Congenital heart surgery in infants: Effects of acute kidney injury on outcomes

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Objectives: We sought to characterize factors and outcomes associated with postoperative acute kidney injury in infants undergoing cardiac surgery.

Methods: We retrospectively studied 430 infants (<90 days) who underwent heart surgery for congenital defects. With a pediatric modified version of the Acute Kidney Injury Network classification, we performed statistical analyses to detect factors and outcomes associated with postoperative acute kidney injury.

Results: Postoperative acute kidney injury occurred in 225 patients (52%): 135 patients (31%) reached maximum acute kidney injury stage I, 59 (14%) reached stage II, and 31 (7%) reached stage III. On multivariable analysis, single-ventricle status (odds ratio, 1.6; 95% confidence interval, 1.08–2.37; $P = .02$), cardiopulmonary bypass (odds ratio, 1.2; 95% confidence interval 1.01–1.47; $P = .04$), and higher reference serum creatinine (odds ratio, 5.1; 95% confidence interval, 1.94–13.2; $P = .0009$) were associated with postoperative acute kidney injury. Thirty-two (7%) patients died in the hospital. Multivariable logistic regression showed that more severe acute kidney injury was associated with in-hospital mortality (maximum acute kidney injury stage II odds ratio, 5.1; 95% confidence interval, 1.7–15.2; $P = .004$; maximum acute kidney injury stage III odds ratio, 9.46; 95% confidence interval, 2.91–30.7; $P = .0002$) and longer mechanical ventilation and inotropic support. All acute kidney injury stages were associated with longer intensive care durations. Stage III acute kidney injury was associated with systemic ventricular dysfunction at hospital discharge.

Conclusions: Perioperative acute kidney injury is common in infant heart surgery and portends a poor clinical outcome. (J Thorac Cardiovasc Surg 2012;143:368-74)

Acute kidney injury (AKI) is a well-known risk factor for increased morbidity and mortality in hospitalized adults and children.¹⁻⁴ In adults, in whom the incidence of AKI may be as high as 34%, AKI is also associated with intensive care unit (ICU) stay and hospital costs.^{3,5-8} In adults who undergo cardiac surgery, postoperative AKI is associated with long-term mortality, independent of other complications and comorbidities; this risk may be higher for patients who require renal replacement therapy.⁹ Even a modest postoperative increase in the serum creatinine level (≥ 0.3 mg/dL) in patients who undergo cardiac surgery may predict a poor postoperative outcome.^{6,9-11}

Recently, the Acute Dialysis Quality Initiative issued a consensus-based, multidimensional, graded classification system known as *RIFLE* (Risk, Injury, Failure, Loss, and End-Stage Kidney Disease)^{1,2,12,13} to classify AKI. Degrees of AKI severity are classified as risk, injury, or failure, according to the extent of increases in the serum creatinine level, decreases in the glomerular filtration rate, or prolonged oligoanuria.² These criteria have been validated as predictive of mortality in studies encompassing different patient populations, including cardiac surgical patients.^{1-3,13,14} A pediatric modified version of this classification system, pRIFLE, has also been developed and validated.¹

The Acute Kidney Injury Network (AKIN) established a system that classifies AKI into stages I through III on the basis of small (≥ 0.3 mg/dL) increases in serum creatinine levels or oligoanuria in 48 hours.¹² Several researchers have compared the AKIN and RIFLE criteria for efficacy in predicting morbidity and mortality in critically ill patients and have not found any statistically significant differences in outcome.¹³⁻¹⁵

Studies of AKI in pediatric cardiac surgery have been limited to patients who require renal replacement therapy. Zappitelli and coworkers¹¹ found that small increases in the serum creatinine level in the immediate postoperative period predict the development of AKI according to the pRIFLE criteria and that moderate to severe AKI is

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Abbreviations and Acronyms

AKI	= acute kidney injury
AKIN	= Acute Kidney Injury Network
CI	= confidence interval
OR	= odds ratio
CPB	= cardiopulmonary bypass
ICU	= intensive care unit
LCOS	= low cardiac output syndrome
pRIFLE	= pediatric modified RIFLE classification
RACHS-1	= Risk Adjustment for Congenital Heart Surgery
RIFLE	= Risk, Injury, Failure, Loss, and End-Stage Kidney Disease

associated with increased morbidity and mortality. We undertook a retrospective study of hospitalized infants who underwent surgery for congenital heart disease to identify factors and outcomes associated with postoperative AKI by using the AKIN classification system.

