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ORIGINAL ARTICLE

Kidney Disease: Improving Global Outcomes in neonates with acute kidney injury after cardiac surgery

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Abstract

Background Acute kidney injury (AKI) after cardiac surgery (CS-AKI) in children with congenital heart disease is a serious complication closely associated with high morbidity and mortality. Kidney Disease: Improving Global Outcomes (KDIGO) AKI staging demonstrates high sensitivity for detecting AKI and predicting associated in-hospital mortality. However, neonatal-modified KDIGO criteria (n-KDIGO), recently introduced as a standard diagnostic tool, for CS-AKI have not been fully validated. Here, we evaluated the incidence of risk factors and postoperative outcomes of neonatal CS-AKI.

Methods We retrospectively studied 114 consecutive neonates who underwent cardiac surgery at the Kagoshima University Hospital. CS-AKI was classified using the n-KDIGO criteria. Risk adjustment in congenital heart surgery (RACHS-1) score was used to predict the complexity-adjusted mortality and % fluid overload (%FO) was used to monitor fluid balance in pediatric cardiac surgery.

Results Among 81 patients, neonatal CS-AKI occurred in 57 (70.4%) patients according to n-KDIGO criteria. Of these, 28 (34.6%) patients reached n-KDIGO 1, 17 (21.0%) reached n-KDIGO 2, and 12 (14.8%) reached n-KDIGO 3. Patients with CS-AKI had significantly higher vasoactive-inotropic score levels, longer operative times, and higher %FO than patients without CS-AKI. Notably, increased duration of cardiopulmonary bypass times and %FO were risk factors for the development of neonatal CS-AKI. The n-KDIGO-based severe AKI grade had higher risk of in-hospital mortality; however, the n-KDIGO-based mild AKI grade was not associated with any postoperative outcomes.

Conclusions CS-AKI based on n-KDIGO criteria is common in neonates and is closely associated with higher mortality, especially in patients with severe CS-AKI.

Keywords Acute kidney injury · Neonate · Cardiac surgery · Congenital heart disease

Introduction

Postoperative acute kidney injury (AKI) occurs in 30–45% of children after cardiac surgery for congenital heart disease (CHD) [1, 2]. Despite the abundant research on pediatric AKI, most studies have excluded neonates. Severe CHD necessitates palliative repair or complete repair early in life during the neonatal period, however, little is known about the effects of cardiac surgery-associated AKI (CS-AKI) on clinical outcomes. A number of neonatal AKI studies have been performed based on pediatric Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (pRIFLE) and Acute Kidney Injury Network (AKIN) criteria [3, 4]. However, the complex and multifactorial etiology of AKI, immaturity of neonatal tubular function and changes in glomerular filtration rate, and the use of differing validated criteria make it difficult to determine the true incidence and outcomes of neonatal CS-AKI [5, 6]. In 2012, an updated consensus definition of AKI was proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) group to reconcile subtle differences in the pRIFLE and AKIN criteria to establish a common definition known as the KDIGO criteria [7]. In addition, a modification of the KDIGO

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criteria defined as neonatal-modified KDIGO (n-KDIGO) was introduced as the standardized criteria of neonatal AKI to allow for consistency across studies [8, 9]. This study aimed to evaluate incidence, risk factors, and postoperative short-term outcomes (e.g., intensive care unit [ICU] length of stay, renal replacement therapy requirement, and in-hospital mortality within 30 days) of neonatal CS-AKI after cardiac surgery according to n-KDIGO criteria and to validate whether n-KDIGO AKI criteria could describe clinically relevant neonatal CS-AKI in this cohort.

Materials and methods

Patient enrolment and characteristics

We performed a retrospective cohort study of 114 consecutive neonates (≤ 28 days of age) who underwent cardiac surgery for CHD at the Kagoshima University Hospital (Kagoshima, Japan) from May 2010 to January 2018. Premature infants, those with preexisting genetic and chromosomal abnormalities, or neonates with preexisting brain or kidney abnormalities were excluded. Eighty-one neonates were ultimately enrolled in this study. The Kagoshima University Ethics Committee approved the study, which was performed in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki. Parental and patient informed consents were waived.

