



# Acute Kidney Injury in Infants Undergoing Cardiac Surgery Under Cardiopulmonary Bypass

## Abstract

**Background:** Cardiac surgery-associated acute kidney injury (CS-AKI) is a significant complication associated with substantial morbidity and mortality. Infants are at a significant risk of developing this complication. There is a need to identify risk factors for CS-AKI in this population. This study aimed to assess the incidence, risk factors, and outcomes of CS-AKI, specifically in infants <1 year old undergoing cardiac surgery under cardiopulmonary bypass. **Materials and Methods:** We conducted a prospective observational study at a single tertiary care center from September 2022 to September 2023. All infants <1 year old undergoing cardiac surgery under cardiopulmonary bypass were included. Data on preoperative, intraoperative, and postoperative factors were collected. The primary aim was to study the incidence of acute kidney injury (AKI) and fluid overload (FO). Secondary outcomes included the need for dialysis, length of intensive care unit (ICU) stay, and mortality. **Results:** AKI was seen in 47 (33.6%) out of 140 infants. Cumulative fluid overload % in the overall cohort was -12% (-18% - -8%) [AKI group -18% (-33% to -15%) and non-AKI group -10% (-14% to -7%)  $p < 0.001$ ]. Significant AKI predictors included younger age, cyanotic heart disease, prolonged aortic cross-clamp (ACC) times ( $p < 0.001$ ), sepsis ( $p = 0.002$ ), and prolonged ventilation (>48 hours,  $p < 0.001$ ). Mortality was 2.9% ( $n = 4$ ); all deceased patients developed sepsis and required kidney replacement therapy (KRT). Multivariable analysis showed that cyanotic heart disease (OR 2.53, 95% CI: 1.06–6.00), prolonged ACC time (OR 3.78, 95% CI: 1.54–9.25), and prolonged ventilation (OR 6.01, 95% CI: 1.98–18.21) were independently associated with AKI. The length of ICU and hospital stay was significantly longer in infants with AKI ( $p < 0.001$ ). **Conclusion:** CS-AKI is common in infants, particularly those with cyanotic heart disease, prolonged surgery times, and sepsis. AKI is associated with higher morbidity, prolonged ICU stays, and increased mortality. Further research is needed to develop better predictive tools and early AKI biomarkers in this population, and strategies to reduce risk factors like prolonged ACC times and sepsis.

**Keywords:** Acute kidney injury, Cardiopulmonary bypass, Cardiac surgery, Pediatrics

## Introduction

Cardiac surgery-associated acute kidney injury (CS-AKI) in pediatric patients is common, with a 19% to 29% incidence and up to 30% long-term mortality rate.<sup>1</sup> CS-AKI develops due to renal ischemia, reperfusion injury, inflammation, and cardiopulmonary bypass (CPB)-induced hemolysis.<sup>2</sup> CS-AKI development is associated with higher mortality, more complicated hospital course, and higher infection risk.<sup>3</sup> Infants with AKI are at higher risk of developing hypertension, proteinuria, and chronic kidney disease later in life.<sup>4,5</sup>

Many risk factors for CS-AKI are non-modifiable. CS-AKI is associated with

perioperative factors, including hypoxemia, prolonged CPB time, systemic inflammation, low cardiac output states, and nephrotoxic medications.<sup>6</sup> Postoperatively, sepsis, fluid overload (FO), and nephrotoxic agent-use are risk factors.<sup>7</sup> There are numerous pre-operative factors responsible for CS-AKI development, including lower birth weight or young age.<sup>7</sup> Several studies have identified that younger age groups, particularly infants <12 months, are susceptible to developing AKI after cardiac surgery.<sup>7–9</sup> There have been limited studies on this vulnerable population in resource-limited settings.<sup>10</sup> Therefore, this study's objective was to identify the incidence and risk factors for CS-AKI in infants.