MATERIALS AND METHODS

After the study was approved by the Baylor College of Medicine institutional review board, we reviewed hospital medical records, nursing records, the laboratory database, the pediatric cardiology medical records system (CardioIMS; Emageon, Inc, Birmingham, Ala), and the cardiac surgical database. All infants (<90 days old) who underwent surgery for congenital heart disease from January 1, 2003, through December 31, 2008, before initial hospital discharge were eligible for the analysis. Infants who underwent cardiac surgery before 90 days of age but after the initial hospital discharge were excluded from the analysis. Additionally, infants were excluded if they were born before 34 weeks' gestational age or if their only operation was either patent ductus arteriosus ligation or pacemaker implantation. Also, infants were excluded if the daily nursing record was incomplete or unavailable or if clinical data were unavailable from the hospital medical record.

Pediatric AKI was defined according to our modified version of the AKIN criteria (Table 1). We made 2 modifications to these criteria. First, we changed the urinary output criteria to use 8-hour increments instead of 6-hour increments, to be consistent with the definition of oligoanuria validated by the pRIFLE criteria, which provide the only validated metric of AKI in children. Second, because peritoneal dialysis is used routinely at our institution for perioperative fluid and electrolyte management, we did not use renal replacement therapy as a criterion for AKI. Instead, we defined the maximum AKI stage on the basis of either urinary output or serum creatinine criteria. Preoperative AKI was defined as attainment of at least stage I AKI by the AKIN criteria at any time before the index cardiac operation. Postoperative AKI was identified by a rise of at least 0.3 mg/dL in serum creatinine level in any 48-hour interval during the first 5 days after index surgical intervention (eg, if a patient had a serum creatinine rise of 0.3 mg/dL on postoperative day 5, the creatinine measurement taken on postoperative day 3 was considered the reference measurement) or by oligoanuria of less than 0.5 mL/(kg · h) in an 8-hour period after the operation. In patients with an indwelling urinary catheter, urinary output was measured with that indwelling urinary catheter on an hourly basis. Laboratory values, including serum lactate, serum creatinine, and blood urea nitrogen levels, were

obtained at least once daily according to the institutional clinical protocol. Indications for peritoneal dialysis included evidence of postoperative low cardiac output syndrome (LCOS), perioperative oligoanuria of less than 1 mL/(kg · h) in a period of 4 to 6 hours, and nonresponsiveness to bolus doses of furosemide. Peritoneal dialysis was usually initiated in the first 4 to 6 hours after the patient returned from the operating room, before we could detect AKI according to the AKIN criteria.

We abstracted the following demographic and clinical data: gestational age, age at time of surgery, sex, preoperative weight, and postoperative hospital stay. We defined low weight at surgical intervention as less than 3 kg and young age as less than 10 days after birth at the time of surgery. Clinical data included cardiac diagnosis, single-ventricle status, preoperative serum creatinine level, preoperative exposure to aminoglycosides, Risk Adjustment for Congenital Heart Surgery (RACHS-1) category, urinary output on an hourly basis, laboratory values, systemic ventricular function on echocardiography, intraoperative data, preoperative and postoperative mechanical ventilation, and inotropic support. Preoperative AKI was defined as occurring in the period between the index hospital admission and index surgical intervention. Cardiopulmonary bypass (CPB) time was analyzed as an ordinal variable on the basis of the distribution of CPB times in our patient cohort (0, no CPB; 1, CPB time <180 minutes; 2, CPB time 181–240 minutes; 3, CPB time >240 minutes). The primary end points were postoperative AKI and in-hospital mortality. The secondary end points were hospital stay, prolonged ICU stay, duration of mechanical ventilation, duration of postoperative inotropic support, systemic ventricular systolic function on echocardiography, and serum creatinine level at hospital discharge. We considered ICU stay, mechanical ventilation, and inotropic support to be prolonged if their duration was in the top quartile for our patient cohort. For prolonged ICU stay, we defined the cutoff as at least 14 days, and for prolonged duration of mechanical ventilation and duration of inotropic therapy, we defined the cutoff as at least 7 days.

Ventricular systolic function was rated qualitatively as normal, mildly depressed, moderately depressed, or severely depressed. Thirty randomly selected echocardiograms obtained at hospital discharge were reviewed by 2 independent, blinded echocardiologists to determine interobserver variability.

For statistical analysis, Statistical Analysis Software (version 9.1; SAS Institute, Inc, Cary, NC) was used. Continuous variables are presented as mean ± SD or median with interquartile range as appropriate. The Student *t* test was used to analyze continuous variables. The Mann-Whitney U test was used for nonparametric data. The χ^2 and Fisher Exact tests were used to evaluate bivariable associations with postoperative AKI and adverse outcomes associated with postoperative AKI.