Data collection

We retrospectively reviewed patient clinical characteristics including age, sex and weight at the time of surgery, the presence of cyanotic CHD, and preoperative serum creatinine (SCr). Individual operative risk mortality was classified into six categories using the Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1) score [10]. Intraoperative variables including cardiopulmonary bypass (CPB) time (minutes) and cross-clamp time (minutes) were assessed. We recorded postoperative data including urine output (ml/kg/h), maximum fluid overload (%FO) (i.e. (Daily (Fluid in [liters] – Fluid out [liters]) × 100/ICU admission patient weight [kg]) [11, 12] and the maximum vasoactive-inotrope score (VIS) (i.e., dopamine dose [μg/kg/min] + dobutamine dose [μg/kg/min] + 100 × epinephrine dose [μg/kg/min] + 10 × milrinone dose [μg/kg/min] + 25 × olprinone dose [μg/kg/min] + 100 × norepinephrine dose [μg/kg/min]) within the first 48 h after cardiac surgery [13]. We also evaluated the association between neonatal CS-AKI and postoperative short-term outcomes (renal replacement therapy and CS-AKI related in-hospital mortality within 30 days after cardiac surgery). Persisting oliguria accompanied by a rising SCr that cannot be reversed with diuretic therapy or refractory acidosis with electrolyte abnormalities is an indication for renal replacement therapy. We classified patients by levels of serum creatinine and/or urine output according to n-KDIGO criteria [8, 9]. The n-KDIGO criteria were defined as follows: n-KDIGO 0, no change in SCr or an increase in SCr level < 0.3 mg/dL or urine output ≥ 0.5 mL/kg/h; n-KDIGO 1, an increase in SCr level by 0.3 mg/dL within 48 h or more an increase to 1.5- to 2.0-fold of the lowest preoperative SCr value within 7 days or urine output < 0.5 mL/kg/h for 6–12 h; n-KDIGO 2, an increase to 2.0- to 3.0-fold of the lowest preoperative SCr value or urine output < 0.5 mL/kg/h for ≥ 12 h; n-KDIGO 3, an increase to > 3.0-fold of the lowest preoperative SCr value or requirement of renal replacement therapy, urine output < 0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h.

Outcome measures

The primary outcome measures in our cohort were all-cause in-hospital mortality within 30 days after cardiac surgery stratified by n-KDIGO AKI criteria. Secondary outcomes were incidence, risk factors, and other postoperative short-term outcomes (intensive care unit [ICU] length of stay and renal replacement therapy requirement).

Statistical analysis

Continuous variables are presented as median values with interquartile range (25th, 75th percentile). Categorical variables are presented as frequencies and percentages. Baseline comparisons between patients with and without CS-AKI were performed using the Mann–Whitney *U* test. The *p* values for categorical variables are based on a two-sided χ^2 or Fisher's exact tests as appropriate. The *p* values for categorical variables regarding the relationship between RACHS-1 and CS-AKI or n-KDIGO grade are based on two-sided Fisher's exact tests. A comparison of the CS-AKI grades according to n-KDIGO criteria was performed by the Kruskal–Wallis test for continuous variables. A multivariate logistic regression analysis was performed to identify the risk factors for CS-AKI and postoperative short-term renal replacement therapy and in-hospital mortality in CS-AKI patients. Survival curves for in-hospital mortality within 30 days after cardiac surgery were constructed using the Kaplan–Meier method. For comparisons of groups, the log-rank test was used to determine survival. The Cox proportional hazard regression model was used to identify in-hospital mortality within 30 days after cardiac surgery. A *p* value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics for Windows, Version 25.0 (SPSS Japan Inc., Tokyo, Japan).

