

## Original Research Article

# Acute kidney injury as a predictor of poor outcome post cardiopulmonary bypass in children

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## ABSTRACT

**Background:** We objective of the current study was to identify the prevalence of AKI and classify them based on Acute Kidney Injury Network (AKIN) staging system. We also evaluated the outcome of patients developing AKI and identified the associated risk factors.

**Methods:** This retrospective study was conducted in pediatric cardiac ICU of a tertiary care hospital. Patient < 18 years who underwent cardiac surgery on cardiopulmonary bypass (CPB) for congenital heart disease were enrolled in the study. AKI was defined as increase in serum creatinine  $\geq 0.3$  mg/dl within 48 hours or 1.5 times or more from baseline within the first 7 days post-surgery.

**Results:** Nine hundred and twenty children were enrolled in the study. Three hundred and twelve (34%) children developed AKI with 202 (20%) developing stage I, 92 (10%) stage II and 18 (2%) stage III. Resolution was achieved in all the patients and none developed chronic kidney disease. Risk factors for AKI were higher CPB time, higher aortic cross clamp time, significant arrhythmias and higher inotropic requirement at admission. Children with stage 2 and 3 disease had higher odds for requirement of mechanical ventilation > 24 hours and > 72 hours, length of ICU stay > 5 days and in hospital mortality.

**Conclusions:** AKI following cardiac surgery is common. Although majority of the cases are mild disease and self-limiting it can significantly affect the outcome of these patients.

**Keywords:** Acute kidney injury, Aortic cross clamp, Cardiopulmonary bypass, Pediatric cardiac surgery, Vasoactive inotropic score

## INTRODUCTION

Acute Kidney Injury (AKI) is a well-known risk factor for increased morbidity and mortality in hospitalized children and adult and is associated with increased length of hospital stay and hospital cost.<sup>1-6</sup> Even a modest postoperative increase in the serum creatinine level ( $\geq 0.3$  mg/dl) in patients who undergo cardiac surgery may predict a poor post-operative outcome.<sup>4,7-8</sup> Studies of AKI in children undergoing cardiac surgery reported an overall prevalence of 11% to 52%, the majority (57%-

61%) being mild disease.<sup>1,9-11</sup> Considering the high associated mortality which has been reported between 20 – 79% depending on the definition used AKI is considered to be an important determinant of outcome in patients undergoing cardiac surgery.<sup>12</sup> We undertook the current study to identify the prevalence of AKI in our cohort of patient and classify them based on acute kidney injury network (AKIN) staging system. We also evaluated the outcome of patients developing AKI based on severity and identified the risk factors for the development of AKI.

## METHODS

The cohort in the present study was retrospectively enrolled from our 65 bedded Pediatric cardiac ICU during the period of June to November 2015. This study was approved by the institutional review board of the hospital. Included patients were children less than 18 years of age undergoing cardiac surgery on cardio-pulmonary bypass (CPB) for congenital heart disease. Exclusion criterion included patients with prior renal disease, deranged renal functions in the pre-operative period, dialysis requirement in pre-operative period and patients with other congenital anomalies.

Data were collected from the analysis of case records and ICU charts of the patients. Preoperative variables recorded included age at operation, sex, weight, mechanical ventilator support, diagnosis and procedure performed. Intraoperative variables recorded were CPB time, need for and duration of aortic cross clamp (AXC). Postoperative variables included unplanned reoperation, need for mechanical circulatory support (e.g. extracorporeal membrane oxygenation) and inhaled nitric oxide (iNO) within the first 48 hours, left ventricular ejection fraction by 2D echocardiography performed by pediatric cardiologist, significant cardiac arrhythmias during the initial 48 hours and post-operative sepsis. Inotropic or vasopressor medications used were recorded at admission, 24 hours and 48 hours of admission. Fluid balance was assessed each day and calculated as percentage of body weight using formulae:  $(\text{total fluid in (L)} - \text{total fluid out (L)} / \text{body weight (kg)}) \times 100$ .