Multivariable logistic regression modeling was performed to determine the odds of postoperative AKI and to assess the effect of AKI on primary and secondary outcomes. All potential covariates determined by means of univariate analysis ($P < .15$; Table 2) were included in the multivariable logistic regression models. One of these models was used to test for associations between postoperative AKI and the following factors: age, weight, sex, single-ventricle status, exposure to preoperative aminoglycosides, preoperative AKI, CPB, RACHS-1 surgical score, maximum preoperative lactate level, maximum preoperative serum creatinine level, preoperative systemic ventricular dysfunction (as documented by echocardiography), lowest intraoperative temperature in patients requiring CPB, and preoperative mechanical ventilation or inotropic therapy. To detect associations between postoperative AKI and mortality and secondary end points, we included the following covariates: age, weight, sex, single-ventricle status, exposure to preoperative aminoglycosides, maximum preoperative lactate level, preoperative AKI, CPB, lowest intraoperative temperature, RACHS-1 category, preoperative AKI, systemic ventricular dysfunction (as documented by echocardiography), postoperative cardiopulmonary resuscitation, and need for mechanical circulatory support. Model retention was determined by means of forward stepwise regression. Data are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

TABLE 1. Pediatric modified Acute Kidney Injury Network criteria

AKI stage	Urinary output criteria	Serum creatinine criteria
I	<0.5 mL/(kg · h) in 8 h	Increase in serum creatinine level by ≥ 0.3 mg/dL or increase to 150%-200% of reference value in 48 h
II	<0.5 mL/(kg · h) in 16 h	Increase of serum creatinine level to 200%-300% of reference value in 48 h
III	<0.3 mL/(kg · h) in 24 h or anuria for 16 h	Increase of serum creatinine level to $>300\%$ of reference value or serum creatinine level of ≥ 4.0 mg/dL with acute rise of ≥ 0.5 mg/dL in 48 h

Criteria are based on the original Acute Kidney Injury Network criteria.¹² *Acute kidney injury* was defined as an abrupt decrease in renal function (in 48 hours), as indicated by the changes in urinary output and serum creatinine level described in the table. *AKI*, Acute kidney injury.

RESULTS

Eight hundred eighty-four infants underwent congenital heart surgery between January 1, 2003, and December 31, 2008. There were 56 in-hospital deaths, for an in-hospital mortality of 6%.

Study Cohort

Of the 884 patients, 229 were excluded from the analysis because their gestational age was less than 34 weeks or

because they were discharged from the hospital before the index surgical intervention. Another 225 patients were excluded because they had missing data or incomplete medical records. The remaining 430 infants, 241 (56%) of whom were male, met enrollment criteria and were included in the analysis.

At the initial operation, the infants had a median age of 7 days (interquartile range, 5–13 days) and a median weight of 3.1 kg (interquartile range, 2.8–3.5 kg). Two hundred two patients (47%) had functional single ventricle. Two hundred forty-nine patients (58%) required preoperative mechanical ventilation, and 146 (34%) required preoperative inotropic medications. Ninety-eight patients (23%) were exposed to aminoglycosides preoperatively. The mean reference serum creatinine level for the entire cohort was 0.7 ± 0.5 mg/dL. Preoperative AKI was found in 136 patients (32%): 107 patients (25%) reached maximum AKI stage I, 26 patients (6%) reached stage II, and 3 patients (1%) reached stage III. The remaining 294 patients (68%) had no AKI. Eleven patients (3%) required postoperative circulatory support. Fifty-six patients (13%) had evidence of systemic ventricular systolic dysfunction on the preoperative echocardiogram. Three hundred twenty patients (74%) underwent CPB during corrective or palliative surgery. Table 2 shows the distribution of

TABLE 2. Characteristics of infants with and without postoperative acute kidney injury: Univariate analysis