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DOI: 10.25259/IJN\_644\_2024



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**How to cite this article:** Sharma R, Gulia M, Bhan A, Akole R, Hu J, Mir FA, et al. Acute Kidney Injury in Infants Undergoing Cardiac Surgery Under Cardiopulmonary Bypass. Indian J Nephrol. doi: 10.25259/IJN\_644\_2024

Received: 25-10-2024  
Accepted: 25-03-2025  
Online First: 11-06-2025  
Published: \*\*\*

## Materials and Methods

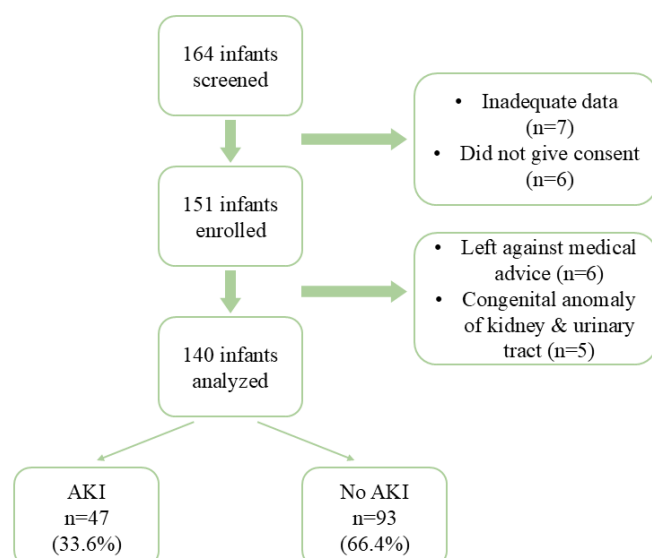
The primary aim was to assess AKI and FO incidence in the post-operative setting of infants undergoing cardiac surgery. Secondary aims included assessing AKI risk factors and outcomes in infants undergoing cardiac surgery, including the need for dialysis, duration of ventilation, length of stay in ICU, and mortality.

This was a prospective, observational study conducted in the pediatric cardiothoracic unit. All infants <1 year old undergoing any cardiac surgery under CPB from September 2022 to September 2023 were included [Figure 1]. Informed consent was obtained from all parents prior to inclusion. This study was approved by the Institutional Review Board (IRB approval number:1491/2022) and Institutional Ethics Committee (IEC approval number: 2144104280).

Patients with pre-existing renal dysfunction (baseline eGFR<60 mL/min/1.73 m<sup>2</sup> or structural kidney abnormalities), need for pre-operative mechanical ventilation or extracorporeal therapy, need for pre-operative vasopressors, and post-kidney transplant were excluded.

Demographic variables, including age, sex, and ethnicity, were recorded. General medical data, including type of heart disease, diagnosis, acyanotic/cyanotic heart disease, and any previous cardiac surgery, were noted.

Pre-operative laboratory information, including pre-operative weight, height, estimated glomerular filtration rate (eGFR), and serum creatinine, were recorded. The GFR was estimated using the revised pediatric Schwartz formula.<sup>11</sup> Urine was collected via Foley catheter, or by using a clean-catch sample in those without urinary catheters.



**Figure 1:** Study flow. AKI: Acute kidney injury.

Intra-operative data, including duration of the operation, time on CPB, aortic cross clamp (ACC) time, and the Risk Adjustment for Congenital Heart Surgery (RACHS-1) score, were recorded. The RACHS-1 score is a consensus-based tool defining short-term mortality risk in children undergoing surgery for congenital heart disease, based on the procedure.

Post-operative information included blood cultures, daily serum creatinine, hourly urine output, complete blood count, and liver function tests. Additionally, any post-operative complications such as the need for re-exploration, prolonged ventilation, need for re-intubation, nephrotoxic medication administration, and death were noted. AKI development was defined by KDIGO guidelines.<sup>12</sup> The definitions of AKI stages was based on standard KDIGO criteria.

The FO with daily and cumulative fluid balance was calculated based on daily weight records. We defined CS-AKI based on information and lab values assessed within 7 post-op days or until hospital discharge, whichever came first.

Data pertaining to mechanical ventilator support duration, NSAIDs/nephrotoxic drug use, duration of hospital stay, duration of pediatric ICU (PICU) stay, sepsis, transaminitis (more than 2x the upper normal limit), need for KRT, need for re-exploration/second operation, and in-hospital mortality were noted.

