Urinary biomarkers and renal near-infrared spectroscopy predict intensive care unit outcomes after cardiac surgery in infants younger than 6 months of age

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Objective: To assess the ability of urinary acute kidney injury biomarkers and renal near-infrared spectroscopy (NIRS) to predict outcomes in infants after surgery for congenital heart disease.

Methods: Urinary levels of neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), and cystatin C were measured preoperatively and postoperatively in 49 infants younger than 6 months of age. Renal NIRS was monitored for the first 24 hours after surgery. A composite poor outcome was defined as death, the need for renal replacement therapy, prolonged time to first extubation, or prolonged intensive care unit length of stay.

Results: Forty-two (86%) patients had acute kidney injury as indicated by at least Acute Kidney Injury Network/Kidney Disease: Improving Global Outcomes (AKIN/KDIGO) stage 1 criteria, and 17 (35%) patients had poor outcomes, including 3 deaths. With the exception of KIM-1, all biomarkers demonstrated significant increases within 24 hours postoperatively among patients with poor outcomes. Low levels of NGAL and IL-18 demonstrated high negative predictive values (91%) within 2 hours postoperatively. Poor outcome infants had greater cumulative time with NIRS saturations less than 50% (60 vs 1.5 minutes; $P = .02$) in the first 24 hours.

Conclusions: Within the first 24 hours after cardiopulmonary bypass, infants at increased risk for poor outcomes demonstrated elevated urinary NGAL, IL-18, and cystatin C and increased time with low NIRS saturations. These findings suggest that urinary biomarkers and renal NIRS may differentiate patients with good versus poor outcomes in the early postoperative period, which could assist clinicians when counseling families and inform the development of future clinical trials. (J Thorac Cardiovasc Surg 2013;146:861-7)

Supplemental material is available online.

Acute kidney injury (AKI) is a common and potentially serious complication after surgery for congenital heart disease. Depending on the study population and criteria used to define AKI, contemporary studies report an incidence ranging from 5.5% to 50%, with associated mortality ranging from 20% to 61%.¹⁻³ Well-established risk factors include young age, low weight, increased duration of cardiopulmonary

bypass (CPB), and postoperative hemodynamic instability.¹⁻³ Although they represent a high-risk population, infants often only comprise a small proportion of the study patients, and, because AKI is ill-defined in neonates, they are often entirely excluded.⁴

To standardize the definition of AKI, expert consensus groups have created the RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) and AKIN (Acute Kidney Injury Network) scoring systems, which are based on changes in serum creatinine (S_{Cr}) and urine output.^{5,6} Modification and application of the RIFLE criteria to pediatrics (pRIFLE) has been shown to predict morbidity and mortality in critically ill children.⁷ In addition, a modified version of the AKIN criteria has also been shown to portend a poor clinical outcome in infants after surgery for congenital heart disease.⁸ Although these systems represent important advancements in the standardization of AKI diagnosis, they have limited clinical utility in the perioperative period owing to delayed and unpredictable changes in S_{Cr} and urine output after CPB. Creatinine-based measures of AKI are particularly limited in neonates owing to the influence of maternal S_{Cr} , low glomerular filtration rates, and effect of serum bilirubin on the assay itself.⁴

Efforts to improve the sensitivity, accuracy, and timeliness of AKI diagnosis have resulted in the clinical testing

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This work was supported by funds from the Division of Pediatric Cardiology and by a Child Health Research Center Career Development Award (National Institutes of Health, K12 HD 028820) to N.B.B.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication June 3, 2012; revisions received Oct 6, 2012; accepted for publication Dec 5, 2012; available ahead of print Jan 14, 2013.

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0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2012.12.012>

Abbreviations and Acronyms

AKI	= acute kidney injury
AKIN	= Acute Kidney Injury Network
CPB	= cardiopulmonary bypass
ECMO	= extracorporeal membrane oxygenation
ICU	= intensive care unit
IL-18	= interleukin 18
KDIGO	= Kidney Disease: Improving Global Outcomes
KIM-1	= kidney injury molecule-1
NGAL	= neutrophil gelatinase-associated lipocalin
NIRS	= near-infrared spectroscopy
pRIFLE	= RIFLE criteria modified to pediatrics
RACHS-1	= Risk Adjustment for Congenital Heart Surgery 1
RIFLE	= Risk, Injury, Failure, Loss, End-stage kidney disease
RRT	= renal replacement therapy
rSO ₂	= regional oxyhemoglobin saturation
S _{Cr}	= serum creatinine

of renal injury biomarkers. The molecules neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), kidney injury molecule-1 (KIM-1), and cystatin C are increased in the blood and/or urine of critically ill adults and children with AKI in a variety of clinical settings.⁹ After surgery for congenital heart disease, these biomarkers are elevated within 12 hours of CPB in patients in whom AKI develops by S_{Cr}.¹⁰⁻¹³