Characteristics	All patients (n = 430)	Postop AKI (n = 225)	No postop AKI (n = 205)	P value
Age at surgery (d, median and IQR)	7 (5–13)	7 (4–11)	8 (5–15)	.016
Female (%)	44%	44%	44%	.98
Weight at surgery (kg, median and IQR)	3.1 (2.8–3.5)	3.1 (2.8–3.4)	3.1 (2.8–3.4)	.79
Preoperative serum creatinine (mg/dL, mean $\pm$ SD)	0.7 ± 0.5	0.7 ± 0.6	0.6 ± 0.2	.03
Single ventricle (%)	47%	53%	41%	.007
Preoperative AKI (AKIN criteria, %)	32%	37%	27%	.014
Preoperative mechanical ventilation (%)	58%	63%	61%	.81
Preoperative inotropic therapy (%)	34%	40%	28%	.009
Maximum preoperative serum lactate level (mmol/L, mean $\pm$ SD)	3.5 ± 3.0	3.7 ± 2.9	3.4 ± 3.0	.24
Preoperative aminoglycoside exposure (%)	22%	23%	21%	.68
Ventricular dysfunction on echocardiography (%)	13%	12%	14%	.75
Cardiopulmonary bypass (%)	74%	83%	65%	<.0001
Bypass time (no.)*				.02
No cardiopulmonary bypass	110 (26%)	38 (17%)	72 (35%)	
<180 min	128 (30%)	77 (34%)	51 (25%)	
181–240 min	109 (25%)	56 (25%)	53 (26%)	
>240 min	64 (15%)	39 (17%)	25 (12%)	
Lowest intraoperative temperature ($^{\circ}$ C, mean $\pm$ SD)	20.8 ± 4.5	20.7 ± 4.4	21 ± 4.6	.6
RACHS-1 category (no.)				<.0001
1–2	32 (7%)	6 (3%)	26 (13%)	
3	141 (33%)	60 (27%)	86 (42%)	
4	164 (38%)	104 (46%)	60 (27%)	
5–6	88 (21%)	55 (24%)	33 (16%)	
Peritoneal dialysis use (%)	53%	68%	37%	<.0001

Postop, Postoperative; AKI, acute kidney injury; IQR, interquartile range; AKIN, Acute Kidney Injury Network; RACHS, Risk Adjustment for Congenital Heart Surgery. *Fifteen patients with acute kidney injury and 4 patients without acute kidney injury did not have bypass times recorded.

RACHS-1 categories in patients with and without postoperative AKI. Two hundred twenty-eight patients (53%) received postoperative peritoneal dialysis for fluid and electrolyte management.

Incidence of and Factors Associated With Postoperative AKI

Postoperative AKI occurred in 225 patients (52%). One hundred thirty-five (31%) of these patients reached maximum AKI stage I, 59 (14%) reached stage II, and 31 (7%) reached stage III. Urinary output criteria were used to assign the maximum AKI stage in 32 (23%) of the 135 patients with stage I AKI, 30 (51%) of the 59 patients with stage II AKI, and 29 (94%) of the 31 patients with stage III AKI.

Table 2 shows the characteristics and outcomes of patients with and without postoperative AKI, as assessed by univariate analysis. Forty-two infants were younger than 2 days old at the index surgical intervention. Those with AKI were younger (median, 7 days; interquartile range, 4–11 days; vs median, 8 days; interquartile range, 5–15 days; $P = .016$) and were more likely to have functional single ventricle (53% vs 41%; $P = .007$), were more likely to require preoperative inotropic support (40% vs 28%; $P = .009$), had higher serum creatinine levels immediately before surgery (0.7 ± 0.6 vs 0.6 ± 0.2 mg/dL; $P = .03$), were more likely to have preoperative AKI (37% vs 26%; $P = .014$), and more frequently required CPB (incidence, 83% with CPB vs 65% without CPB; $P < .0001$). When analyzed as an ordinal variable, duration of CPB was predictive of postoperative AKI (Table 2). Higher RACHS-1 categories were associated with higher incidence of postoperative AKI (Table 2). Sex, preoperative weight, preoperative serum lactate levels, preoperative systemic ventricular function, exposure to preoperative aminoglycosides, and mechanical ventilation were not associated with postoperative AKI.

All 430 patients were included in the multivariable model (C statistic, 0.8). The analysis showed that an elevated reference serum creatinine level (OR, 5.1; 95% CI, 1.9–13.2; $P = .0009$), single-ventricle status (OR, 1.6; 95% CI, 1.1–2.4; $P = .02$), and need for CPB (OR, 1.2; 95% CI, 1.01–1.5; $P = .04$) were associated with postoperative AKI. In the multivariable model, neither preoperative AKI nor a higher RACHS-1 category was predictive of postoperative AKI. We analyzed data from 89 patients (21%) with moderate to severe postoperative AKI (AKIN stages II and III) to identify unique factors associated with this degree of AKI. We found that single-ventricle status (OR, 1.8; 95% CI, 1.1–3.0; $P = .01$) and preoperative AKI (OR, 1.7; 95% CI, 1.02–2.74; $P = .04$) were associated with greater odds of moderate to severe postoperative AKI by the AKIN criteria.

