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.
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. 17.4%)

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 |
|       |       | Anuria for ≥12 h |

Table 2. Characteristics of pediatric 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%)       |              |
| > 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        |
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                            |                               |               |                  | 0.384       |
| Male                              | 301 (80.7%)                   | 83 (77.6%)    | 218 (82.0%)      |             |
| 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%)    |                  |             |
Avoid vasopressors
Maintain sufficient perfusion pressure
Discontinuing angiotensin converting enzyme inhibitors and receptor blockers
Tight glycemic control
Tight glycemic control
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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                        |

**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...
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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 controversy 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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