Near-infrared spectroscopy (NIRS) uses an infrared light source to measure regional oxyhemoglobin saturation (rSO₂) continuously and noninvasively 1.5 to 2 cm into the tissue bed of interest.¹⁴ It has the advantage of being noninvasive, real time, and specific to the organ of interest. Saturation values obtained from cerebral and flank NIRS probes are correlated with invasive mixed venous oxygen saturations after surgery for congenital heart disease.¹⁵ In addition, low rSO₂ values have been correlated with injury to the brain, gut, and kidney after CPB in children.¹⁶⁻¹⁸

To date, urinary biomarkers and renal NIRS have not been simultaneously evaluated after surgery for congenital heart disease and correlated with outcome. We hypothesized that infants with perioperative kidney injury identified by elevated urinary biomarkers or low renal NIRS values would have comparatively poorer clinical outcomes.

METHODS

This prospective study was approved by the Institutional Review Board at the University of Michigan. Infants under 6 months of age undergoing

cardiac surgery with CPB between July 2009 and July 2010 were eligible for enrollment. Fifty families were approached, and 1 family declined participation in the study. Premature infants less than 35 weeks' gestation were excluded. After parental or guardian informed consent was obtained, patient demographic and surgical information was collected. Surgical complexity was ranked according to the Risk Adjustment for Congenital Heart Surgery 1 (RACHS-1) scoring system.¹⁹ Postoperative hemodynamic status was estimated by calculation of a daily maximum vasoactive-inotropic score (VIS) for the first 3 days after surgery as per the equation below²⁰:

$$\begin{aligned} \text{VIS} = & \text{dopamine dose } (\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \\ & + \text{dobutamine dose } (\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \\ & + 100 \cdot \text{epinephrine dose } (\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \\ & + 10 \cdot \text{milrinone dose } (\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \\ & + 10,000 \cdot \text{vasopressin dose } (\text{units} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \\ & + 100 \cdot \text{norepinephrine dose } (\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \end{aligned}$$

All patients received routine standard of care during the study period, which included the use of dextrose-containing crystalloid solutions (75-100 mL · kg⁻¹ · d⁻¹) during the first 24 to 48 hours postoperatively, followed by the initiation of total parenteral nutrition. Patients were started on bolus furosemide (1 mg/kg per dose every 6 hours) within the first 24 hours postoperatively. One of the study patients had a peritoneal drain placed for mild abdominal compartment syndrome. Primary providers were aware that the patients were enrolled in a study looking at AKI and outcomes.

Biomarkers

Preoperative urine samples were collected from a bag specimen or indwelling catheter placed in the operating room before initiation of CPB. Postoperative urine samples were obtained from the Foley catheter on admission to the intensive care unit (ICU) and at 2, 6, 12, and 24 hours. The samples were centrifuged (2000 rpm, 5 minutes), divided into aliquots, and stored (−80°C) until analysis. Urinary concentrations of NGAL, IL-18, KIM-1, and cystatin C were measured using commercially available enzyme-linked immunosorbent assay kits from R&D Systems (Minneapolis, Minn).

Near-Infrared Spectroscopy

After arrival in the ICU, a Somanetics (Troy, Mich) INVOS Pediatric NIRS sensor was placed over the right flank and continuous rSO₂ was recorded in 30-second intervals for the first 24 hours after surgery. The primary caregivers were blinded to the data during the collection period and no clinical interventions were made on the basis of the NIRS values. Faulty NIRS probes were discovered in 2 patients after completion of the observation period. Because of the impact of extracorporeal membrane oxygenation (ECMO) on oxygen saturation, in 6 patients NIRS data were censored from analysis.

Acute Kidney Injury

S_{Cr} was measured preoperatively and postoperatively, then once daily as part of routine daily laboratory studies. AKI was defined using criteria proposed by the Acute Kidney Injury Network and Kidney Disease Improving Global Outcomes group, and recently validated in a study of infants with congenital heart disease.^{6,8,21} Infants had AKI if they met AKIN stage 1 criteria, defined as an increase in S_{Cr} by either 0.3 mg/dL or more or a 50% rise from preoperative baseline within the first 3 days postoperatively.

Outcome Measures

Owing to the relatively small size of our patient population and our low mortality and renal replacement therapy (RRT) rates, a composite poor

outcome was used. A poor outcome was defined as any of the following: (1) death within 30 days of surgery; (2) need for RRT; (3) prolonged time to first extubation (upper quartile ≥ 6.5 days); or (4) prolonged ICU length of stay (upper quartile ≥ 9.9 days). Normative values for ventilator time and ICU length of stay were obtained from a contemporary internal database of infants less than 6 months of age ($n = 395$) who have undergone cardiac surgery.