Mortality

Thirty-two patients (7%) died during the postoperative period. There was a significant difference in mortality between patients with postoperative AKI and those without postoperative AKI (26 patients, 12%, vs 6 patients, 3%; $P = .0007$). We performed multivariable logistic regression (including all 430 patients, C statistic, 0.8) and found that factors associated with postoperative in-hospital mortality included functional single ventricle (OR, 2.6; 95% CI, 1.1–6.2; $P = .03$), circulatory support (OR, 7.0; 95% CI, 1.8–28; $P = .006$), and moderate to severe postoperative AKI (stage II OR, 5.1; 95% CI, 1.7–15.2; $P = .004$; stage III OR, 9.5; 95% CI, 2.9–30.7; $P = .0002$). The results (Table 3) showed that mortality risk increases with AKI stage.

Postoperative Outcomes Associated With AKI

Higher stages of postoperative AKI were associated with greater odds of prolonged ICU stay (398 patients; C statistic, 0.8), with a stage I OR of 2.2 (95% CI, 1.2–3.9; $P = .01$), a stage II OR of 3.0 (95% CI, 1.4–6.2; $P = .003$), and a stage III OR of 3.8 (95% CI, 1.6–9.2; $P = .003$). Functional single ventricle (OR, 2.8; 95% CI, 1.7–4.6; $P = .009$), low preoperative weight (OR, 2.0; 95% CI, 1.2–3.3; $P = .005$), and postoperative peritoneal dialysis (OR, 1.8; 95% CI, 1.1–3.1; $P = .03$) were all associated with greater odds of a prolonged ICU stay (Table 4). Stage II and III maximum AKI stage strata were associated with prolonged mechanical ventilation (Table 5) and the need for postoperative inotropic therapy (Table 6). We did not find any relationship between postoperative AKI and the duration of hospitalization. Postoperative AKI stage III was independently associated with systemic ventricular systolic dysfunction on echocardiography at hospital discharge (OR, 5.1; 95% CI, 2.1–12.3; $P = .0003$).

Perioperative Use of Peritoneal Dialysis

Two hundred ninety-eight patients (68%) had peritoneal dialysis catheters placed in the operating room or during the immediate postoperative period, and 228 patients (53%) received peritoneal dialysis perioperatively for fluid and

TABLE 3. Factors independently associated with mortality in infants with acute kidney injury

Factor	Odds ratio	95% Confidence interval	P value
No AKI	Reference	—	—
AKI stage I	1.3	0.4–4.1	.70
AKI stage II	5.1	1.7–15.2	.004
AKI stage III	9.5	2.9–30.7	.0002
Single ventricle	2.6	1.1–6.2	.03
Circulatory support	7.0	1.8–28	.006

Model fit C statistic, 0.8. Patients without acute kidney injury were the reference group for these comparisons. AKI, Acute kidney injury.

TABLE 4. Outcomes in infants with postoperative acute kidney injury: Univariable analysis

Factor	All patients (n = 430)	Postop AKI (n = 225)	No postop AKI (n = 205)	P value
Duration of postop mechanical ventilation (d)	4 (3–6)	5 (3–7)	3 (2–5)	.013
Duration of postop inotropic therapy (d)	5 (3–6)	6 (4–8)	4 (3–6)	<.0001
Intensive care unit stay (d)	7 (1–14)	8 (4–20)	6 (1–10)	.0001
Hospital stay (d)	23 (16–38)	24 (17–45)	21 (15–35)	.002
In-hospital mortality (%)	7.4%	11.6%	2.9%	<.0001

Results are reported as median with interquartile range unless otherwise noted. *Postop*, Postoperative; *AKI*, acute kidney injury.

electrolyte management. Eighty (59%) of 135 patients with postoperative stage I AKI, 46 (78%) of 59 patients with postoperative stage II AKI, and 27 (87%) of 31 patients with postoperative stage III AKI received peritoneal dialysis. Sixty-eight percent of the patients who had development of postoperative AKI received peritoneal dialysis during the perioperative course, whereas only 37% of patients without AKI received peritoneal dialysis ($P < .0001$). We compared the characteristics of patients who received perioperative peritoneal dialysis with those of patients who did not receive peritoneal dialysis. Patients who underwent peritoneal dialysis were more likely to have had preoperative inotropic support (35% vs 26%; $P = .017$), to have required CPB (83% vs 53%; $P < .0001$), and to have had preoperative AKI (38% vs 24%; $P = .002$). Age at surgery, weight, and sex were not associated with the need for postoperative peritoneal dialysis.