AKI was defined as increase in serum creatinine  $\geq 0.3$  mg/dl within 48 hours of surgery or 1.5 times or more from baseline within the first 7 days after surgery.<sup>1</sup> The definition and severity of AKI was based on AKIN staging system.<sup>13</sup> Urine output was not taken into consideration for classification as majority of the patients were on diuretics as a part of routine management. Need for dialysis was not considered in the diagnosis as many of our patients required peritoneal dialysis for fluid management. Baseline serum creatinine was taken as most recent pre-operative value within 7 days prior to surgery. Post-operative serum creatinine was obtained daily on day 1 to day 3 of admission and was monitored closely thereafter if AKI was present till resolution which was defined as serum creatinine within 1.5 times of the baseline value.

Vasoactive Inotropic Score was calculated using formulae:  $\text{VIS} = \text{dopamine dose } (\mu\text{g/kg/min}) + \text{dobutamine dose } (\mu\text{g/kg/min}) + 100 \times \text{epinephrine dose } (\mu\text{g/kg/min}) + 10 \times \text{Milrinone dose } (\mu\text{g/kg/min}) + 10000 \times \text{vasopressin dose } (\mu\text{g/kg/min}) + 100 \times \text{norepinephrine dose } (\mu\text{g/kg/min})$ .<sup>14</sup> Severe left ventricular dysfunction was defined as ejection fraction less than 40% and significant arrhythmia as any deviation from normal sinus rhythm requiring treatment or causing hemodynamic instability. Underweight was defined as weight for age

less than 2 standard deviation for age based on standard charts. Procedure were classified for risk stratification using risk adjustment for congenital heart surgery (RACHS) score and Aristotle Basic complexity scoring system.<sup>15-16</sup> Outcome evaluated were need of mechanical ventilation for more than 24 and 72 hours, length of ICU stay more than 5 days and in-hospital mortality.

All statistical analysis was performed using SPSS 22 software. Mean with standard deviation and median with range were used to describe continuous data whereas absolute count with percentage was used for categorical data. Univariate analyses were performed using Mann-Whitney U test for continuous variables and Chi square test or Fisher's exact test for categorical variables. Multivariate logistic regression models were used to evaluate independent risk factors of AKI. For the multivariate analysis, all significant variables ( $p < 0.1$ ) from the univariate analyses were utilized in a stepwise approach. P value  $< 0.05$  was considered as significant.

## RESULTS

A total of 1067 case records of patients undergoing surgery for congenital heart disease were analysed. Among them 115 were performed without CPB and 25 had congenital anomalies, 5 had deranged renal functions in pre-operative period and 2 case records had inadequate information. Nine-hundred and twenty cases were finally enrolled in the study. Mean age of the cases in the study was  $46.2 \pm 48.2$  months with male female ratio of 1.3:1. Commonest procedure performed was VSD closure (34.8%) and TAPVC repair (19.5%). Majority of the patients had acyanotic heart disease (59.1%). No patient underwent category 5 and 6 procedure and majority (66.1%) of the procedure were classified as RACHS category 2. Mean CPB time in the study was  $83.69 \pm 48.9$  minutes and AXC time was  $50.34 \pm 36.4$  minutes. Six patients (0.7%) required ECMO support or iNO. Thirty two (3.5%) patients underwent unplanned re-exploration and 42 (4.6%) developed sepsis during the post-operative period. One hundred and forty four (15.6%) patients had severe LV dysfunction and 108 (11.7%) had arrhythmias in the post-operative period. The characteristics of cases by AKI status is shown in Table 1.

Three hundred and twelve (34.0%) patients developed AKI. Majority of the patients (n-202; 22%) were classified as stage 1 disease by AKIN whereas 92 (10%) and 18 (2%) were classified as stage 2 and 3 disease respectively Table 2.

Majority of the patients developed AKI during the first 48 of surgery (n-305; 97.8%) with 61.9% developing (n-193) within the first 24 hours. Resolution was achieved in 296 (94.8%) cases within 7 days with 59.3% (n-185) resolving within 24 hours and 26.3% (n-82) within the next 24 hours. In 2 cases resolution took more than 14 days and no child developed end stage kidney disease. Negative fluid balance was achieved in 98% patients who

did not developed AKI and 85% of the patients with AKI within first 48 hours of admission.