Results

Clinical characteristics of patients with CS-AKI and without CS-AKI according to n-KDIGO criteria

During the study period, 81 consecutive neonates underwent cardiac surgery for CHD. All patients had received continuous infusion of loop diuretics after cardiac surgery. Fifty-seven patients (70.4%) had CS-AKI defined according to n-KDIGO criteria. The requirement of complete repair during the neonatal period, postoperative VIS levels, duration of CPB time and cross-clamp time, urine output, and %FO were significantly different between patients with and without CS-AKI (Table 1). We also performed receiver-operating characteristic (ROC) analysis to assess the utility of VIS, CPB time, cross-clamp time, urine output, and %FO for diagnosing neonatal CS-AKI. An investigational analysis revealed that the area under curve (AUC) for VIS levels (0.774 [95% confidence interval (CI), 0.667–0.880]; $p < 0.001$), the AUC for CPB time (0.788 [95% CI 0.671–0.906]; $p < 0.001$), the AUC for urine output (0.762 [95% CI 0.641–0.884]; $p < 0.001$) and the AUC for %FO (0.727 [95% CI 0.614–0.839]; $p < 0.001$) had moderate accuracy.

Risk factors for CS-AKI according to n-KDIGO criteria

Multivariate logistic regression analysis revealed that increased CPB time and %FO (OR 1.01; 95% CI 1.01–1.02; $p = 0.003$ and OR 1.40; 95% CI 1.05–1.86; $p = 0.023$, respectively) (Nagelkerke's R^2 0.37 and Hosmer–Lemeshow goodness-of-fit test $\chi^2 = 8.35$, $p = 0.400$) were independent risk factors for the development of CS-AKI.

Comparison of clinical characteristics of patients with CS-AKI classified by n-KDIGO criteria

In the study population, among 57 patients with CS-AKI, 28 (34.6%) patients achieved n-KDIGO 1, 17 (21.0%) patients achieved n-KDIGO 2 and 12 (14.8%) patients achieved n-KDIGO 3. There were no significant differences in clinical

Table 1 Clinical characteristics of patients with and without CS-AKI according to n-KDIGO criteria

Characteristics[a]	CS-AKI ($n = 57$)	No CS-AKI ($n = 24$)	p value
Age (days) at cardiac surgery	15 (0–26)	18 (7–26)	0.121
Male sex	35 (61.4%)	14 (58.3%)	0.798
Weight (kg) at cardiac surgery	3.0 (2.6–3.3)	2.6 (2.4–2.9)	0.308
Cyanotic CHD	47 (82.5%)	18 (75.0%)	0.444
RACHS-1 score			0.174
Category 1	0	0	
Category 2	7	5	
Category 3	10	10	
Category 4	24	8	
Category 5	14	1	
Category 6	2	0	
Lowest preoperative SCr			
SCr (mg/dL)	0.45 (0.42–0.68)	0.51 (0.42–0.62)	0.301
Surgical procedure			**< 0.001**
Palliation	13	16	
Total correction	44	8	
Operative time			
CPB time (min)	134 (69–194)	0 (0–113)	**< 0.001**
Cross-clamp time (min)	64 (0–98)	0 (0–35)	**0.005**
Postoperative			
Vasoactive-inotropic score	16 (11–20)	8 (4–14)	**< 0.001**
Urine output (mL/kg/h)	2.0 (1.2–3.1)	3.4 (2.1–4.7)	**0.002**
%FO	3.6 (2.0–5.5)	1.9 (0.9–2.9)	**0.006**

Statistically significant values are in bold

CHD congenital heart disease, *CPB* cardiopulmonary bypass, *CS-AKI* acute kidney injury after cardiac surgery, *FO* fluid overload, *n-KDIGO* neonatal-modified Kidney Disease: Improving Global Outcomes, *RACHS-1* risk adjustment in congenital heart surgery, *SCr* serum creatinine

[a]Data are expressed as median values and interquartile range (25th, 75th percentile), or as numbers (proportion, %)

characteristics except for weight at surgery, preoperative SCr levels and %FO ($p=0.038$, $p=0.008$, and $p=0.004$, respectively) across the 3 different n-KDIGO groups (Table 2).