DISCUSSION

We modified the AKIN classification criteria and have been the first to use this modification to assess the incidence, severity, and risks of AKI with regard to perioperative outcomes in infants who have undergone cardiac surgery. Our findings are in agreement with those of several previous studies, which have shown that small changes in kidney function can predict outcomes in critically ill patients, including children who undergo cardiac surgery.^{10,11,16} Although our patients with stage I AKI did not have greater mortality than did patients without AKI,

such patients may be susceptible to additional comorbidities associated with a prolonged ICU stay. Our frequent use of peritoneal dialysis and the fact that our patients were neonates may have caused us to underestimate the true incidence of stage I AKI in our cohort and therefore to underestimate the effects of stage I AKI on our primary and secondary outcomes.

Nonetheless, in our study the postoperative incidence of AKI (54%), particularly moderate to severe AKI, was higher than that previously reported by others.^{11,14} This difference may be due to our use of a smaller absolute change in serum creatinine level as a diagnostic criterion for AKI or to the sensitivity of our urinary output criteria: 51% of cases of stage II AKI and 94% of cases of stage III AKI were detected by application of the urinary output criteria. Previously, researchers have used renal replacement therapy as a criterion for postoperative AKI; we chose not to do so because widespread institutional practice variations may limit the utility of this criterion for comparative analyses.^{15,17}

Like previous investigators, we found that the need for CPB during surgical intervention was independently associated with postoperative AKI.^{7,11,17,18} When we treated CPB as an ordinal variable, we found that longer CPB time was associated with greater odds of postoperative AKI. These results are consistent with those of previous studies of AKI, which found an association between longer CPB times and the development of AKI. The injury associated with CPB is multifactorial and incompletely understood but may be due, in part, to CPB-induced hypothermia.¹⁹ We did not find an association between hypothermia and postoperative AKI. In addition, we identified a hitherto

TABLE 5. Factors independently associated with prolonged postoperative mechanical ventilation in infants with acute kidney injury

Factor	Odds ratio	95% Confidence interval	P value
No AKI	Reference		—
AKI stage I	1.8	0.9–3.8	.11
AKI stage II	2.7	1.1–6.2	.02
AKI stage III	3.6	1.4–9.5	.01
Circulatory support	4.3	1.2–15.8	.03
Preoperative exposure to aminoglycosides	2.1	1.1–3.9	.02

Model fit C statistic, 0.8. *AKI*, Acute kidney injury.

TABLE 6. Factors independently associated with prolonged postoperative inotropic therapy in infants with acute kidney injury

Factor	Odds ratio	95% Confidence interval	P value
No AKI	Reference		—
AKI stage I	1.6	0.8–3.0	.18
AKI stage II	2.8	1.3–5.9	.007
AKI stage III	4.3	1.7–10.9	.002
Single ventricle	2.3	1.3–3.9	.009
Circulatory support	9.1	1.8–47.0	.003

Model fit C statistic, 0.8. *AKI*, Acute kidney injury.

undescribed association between functional single-ventricle heart disease and postoperative AKI. Regional blood-flow alterations have recently been implicated in cerebral white-matter injury after palliation of single ventricle.²⁰ Similar regional blood-flow perturbations may play a role in postoperative AKI, as well.

The RACHS-1 category was associated with postoperative AKI in the univariate analysis but not in the multivariable model (data not shown). The reasons behind this finding are unclear but may relate to the fact that patients with functional single ventricle typically require operations that are of greater surgical complexity in terms of RACHS-1 category, such that patients with functional single ventricles would account for much of the variance noted in the multivariable model. Another possible explanation is that the sample size may have been inadequate to detect differences by multivariable analysis.

In our series, we found that higher postoperative AKI stages were associated with a significant stepwise increase in mortality risk. Zappitelli and coworkers¹¹ associated moderate to severe AKI (pRIFLE injury and failure) with increased hospital mortality in children of all ages who underwent cardiac surgery (mean age at operation, 2.8 ± 4.7 years). Our study focused specifically on infants who underwent such surgery. The underlying reasons for the increase in AKI-related mortality risk are not well understood but may include worsening fluid overload and pulmonary mechanics; these necessitate prolonged mechanical ventilation and potentially increased exposure to invasive infection.²¹ In addition, recent basic science evidence suggests that kidney injury or failure can lead to cardiac dysfunction as a result of interorgan “crosstalk”²² that is independent of the adverse renal consequences of serum electrolyte and fluid dysregulation. The potential mediators of this crosstalk include cytokines and chemokines, which were unmeasured in our cohort. Simultaneous cardiac and renal dysfunction is referred to as *cardiorenal syndrome*.²³