**Table 1: Characteristics of the cases in the cohort with relation to AKI status.**

Characteristic	AKI (n-312)	No AKI (n-608)	p value
Pre-operative variables			
Age (months) Mean ± SD	47.15±51.5	45.67±46.5	0.661
Sex			
Male	176 (33.7%)	346 (66.3%)	0.885
Female	136 (34.2%)	262 (65.8%)	
Diagnosis			
Acyanotic	162 (29.8%)	382 (70.2%)	0.001
Cyanotic	150 (39.9%)	226 (60.1%)	
Nutritional status			
Underweight	194 (35.3%)	356 (64.7%)	0.288
Adequate	118 (31.9%)	252 (68.1%)	
RACHS 1 category			
1	40 (24.5%)	123 (75.5%)	0.000
2	204 (33.3%)	409 (66.7%)	
3	34 (47.2%)	38 (52.8%)	
4	34 (47.2%)	38 (52.8%)	
Aristotle basic score (mean ± SD)	7.03±2.2	6.48±2.1	0.000
Intra-operative variables			
CPB time (mean±SD)	94.76±58.4	78.01±42.2	0.000
AXC time (mean±SD)	56.77±42.9	47.04±32.1	0.000
Post-operative variables			
Unplanned re-exploration	18 (56.2%)	14 (43.8%)	0.007
Sepsis	26 (61.9%)	16 (38.1%)	0.000
Severe LV dysfunction	61 (42.3%)	83 (57.6%)	0.020
Arrhythmia	54 (50.0%)	54 (50.0%)	0.000
Requirement of ECMO	4 (66.7%)	2 (33.3%)	0.089
Requirement of iNO	6 (100.0%)	0 (0%)	0.001
VIS score (mean±SD)			
At admission	9.37±4.2	7.59±4.4	0.000
24 hours	7.88±5.2	6.28±4.8	0.000
48 hours	4.39±5.5	2.81±4.1	0.000

Univariate analysis of the peri-operative variables in the study found AKI to be more common in patients with cyanotic heart disease, higher RACHS risk category, procedure with higher Aristotle basic complexity score, higher mean CPB and AXC time. No association was found between age, sex and nutritional status of the children with AKI in the study. After adjusting for other variables, patients undergoing procedure with higher CPB and AXC time were more likely to develop AKI. Patients requiring CPB for more than 120 minutes had 2.13 times (p=0.05) more odds of developing AKI and those who with CPB time of 61 - 120 minutes had 1.99 times (p=0.03) more odds. Similarly patients requiring aortic cross clamping for < 90 minutes had 5.37 times (p<0.001) more odds for AKI and those requiring > 90

minutes had 6.21 times (p <0.001) more odds compared to those who do not required aortic cross clamping. Higher RACHS score and higher Aristotle basic complexity score were not found to be significantly associated with AKI in multivariate regression analysis Table 3.

**Table 2: Grading of acute kidney injury according to the AKIN grading system.**

Grade	Frequency	Percentage
No AKI	608	66.0%
Stage 1	202	22.0%
Stage 2	92	10.0%
Stage 3	18	2.0%

**Table 3: Multivariate adjusted risk for AKI in the cohort.**

Variable	p value	Odds ratio	95% confidence interval
Cyanotic CHD	0.835	1.06	0.66 - 1.69
<b>RACHS category</b>			
1 and 2		1	
3	0.413	0.77	0.42 - 1.43
4	0.936	1.04	0.39 - 2.75
<b>Aristotle basic complexity level</b>			
Level 1 and 2		1	
Level 3	0.823	0.94	0.56 - 1.58
Level 4	0.744	0.84	0.31 - 2.30
<b>CPB time</b>			
< 60 minutes		1	
61 - 120 minutes	0.049	1.99	1.01 - 3.99
>120 minutes	0.033	2.13	1.79 - 3.85
<b>AXC time</b>			
Not required		1	
< 90 minutes	0.000	5.37	2.20 - 13.11
>90 minutes	0.001	6.21	1.96 - 19.70
Unplanned re-exploration	0.433	1.39	0.61 - 3.14
Sepsis	0.446	0.73	0.34 - 1.59
Severe LV dysfunction	0.698	0.92	0.59 - 1.41
Arrhythmia	0.042	1.65	1.02 - 2.68
Requirement of ECMO	0.495	0.53	0.09 - 3.27
Requirement of iNO	0.996	0.00	0.00
VIS at admission >10	0.045	1.49	1.02 - 2.19
VIS at 24 hours >8	0.927	1.02	0.72 - 1.45
VIS at 48 hours >5	0.674	0.91	0.59 - 1.41

