hyperglycemia is a common complication and is reported in 33.7–74% in non-diabetic patients after cardiac surgery[27]. Novel biomarkers of kidney injury such as neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), cystatin C (CysC), have the potential to facilitate the early diagnosis of CSA-AKI[29]. Fenoldopam, a short acting dopamine A1 receptor agonist, may reduce RRT and mortality in critically ill patients and in patients undergoing cardiovascular surgery[30].

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

Table4

Preoperatively	Intraoperatively	Postoperatively
Avoiding or minimizing contrast media	Avoid prolonged CPB, ACX	Maintain hemodynamics (dobutar
Nephrotoxic drugs	Avoid hypotension	Avoid vasopressors
Optimize renal function	Maintain sufficient perfusion pressure	Balanced fluid and salt administra
Optimize hemodynamics'		Early diagnosis and institution of
Rehydration		Discontinuing angiotensin convert
Delay surgery if needed, Tight glycemic control	Tight glycemic control	Tight glycemic control

Limitation of study

The main limitation of this study being retrospective, small number and single center. Another limitation was not considering other criteria for AKI especially in pediatrics because of controversiality on choosing the definitive criteria for this group

Conclusion

CSA-AKI is a common and significant complication that affect the results of cardiac surgery 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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