## Statistical analysis

The data were entered into Microsoft Excel, and SPSS version 24 was used for the statistical analysis. All the variables were tested for normality using the Kolmogorov-Smirnov test. Categorical variables were summarized as frequencies and percentages, and continuous variables as medians and inter-quartile ranges (IQR; 25<sup>th</sup> to 75<sup>th</sup> percentiles). The main outcome was to identify AKI predictors and mortality among infants undergoing cardiac surgery. Univariate analysis (using the Chi-square or Fischer exact test for categorical variables and the Wilcoxon's rank-sum test for continuous variables) was conducted to assess the relationship between different variables and AKI/mortality. A multivariable logistic regression technique with backward elimination was used to determine the association between different variables and AKI, after adjusting for different confounders. The multi-collinearity of variables was assessed using a correlation matrix, and those with a correlation coefficient  $\geq 0.8$  were excluded from the multivariate analysis. A two-tailed p-value <0.05 was considered statistically significant.

## Results

A total of 140 infants who underwent cardiac surgery under CPB were included. The median (IQR) age was 4 (2 - 9) months [10 (7.1%) aged <1 months], and 107 (76.4%)

were boys. The median (IQR) ACC time was 47 (36 - 61) minutes, CPB time was 64 (51 - 85) minutes, pre-operative creatinine was 0.3 (0.2 - 0.4) mg/dL, cumulative FO was -12% (-18% - -8%), and duration of procedure was 5 (4 - 5) hours. Of them, 74 (52.9%) had acyanotic heart disease, 20 (14.3%) had previous cardiac surgery, 34 (24.3%) had RACHS stage  $\geq 3$ , 44 (31.4%) had developed sepsis, 10 (7.1%) required re-exploration/second operation, and 23 (16.4%) required prolonged ventilation ( $>48$  hours).

AKI incidence was 33.6% (47/140 infants) [Stage 1: 26 (55.3%), Stage 2: 14 (29.8%), and Stage 3: 7 (14.9%)]. Six (12.8%) infants with AKI needed KRT. The infants developed AKI at the median (IQR) of 2 (1 - 3) post-operative days, and the infants with AKI recovered at the median (IQR) of 5 (4 - 6) post-operative days. Cumulative fluid overload (%) in the overall cohort was -12% (-18% - -8%) [AKI group -18% (-33% - -15%) and non-AKI group -10% (-14% - -7%)  $p < 0.001$ ]. There was 2.9% (4/140) mortality.

The infants with AKI were younger [median (IQR) age: 3 (1 - 8) vs. 5 (3 - 10) months;  $p = 0.010$ ] than those without AKI. Cyanotic heart disease, RACHS stage  $\geq 3$ , with ACC time ( $>60$  mins), sepsis development, re-exploration/second operation, prolonged ventilation, and re-intubation was more in infants with AKI than without [Table 1].

Multivariate logistic regression analysis showed significant association between prolonged ventilation ( $\geq 48$  hours) [Odds ratio (95% CI): 6.01 (1.98 - 18.21)], ACC ( $\geq 60$  minutes) [3.78 (1.54 - 9.25)], type of heart disease (cyanotic) [2.53 (1.06 - 6.00)], and AKI. The multivariate analysis was adjusted for age ( $<1$  or  $\geq 1$  month), type of heart disease (cyanotic vs. acyanotic), RACHS ( $<3$  vs.  $\geq 3$ ), ACC ( $<60$  or  $\geq 60$  minutes), sepsis (yes or no), hematological complications (yes or no), re-exploration/second operation (yes or no), prolonged ventilation ( $<48$  hours or  $\geq 48$  hours), and re-intubation (yes or no). The mortality incidence was higher among infants with AKI vs. non-AKI [4 (8.5%) vs. 0 (0%);  $p = 0.012$ ] [Table 2].

For all infants, the median (IQR) duration of stay in ICU was 4 (3 - 5) days, and in the hospital was 8 (7 - 10) days. The duration of stay in the ICU [5 (4 - 7) vs. 4 (3 - 4) days;  $p < 0.001$ ] and hospital [9 (8 - 12) vs. 8 (7 - 9) days;  $p < 0.001$ ] was higher among infants with AKI than without AKI [Table 1].