Our data may support the existence of a pediatric cardiorenal syndrome. Single-ventricle status was associated with postoperative AKI, and severe postoperative AKI was associated with systemic ventricular systolic dysfunction. In addition, a postoperative LCOS may contribute to the development of postoperative AKI. Indeed, LCOS may play a primary role in the development of postoperative AKI through decreased renal blood flow or elevated central venous pressure. We did not specifically assess for evidence of LCOS in our patients, although oligoanuria or an abrupt rise in serum creatinine may be reflective of LCOS. We cannot exclude an LCOS as a possible cause of perioperative AKI; postoperative LCOS, which may result in impaired renal blood flow, elevated central venous pressure, and other hemodynamic perturbations, may cause renal injury. Thus this deleterious hemodynamic effect of LCOS supports the concept of a cardiorenal syndrome. Although these

results do not constitute direct evidence of a pediatric cardiorenal syndrome, they are highly suggestive of deleterious interorgan effects between the kidney and the heart in this population. Further assessment of this phenomenon, as well as detailed echocardiographic assessment of systolic and diastolic function, is needed.

Like Zappitelli and coworkers,¹¹ we did not observe an association between the total hospital stay and postoperative AKI. Factors that affect the total hospital stay may be independent of those that prolong the ICU stay. Among infants, in particular, additional factors such as feeding difficulties may increase the hospital stay independent of the ICU stay. We did find a novel association between AKI and the need for prolonged postoperative inotropic therapy and mechanical ventilation.

Whereas the pediatric RIFLE criteria have been validated among critically ill children, including those who undergo cardiac surgery, the AKIN criteria have not previously been applied to cardiac surgery in infants. Because previous studies have shown the significance of a small rise in serum creatinine levels in critically ill children,^{1,10,11,23} we hypothesized that the AKIN criteria, with their 48-hour window and smaller absolute increase in serum creatinine levels, would be a more appropriate measure of postoperative AKI. In addition, we hypothesized that using the urinary output criteria would improve our ability to detect postoperative AKI. We found that urinary output criteria detected moderate to severe AKI more readily than did serum creatinine criteria. In part, this may explain our finding of a higher incidence than previously reported of moderate to severe AKI in children who undergo cardiac surgery. Our results confirm the utility of using small increases in the serum creatinine level and prolonged oligoanuria to detect AKI in critically ill infants.^{10,11,23}

Currently, there are no well-established criteria for neonatal AKI. A low glomerular filtration rate during the first week after birth may not be accompanied by an obvious change in serum creatinine level. Because we based our definition of AKI on the AKIN criteria, it is possible that some neonates had AKI that went undetected because they did not have the expected drop in serum creatinine during the first week after birth or because they underwent surgery before 5 to 7 days after birth. As a result, we may have *underestimated* the incidence of preoperative AKI in this neonatal population. We recognize this as a potential limitation of the study. In addition to predicting outcome, the consensus-based definitions should encourage the clinician to detect AKI earlier and to use treatments aimed at ameliorating AKI earlier. Indeed, although not studied in this population, early detection of moderate to severe AKI by either system may be useful as a standard indication for renal replacement therapy or other empirical therapies aimed at reducing AKI.

Our study's limitations include those inherent in retrospective, single-center studies, in that we relied on the

accuracy and availability of reported data to identify cases of AKI. Furthermore, our sample size precludes a detailed analysis of potentially underdocumented confounding data. Clinical practice variations, including our institution's early and frequent use of peritoneal dialysis, and the lack of clinical practice standardization may have influenced secondary end points and limited their generalizability. Serum creatinine levels may be artificially lower in patients undergoing peritoneal dialysis than in patients who do not undergo peritoneal dialysis. Additionally, although we identified patient characteristics associated with postoperative AKI as well as with adverse outcomes in patients with postoperative AKI, these associations do not prove causality.

The medium- and long-term outcomes of postoperative AKI in infants and children with heart disease remain to be determined. Further research should characterize the relationship between postoperative AKI and fluid overload in infants who undergo surgery for congenital heart disease. Systems for classifying AKI can and should be used at the bedside to risk stratify these infants. Novel urinary biomarkers of AKI may help to improve bedside risk stratification when used in association with current AKI classification systems.^{16,24} Additional research should focus on the relationships among AKI, organ crosstalk, and systemic ventricular systolic and diastolic function.