**Table 4: Association of outcome with development of AKI.**

Outcome	n (%)	p value	Odds ratio (95% CI)
<b>Mechanical ventilation &gt;24 hours</b>			
No AKI	90 (14.8)		1
Stage 1	30 (14.9)	0.986	1.00 (0.64 - 1.57)
Stage 2	36 (39.1)	0.000	3.70 (2.30 - 5.95)
Stage 3	6 (33.3)	0.039	2.88 (1.05 - 7.86)
<b>Mechanical ventilation &gt;72 hours</b>			
No AKI	16 (2.6)		1
Stage 1	6 (2.9)	0.798	1.13 (0.44 - 2.94)
Stage 2	18 (19.6)	0.000	9.00 (4.40 - 18.41)
Stage 3	4 (22.2)	0.000	10.57 (3.13 - 35.70)
<b>Length of PICU stay &gt;5 days</b>			
No AKI	66 (10.9)		1
Stage 1	20 (9.9)	0.709	0.90 (0.53 - 1.53)
Stage 2	28 (30.4)	0.000	3.59 (2.15 - 5.99)
Stage 3	6 (33.3)	0.006	4.11 (1.49 - 11.31)
<b>In hospital mortality</b>			
No AKI	4 (0.7)		1
Stage 1	2 (1.0)	0.636	1.51 (0.25 - 8.31)
Stage 2	12 (13.0)	0.000	22.65 (7.13 - 71.92)
Stage 3	2 (11.1)	0.001	18.88 (3.22 - 110.65)

Among the post-operative variables unplanned re-exploration, sepsis, severe LV dysfunction, arrhythmia in early post-operative period, requirement of ECMO or iNO and higher mean VIS score at admission, 24 hours and 48 hours were significantly associated with AKI in univariate analysis. After adjusting for other variables only early post-operative arrhythmia (p=0.04; OR=1.65) and VIS score at admission > 10 (p=0.04; OR=1.49) were significantly associated with AKI.

Patients with stage 2 AKI had 3.70 times (p <0.001) higher odds for ventilation > 24 hours and 9.0 times (p <0.001) higher odds for ventilation > 72 hours than those without AKI. Similarly patients with stage 3 AKI had 2.88 times (p=0.039) higher odds for ventilation > 24 hours and 10.57 times (p<0.001) for ventilation > 72 hours than those without AKI. Length of hospital stay > 5 days had 3.59 and 4.11 times higher odds in patients with stage 2 and stage 3 AKI respectively compared to those without AKI. Increased risk of mortality was also found to be significantly higher in patients with stage 2 (p<0.001; OR=27.65) and 3 (p=0.001; OR=18.88) AKI compared to those without Table 4. However no difference in outcome was found between patients with AKI stage 1 and those without AKI.