## Discussion

This is the first ever Indian study specifically looking at CS-AKI epidemiology and risk factors in infants  $<1$  year old. The CS-AKI incidence in this cohort is within the

**Table 1: Comparison of variables among infants with and without AKI**

	Descriptive characteristics of the included 140 infants	AKI		p value
		Yes (n=47)	No (n=93)	
Age ( $<1$ month)	10 (7.1%)	7 (14.9%)	3 (3.2%)	0.031
Age (months)	4 (2 - 9)	3 (1 - 8)	5 (3 - 10)	0.010
Weight (kg)	5 (3.7 - 6.4)	4.3 (3.1 - 5.4)	5.4 (3.8 - 7)	$<0.001$
Length (cm)	60 (52 - 67)	54 (50 - 64)	62 (54 - 68)	0.003
Sex (Male)	107 (76.4%)	37 (78.7%)	70 (75.3%)	0.649
Type of heart disease (cyanotic)	74 (52.9%)	34 (72.3%)	40 (43.0%)	0.001
Previous cardiac surgeries (yes)	20 (14.3%)	7 (14.9%)	13 (14.0%)	0.884
RACHS staging	2 (2 - 2)	2 (2 - 3)	2 (2 - 2)	0.001
RACHS ( $\geq 3$ )	34 (24.3%)	18 (38.3%)	16 (17.2%)	0.006
CPB time (minutes)	64 (51 - 85)	78 (57 - 137)	60 (50 - 72)	$<0.001$
ACC time ( $>60$ minutes)	37 (26.4%)	23 (48.9%)	14 (15.1%)	$<0.001$
ACC time (minutes)	47 (36 - 61)	57 (43 - 82)	42 (35 - 52)	$<0.001$
Pre-operative creatinine (mg/dL)	0.3 (0.2 - 0.4)	0.3 (0.2 - 0.4)	0.3 (0.2 - 0.3)	0.573
Duration of procedure (hours)	5 (4 - 5)	5 (5 - 6)	4 (4 - 5)	$<0.001$
Cumulative fluid overload	-12% (-18% - -8%)	-18% (-33% - -15%)	-10% (-14% - -7%)	$<0.001$
Development of sepsis (yes)	44 (31.4%)	23 (48.9%)	21 (22.6%)	0.002
Development of hematological complications (yes)	30 (21.4%)	18 (38.3%)	12 (12.9%)	0.001
Development of transaminitis (yes)	50 (35.7%)	22 (46.8%)	28 (30.1%)	0.051
Re-exploration/Second operation (yes)	10 (7.1%)	9 (19.1%)	1 (1.1%)	$<0.001$
Prolonged ventilation ( $>48$ hours)	23 (16.4%)	17 (36.2%)	6 (6.5%)	$<0.001$
Re-intubation (yes)	17 (12.1%)	11 (23.4%)	6 (6.5%)	0.004
Nephrotoxic drugs (yes)	118 (84.3%)	40 (85.1%)	78 (83.9%)	0.850
Mortality (yes)	4 (2.9%)	4 (8.5%)	0 (0%)	0.012
Duration of ICU stay (days)	4 (3 - 5)	5 (4 - 7)	4 (3 - 4)	$<0.001$
Duration of hospital stay (days)	8 (7 - 10)	9 (8 - 12)	8 (7 - 9)	$<0.001$

AKI: Acute kidney injury, RACHS: Risk adjustment for congenital heart surgery, CPB: Cardiopulmonary bypass, ACC: Aortic cross-clamp, ICU: Intensive care unit.

**Table 2: A multivariate logistic regression model showing the variables significantly associated with AKI**

	B coefficient	Std error	Odds ratio	95% CI	p value
Constant	-2.159	0.393	0.115	-	<0.001
Type of heart disease (acyanotic as reference)	0.926	0.442	2.525	1.06 – 6.00	0.036
ACC (<60 minutes as reference)	1.329	0.457	3.775	1.54 - 9.25	0.004
Prolonged ventilation (<48 hours as reference)	1.794	0.566	6.011	1.98 - 18.21	0.002

Adjusted for age (<1 or ≥1 month), type of heart disease (cyanotic vs. acyanotic), RACHS (<3 vs. ≥3), ACC (<60 or ≥60 minutes), Development of sepsis (yes or no), Development of hematological complications (yes or no), Re-exploration/second operation (yes or no), Prolonged ventilation (<48 hours or ≥48 hours), Re-intubation (yes or no). AKI: Acute kidney injury, ACC: Aortic cross-clamp, CI: Confidence interval.