Short-term outcomes in neonates who underwent cardiac surgery classified by n-KDIGO criteria

The duration of ICU stays, requirement of renal replacement therapy and in-hospital mortality within 30 days after cardiac surgery are shown in Table 3. Eight patients (9.9%) required renal replacement therapy and 7 patients (8.6%) died within 30 days after cardiac surgery. The causes of death in patients with CS-AKI were postoperative low cardiac output syndrome in 2, pulmonary venous occlusion in 1 and severe pulmonary hemorrhage in 1; these contributed to development of severe CS-AKI and resulted in further multiple organ failure. In another 3 CS-AKI patients, the cause of death was severe acute tubular necrosis. A significantly different incidence of ICU stays, renal replacement therapy and in-hospital mortality were observed

Table 2 Comparison of clinical characteristics of CS-AKI patients according to the n-KDIGO grade

Characteristics[a]	n-KDIGO 1 ($n=28$)	n-KDIGO 2 ($n=17$)	n-KDIGO 3 ($n=12$)	p value
Age (days) at surgery	0 (0–20)	18 (15–26)	2 (0–20)	0.055
Male	18 (64.3%)	12 (70.6%)	5 (41.7%)	0.269
Weight (kg) at surgery	3.0 (2.7–3.4)	3.2 (2.9–3.3)	2.7 (2.5–2.9)	**0.038**
Cyanotic CHD	24 (85.7%)	13 (76.5%)	10 (83.3%)	0.733
RACHS-1 score				0.741
Category 1	0	0	0	
Category 2	3	4	0	
Category 3	5	3	2	
Category 4	13	7	4	
Category 5	7	3	4	
Category 6	0	0	2	
Lowest preoperative SCr				
SCr (mg/dL)	0.55 (0.41–0.74)	0.38 (0.30–0.45)	0.51 (0.33–0.80)	**0.008**
Surgical procedure				0.366
Palliation	7	3	3	
Total correction	21	14	9	
Operative data				
CPB time (min)	119 (21–180)	148 (69–221)	158 (23–223)	0.622
Cross-clamp time (min)	63 (0–110)	66 (0–104)	62 (4–84)	0.934
Postoperative				
Vasoactive-inotropic score	15 (11–19)	18 (9–23)	18 (12–24)	0.369
Urine output (mL/kg/h)	2.2 (1.7–3.3)	1.5 (1.1–2.9)	1.2 (0.6–3.5)	0.214
%FO	2.6 (0.8–4.0)	4.3 (2.2–6.5)	5.6 (3.7–8.4)	**0.004**

Statistically significant values are in bold

CHD congenital heart disease, *CPB* cardiopulmonary bypass, *CS-AKI* acute kidney injury after cardiac surgery, *FO* fluid overload, *n-KDIGO* neonatal-modified Kidney Disease: Improving Global Outcomes, *RACHS-1* risk adjustment in congenital heart surgery, *SCr* serum creatinine

[a]Data are expressed as median values and interquartile range (25th, 75th percentile), or as numbers (proportion, %)

Table 3 Postoperative short-term outcomes of patients with CS-AKI classified by n-KDIGO criteria

n-KDIGO[a]	n-KDIGO 0 ($n=24$)	n-KDIGO 1 ($n=28$)	n-KDIGO 2 ($n=17$)	n-KDIGO 3 ($n=12$)	p value
ICU stays (days)	5 (4–7)	5 (4–7)	8 (5–11)	11 (5–22)	0.032
Renal replacement therapy	0	0	1 (1.2%)	7 (8.6%)	< 0.001
In-hospital mortality	0	0	1 (1.2%)	6 (7.4%)	< 0.001

CS-AKI acute kidney injury after cardiac surgery, *ICU* intensive care units, *n-KDIGO* neonatal-modified Kidney Disease: Improving Global Outcomes

[a]Data are expressed as median values and interquartile range (25th, 75th percentile), or as numbers (proportion, %)

across different n-KDIGO groups ($p = 0.032$, $p < 0.001$, and $p < 0.001$, respectively). Multivariate logistic regression analysis revealed that n-KDIGO 3 (OR 16.0; 95% CI 1.6–162.1; $p = 0.019$) was an independent risk factor for in-hospital mortality within 30 days after cardiac surgery. Neonatal CS-AKI patients categorized in the n-KDIGO 3 group were more strongly associated with in-hospital mortality than those in other n-KDIGO groups (hazard ratio 5.3, 95% CI 1.5–18.4, $p = 0.008$) (Fig. 1).