## DISCUSSION

In the current study we found the 34% prevalence of AKI in the cohort which includes children less than 18 years undergoing surgery on CPB. Prevalence of AKI is comparable to the reports in earlier studies (11% to 52%).<sup>1,9-12,17-18</sup> The significant variability in the reported prevalence of AKI might be due to the variable definition used by authors and the age group included. Two most frequently used definition which has been validated in children are pRIFLE and AKIN criterion; both of which are found to be similar statistically in predicting mortality and morbidity in critically ill children.<sup>13,19</sup> pRIFLE criterion without specific post-operative window was used by Zappitelli et al (incidence=35.9%).<sup>[10]</sup> Li et al used AKIN criterion to define AKI within 7 post-operative days (incidence=42%) without including urine output criterion which was included by Blinder et al (incidence=52%).<sup>9,11</sup> Skippen et al used ADQI criterion with AKI (11%) defined as doubling of serum creatinine or urine output less than 0.5ml/kg/hr for 12 hours and Acute renal failure (1%) as tripling of serum creatinine or urine output less than 0.3ml/kg/hr for 24 hours or anuria for 12 hours whereas Penderson et al (11.5%) defined AKI only by the use of dialysis.<sup>12,17</sup> In the current study AKIN criterion was used with a window of 72 hours without taking in consideration urine output as criterion similar to Taylor et al.<sup>18</sup>

Majority (64.7%) of the cases of AKI in the current study were limited to mild disease and developed early in the post-operative period. Baseline renal functions was achieved in all the cases and none developed chronic kidney disease (CKD). This minor alteration in renal

parameter may be due to the physiological alteration occurring during CPB like non-pulsatile perfusion, hypothermia, hypothermia and hemodilution hence recovered early.<sup>20</sup> Mild renal injury following post cardiac surgery has been reported in previous studies; the prevalence being 50-60% of the total cases of AKI.<sup>9,10</sup> Similarly early recovery and less likelihood of progression to CKD has also been reported in earlier studies.<sup>9-11,17,21</sup>

We found prolonged CPB time to be associated with higher odds of developing AKI which was consistent with previous studies.<sup>9-11,21,22</sup> The possible reason of longer CPB time associated with AKI is multifactorial and probably due to the physiological alternation occurring during CPB.<sup>20</sup> In the study higher AXC time was found to be significantly associated with AKI. Aortic cross clamp has been associated with increased mortality and morbidity after cardiac surgery which is probably related to longer duration of ischemia with prolonged cross clamping.<sup>23,24</sup> Sarraf et al found a significant increase in renal complications in patients with AXC time > 60 minutes compared to those with less than 60 minutes.<sup>25</sup> Higher inotropic requirement was also found to be an independent risk factor for AKI in the study. Although longer vasopressor requirement has been associated with AKI in past; in the current study only higher VIS at admission was found to be significant associated risk factor.<sup>10</sup> We also found significant arrhythmia as a risk for AKI in the study which could be explained by the hemodynamic instability caused by arrhythmias and also more intensive and prolonged hospital stay in these patients. Higher RACHS category was found to be associated with AKI by Piggott et al; however in the current study this was not found to be significant.<sup>22</sup> Even though AKI tends to occur more commonly in procedure with higher RACHS score and higher Aristotle score. Younger age has been associated with higher risk of AKI in previous reports; no significant difference could be found in the study.<sup>10,21</sup> AKI was also found to be more common in cyanotic patients, patient requiring unplanned re-exploration, patient having LV dysfunction and post-operative sepsis although no significant association could be established. Low cardiac output and sepsis has also been associated with AKI in previous reports.<sup>17,21</sup>

The current study shows a significant increase in mortality in patients with stage 2 and 3 AKI compared to those without. Similarly significantly higher requirement of prolonged ventilation and length of ICU stay was found in children with stage 2 and 3 AKI compared to those without. However no change in the outcome was observed between those with stage 1 AKI and those without. Prolonged ventilator requirement and length of ICU and hospital stay has been associated with AKI in earlier studies.<sup>9,11,17</sup> Blinder et al reported an increase in mortality, length of mechanical ventilation and prolonged inotropic support in patients with stage 2 and 3 AKI with no significant increase in stage 1 AKI compared to those



without.<sup>9</sup> The limitation of the current study is that urine output was not taken into account in the definition of AKI. We did not assess the tubular function and other markers of kidney injury were also not studied which could have led to large number of missed cases. Also effect of nephrotoxic drugs administered during the perioperative period was not taken into account.

## CONCLUSION

AKI following cardiac surgery is common. Although majority of the cases are mild disease and self-limiting it can significantly affect the outcome of these patients. Patients with longer duration of CPB and AXC and those who required higher inotropic support or developed significant arrhythmias post-operatively are at increased risk.

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