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References

- Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int*. 2007;71:1028-35.
- Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute Dialysis Quality Initiative workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8:R204-12.
- Hoste EA, Kellum JA. RIFLE criteria provide robust assessment of kidney dysfunction and correlate with hospital mortality. *Crit Care Med*. 2006;34:2016-7.
- Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit Care*. 2006;10:R73.
- Ozçakar ZB, Yalçinkaya F, Altas B, Ergün H, Kendirli T, Ateş C, et al. Application of the new classification criteria of the Acute Kidney Injury Network: a pilot study in a pediatric population. *Pediatr Nephrol*. 2009;24:1379-84.
- Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol*. 2005;16:3365-70.
- Dasta JF, Kane-Gill SL, Durtschi AJ, Pathak DS, Kellum JA. Costs and outcomes of acute kidney injury (AKI) following cardiac surgery. *Nephrol Dial Transplant*. 2008;23:1970-4.
- Hobson CE, Yavas S, Segal MS, Schold JD, Tribble CG, Layon AJ, et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation*. 2009;119:2444-53.
- Leacche M, Rawn JD, Mihaljevic T, Lin J, Karavas AN, Paul S, et al. Outcomes in patients with normal serum creatinine and with artificial renal support for acute renal failure developing after coronary artery bypass grafting. *Am J Cardiol*. 2004;93:353-6.
- Lassnigg A, Schmid ER, Hiesmayr M, Falk C, Druml W, Bauer P, et al. Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: do we have to revise current definitions of acute renal failure? *Crit Care Med*. 2008;36:1129-37.
- Zappitelli M, Bernier PL, Saczkowski RS, Tchervenkov CI, Gottesman R, Dancea A, et al. A small post-operative rise in serum creatinine predicts acute kidney injury in children undergoing cardiac surgery. *Kidney Int*. 2009;76:885-92.
- Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:R31.
- Haase M, Bellomo R, Matalanis G, Calzavacca P, Dragun D, Haase-Fielitz A. A comparison of the RIFLE and Acute Kidney Injury Network classifications for cardiac surgery-associated acute kidney injury: a prospective cohort study. *J Thorac Cardiovasc Surg*. 2009;138:1370-6.
- Lopes JA, Fernandes P, Jorge S, Gonçalves S, Alvarez A, Costa e Silva Z, et al. Acute kidney injury in intensive care unit patients: a comparison between the RIFLE and the Acute Kidney Injury Network classifications. *Crit Care*. 2008;12:R110.
- Giuffrè RM, Tam KH, Williams WW, Freedom RM. Acute renal failure complicating pediatric cardiac surgery: a comparison of survivors and nonsurvivors following acute peritoneal dialysis. *Pediatr Cardiol*. 1992;13:208-13.
- Bennett M, Dent CL, Ma Q, Dastrala S, Grenier F, Workman R, et al. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. *Clin J Am Soc Nephrol*. 2008;3:665-73.
- Kist-van Holthe tot Echten JE, Goedvolk CA, Doornaar MB, van der Vorst MM, Bosman-Vermeeren JM, Brand R, et al. Acute renal insufficiency and renal replacement therapy after pediatric cardiopulmonary bypass surgery. *Pediatr Cardiol*. 2001;22:321-6.
- Dent CL, Ma Q, Dastrala S, Bennett M, Mitsnefes MM, Barasch J, et al. Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study. *Crit Care*. 2007;11:R127.
- Kourliouros A, Valencia O, Phillips SD, Collinson PO, van Besouw JP, Jahangiri M. Low cardiopulmonary bypass perfusion temperatures are associated with acute kidney injury following coronary artery bypass surgery. *Eur J Cardiothorac Surg*. 2010;37:704-9.
- Andropoulos DB, Hunter JV, Nelson DP, Stayer SA, Stark AR, McKenzie ED, et al. Brain immaturity is associated with brain injury before and after neonatal cardiac surgery with high-flow bypass and cerebral oxygenation monitoring. *J Thorac Cardiovasc Surg*. 2010;139:543-56.
- Brown KL, Ridout DA, Goldman AP, Hoskote A, Penny DJ. Risk factors for long intensive care unit stay after cardiopulmonary bypass in children. *Crit Care Med*. 2003;31:28-33.
- Kelly KJ. Distant effects of experimental renal ischemia/reperfusion injury. *J Am Soc Nephrol*. 2003;14:1549-58.
- Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008;52:1527-39.
- Karkouti K, Wijeyesundera DN, Yau TM, Callum JL, Cheng DC, Crowther M, et al. Acute kidney injury after cardiac surgery: focus on modifiable risk factors. *Circulation*. 2009;119:495-502.