Discussion

The current n-KDIGO criteria provide the rationale for their use as standardized criteria of neonatal AKI [8, 9] and have been evaluated in preterm infants or low-birth weight infants [4, 14]. However, the application of n-KDIGO criteria for CS-AKI in patients with CHD has not yet been validated. In this study, we first evaluated the incidence, risk factors, and postoperative short-term outcomes of neonatal CS-AKI after cardiac surgery according to n-KDIGO criteria and then determined whether n-KDIGO AKI criteria could describe clinically relevant neonatal CS-AKI in this cohort.

We found that the incidence of neonatal CS-AKI according to n-KDIGO criteria was 70.4% and was much higher than the incidence of CS-AKI in older children [1, 2]. High incidence of neonatal CS-AKI according to n-KDIGO criteria, especially in the severe group, is clinically important, because it independently associated with in-hospital mortality in our cohort. A number of features of neonatal renal physiology such as renal blood flow, glomerular filtration rate, and tubular immaturity are pertinent to high incidence

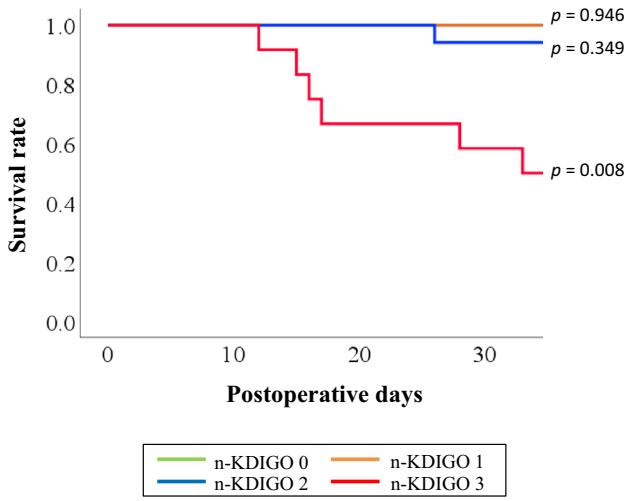

Fig. 1 Survival curves for the entire cohort showing in-hospital mortality within 30 days after cardiac surgery classified by stages of n-KDIGO AKI. *n-KDIGO* neonatal-modified Kidney Disease: Improving Global Outcomes

of neonatal CS-AKI [9]. Moreover, cardiac surgery has a strong effect on perioperative renal ischemia and reperfusion injury, which contribute to the high incidence of neonatal CS-AKI [15, 16]. The need for complex cardiac surgery in the neonatal period, including interventions such as the Norwood procedure or arterial switch procedure, which required longer CPB times, may also contribute to the development of CS-AKI. However, in our cohort, CS-AKI categorized as n-KDIGO grade 1 was not associated with any short-term postoperative outcomes. Our results were similar to previous reports of pediatric CS-AKI [17–19]. A possible explanation to consider is that the potential for renal recovery after acute insults such as CPB may be more robust in pediatric patients, indicating that mild CS-AKI would be irrelevant to postoperative outcomes [19]. Another possible explanation would be that the rapid decline of SCr values during the first weeks of life might not be accurately reflected in the reference values [20], which may lead to misclassification of neonates without biologically significant kidney injury as having CS-AKI. The above raise the need for further consideration of mild CS-AKI to validate these n-KDIGO criteria, and also how to deal with a small rise in SCr values, but technically represents ≥ 1.5-fold increase to qualify n-KDIGO criteria as the standard recommended CS-AKI definition.