range of previously published results, which is partially influenced by the AKI definition being used. We used the KDIGO definition due to its validation in pediatric critical care.<sup>13</sup> Patients who developed CS-AKI were younger and had longer CPB and ACC times. They required prolonged mechanical ventilation, as well as extended ICU and hospital stays. These findings align with previously published results, including the TRIBE consortium data on pediatric AKI, despite the study being conducted in a resource-limited setting.<sup>14</sup> An improved AKI prediction tool beyond serum creatinine is required for CS-AKI. Adding pre-operative albuminuria levels to a clinical model has been found to improve CS-AKI prediction.<sup>15</sup> Validated post-operative monitoring scores, such as the vasoactive-ventilation-renal score, have shown benefit in resource-limited settings.<sup>16</sup> In this study, infants with a high RACHS stage ≥3 did not reach statistical significance on multivariate logistic regression analysis. Previous studies have reported mixed results regarding RACHS-1 score's significance. Some found no significant association between RACHS-1 stages and outcomes, while others identified a correlation.<sup>8,17</sup> This may be due to variability in study size. Biomarkers such as urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary CXCL10, and VCAM may also play a role in CS-AKI prediction.<sup>18</sup> Children with AKI had significantly higher urine levels of NGAL, IL-18, and kidney injury molecule-1 even at long-term follow-ups, suggesting persistent kidney damage.<sup>19</sup>

Cyanotic heart disease was a major risk factor for developing CS-AKI. It leads to hypoxemia, secondary polycythemia, and abnormal arteriovenous shunts altering renal blood flow and intraglomerular hemodynamics, compromising renal function.<sup>20</sup> Aoun *et al.*<sup>21</sup> found that patients with cyanotic heart disease were more prone to develop AKI (78%) compared to those with non-cyanotic heart disease (44%). Similarly, prolonged CPB time and ACC time have been shown to increase AKI risk, suggesting the benefits of limiting ACC time, although some studies have found no association between ACC time and CS-AKI development.<sup>22,23</sup> Similarly, a CPB time >90 minutes has been found to increase the AKI risk.<sup>24</sup>

CS-AKI was associated with increased mortality; all four patients who died developed AKI. All cases also developed sepsis and required KRT. Most also experienced hematological complications, required re-operation, and

had ventilation needs >48 hours. However, the analysis is limited by lesser cases with mortality. Prolonged ventilation is likely due to FO state and pulmonary dysfunction.<sup>25</sup> The need for inotropes, measured by the Vasoactive Inotrope Score, is also correlated with prolonged mechanical ventilation need.<sup>26</sup>

The cumulative fluid overload % in the overall cohort was -12% (-18% - -8%) [AKI group -18% (-33% - -15%) and non-AKI group -10% (-14% - -7%)  $p<0.001$ ]. Our Pediatric Cardiac ICU (PCICU) team used furosemide intermittent 8-12 hourly, post-operatively to prevent FO, so none of the children were post-operatively fluid overloaded.

CS-AKI was associated with an increased length of stay in the PCICU and hospital. Other studies have shown a greater increase in median hospital stay, with ≤7 and ≤4 days for the AKI and non-AKI groups, respectively.<sup>14</sup> Notably, children <1 year appear to have a longer PICU stay compared with older infants [12.6 (3.5) days in comparison to 10.8 (2.4) days, respectively ( $P<0.001$ )].<sup>7</sup> These differences are likely institution-dependent and based on typical cardiac procedures and local surgical practices.

Our study was limited by the lack of serum or urinary biomarkers as they were unavailable.

This study highlights the significant CS-AKI burden in infants <1 year of age, with a 33.6% incidence. We identified several key risk factors, including cyanotic heart disease, prolonged CPB, and ACC, sepsis, and prolonged ventilation. Infants with CS-AKI experienced increased morbidity, prolonged hospital stays, and higher mortality risk, particularly in the presence of sepsis and hematological complications. Despite these findings, further studies are needed to develop better predictive tools and early biomarkers for AKI in pediatric cardiac surgery to improve outcomes in this vulnerable population.

**Conflicts of interest:** There are no conflicts of interest.

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