Neonatal CS-AKI was associated with increased duration of CPB times and %FO. An increased duration of CPB creates a hemodynamic state of loss of pulsatile flow and micro-embolism, while a low cardiac output state after cardiac surgery contributes to generalized hypoperfusion and renal ischemia [21]. Ischemia–reperfusion injury after CPB can occur and may also contribute to CS-AKI [22]. Moreover, neonates undergoing cardiac surgery are at increased risk of fluid overload due to large amounts of fluid per body surface area, hemodilution from CPB, low cardiac output, low oncotic pressure and capillary leak, and impaired renal function [12]. A recent study indicated that postoperative %FO, especially > 5%, was associated with lower output syndrome, prolonged mechanical ventilation, and the development of CS-AKI in pediatric patients [23]. Considering a number of features of neonatal renal physiology [9], our findings suggest that even small differences in %FO after cardiac surgery can lead to the development of CS-AKI, and clinicians should thus pay careful attention to fluid management, diuretic management, and the potential initiation of renal replacement therapy. Risk factors for neonatal CS-AKI discussed above are associative rather than causal and have been classified as intraoperative or postoperative factors, and not patient-related, there is a possibility that adjusting these risk factors might reduce the incidence of neonatal CS-AKI.

As for postoperative outcomes, our study showed that neonatal CS-AKI classified by the n-KDIGO criteria was more strongly associated with longer ICU stays, requirement for renal replacement therapy, and in-hospital mortality.

Further, neonatal CS-AKI categorized by n-KDIGO 3 criteria had a significant increased risk of in-hospital mortality within 30 days after cardiac surgery. Severe n-KDIGO grades of CS-AKI can cause systemic ventricular dysfunction as a result of inter-organ "cross talk" that may mediate cytokines and chemokine release, a phenomenon known as the cardiorenal syndrome [15, 24]. These states also cause sympathetic activation, renin–angiotensin–aldosterone system activation, vasoconstriction, and acid–base and coagulation imbalance, which lead to a vicious cycle of further injury, and result in worse outcomes requiring renal replacement therapy, and increased risk of death [24–27]. Thus, the ability of the n-KDIGO criteria, especially indicating severe grade, to predictably demonstrate an association between neonatal CS-AKI and clinically meaningful outcomes validates the strength of the n-KDIGO CS-AKI definition.

The present study has several limitations. First, it was a single-center retrospective study with a relatively short-term follow-up period. Though we enrolled consecutive neonates who underwent cardiac surgery for CHD with explicitly defined exclusion criteria considered to be influenced SCr values (i.e. premature infants, neonates with preexisting genetic and chromosomal abnormalities or brain or kidney abnormalities), there were significant differences in weight at surgery and lower preoperative SCr levels between patients categorized into the three different n-KDIGO groups. Second, we did not assess the influence of nutrition or physiological time-dependent changes during the first weeks of life on SCr accurately. When interpreting AKI findings based on SCr values in neonates, we need to be cautious, and should be addressed in future prospective studies. Third, the CHD population has vast phenotypic heterogeneity, which may hinder our ability to generalize the effects of CS-AKI in this population. Finally, as this was a retrospective cohort study, we were unable to determine the exact causes and consequences of CS-AKI that led to poor clinical outcomes.

Conclusions

A high incidence of neonatal CS-AKI was observed (70.4%). Increased duration of CPB times and postoperative %FO were associated with an increased risk of neonatal CS-AKI. Further, our study revealed that the severity of neonatal CS-AKI based on n-KDIGO criteria, especially the severe grade, was independently associated with ICU stay, renal replacement therapy requirement, and increased in-hospital mortality within 30 days after cardiac surgery. Although our study raises the need for further consideration of mild CS-AKI to validate the n-KDIGO criteria, utilizing the n-KDIGO criteria, especially for severe CS-AKI, is strongly indicative of clinically relevant CS-AKI and may also be applicable to neonates.

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Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

Ethical approval All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Kagoshima University Ethics Committee, 190055) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Due to the retrospective nature of this study, parental and patient informed consents were waived.

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