Statistical Analysis

Demographic and clinical characteristics were compared using Student's *t* test for continuous variables and Fisher's exact test for categorical variables. The Wilcoxon rank sum test was used to evaluate the association between each continuous biomarker or continuous NIRS saturation value and the risk of a poor outcome at each postoperative hour. To determine an optimal cutoff value for each biomarker for the diagnosis of a poor outcome over time, we generated a receiver operating characteristic curve using a nonparametric approach under repeated measures design.²² Unconditional (exact) odds ratios with their 95% confidence intervals were estimated at each time point using (exact) logistic regression to evaluate a risk of poor outcome for each biomarker above the optimal cutoff obtained from the receiver operating characteristic curve. Owing to the small sample size that limited the ability to perform multivariable analyses, unadjusted odd ratios are presented. All analyses were performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

A total of 49 infants were enrolled during the study period. With the exception of 1 infant who underwent a stage 2 hemi-Fontan operation, all patients underwent surgery for the first time to repair or palliate one of the following primary cardiac diagnoses: ventricular septal defect ($n = 12$), tetralogy of Fallot ($n = 9$), hypoplastic left heart syndrome ($n = 9$), atrioventricular septal defect ($n = 6$), D-transposition of the great arteries ($n = 5$), heterotaxy syndrome ($n = 3$), severe coarctation or interrupted aortic arch with ventricular septal defect ($n = 3$), truncus arteriosus ($n = 1$), or total anomalous pulmonary venous return ($n = 1$). The 3 heterotaxy patients underwent a Ross procedure, Blalock-Taussig shunt, and a hemi-Fontan operation. On the basis of our composite definition, 17 (35%) patients had a poor outcome. Three infants died, 2 required RRT, 12 had a prolonged time to first extubation, and 16 had a prolonged ICU length of stay. Both patients requiring RRT were neonates who were placed on ECMO support after surgery owing to myocardial stun. In both cases, RRT was initiated on postoperative day 2 owing to severe fluid overload. Both of these patients died.

Patients with a poor outcome were more likely to be younger and undergo more complex surgery with a longer CPB time and use of hypothermic circulatory arrest (Table 1). Postoperatively, patients with a poor outcome had higher maximal vasoactive-inotropic score, were more likely to require ECMO support, and had a higher peak postoperative S_{Cr} . The majority of patients (86%) met AKIN/KDIGO (Kidney Disease: Improving Global Outcomes) stage I criteria (S_{Cr} rise of 50% or ≥ 0.3

TABLE 1. Demographics and clinical characteristics

	Poor outcome		<i>P</i> value
	Yes (<i>n</i> = 17)	No (<i>n</i> = 32)	
Sex, N (%)			
Female	5 (29)	9 (28)	1.00
Male	12 (71)	23 (72)	
Age at surgery, d, median (IQR)	7 (5-10)	98 (33-150)	.001
Preoperative weight, kg	3.7 $\pm$ 0.7	4.9 $\pm$ 1.4	.0002
RACHS-1 classification, N (%)			
2 to 4	8 (47)	29 (91)	.001
5 or 6	9 (53)	3 (9)	
CPB time, min	149 $\pm$ 61	84 $\pm$ 35	.001
Aortic crossclamp time, min	52 $\pm$ 40	45 $\pm$ 25	.55
Hypothermic circulatory arrest, N (%)	10 (59)	5 (16)	.003
Postoperative ECMO, N (%)	6 (35)	0 (0)	.001
Maximum vasoactive inotrope score	23 $\pm$ 9	12 $\pm$ 7	<.0001
Peak serum creatinine, mg/dL	0.9 $\pm$ 0.3	0.6 $\pm$ 0.3	.005
Estimated creatinine clearance	30 $\pm$ 10	49 $\pm$ 17	<.0001
Acute kidney injury, N (%)			
No	1 (6)	6 (19)	.40
Yes	16 (94)	26 (81)	
AKIN/KDIGO stage 1	11 (65)	17 (53)	.81
AKIN/KDIGO stage 2	3 (18)	8 (25)	
AKIN/KDIGO stage 3	2 (12)	1 (3)	

Data are presented as mean $\pm$ standard deviation unless otherwise indicated. *IQR*, Interquartile range (25th-75th percentile); *RACHS*, risk adjustment for surgery for congenital heart disease; *CPB*, cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation; *AKIN*, Acute Kidney Injury Network; *KDIGO*, Kidney Disease: Improving Global Outcomes.

mg/dL); however, this AKI classification system did not distinguish between those infants with good and poor outcomes.

Before patients underwent CPB, urinary concentrations of NGAL, IL-18, cystatin C, and KIM-1 were low in all patients (Figure 1). With the exception of KIM-1, all biomarkers demonstrated significant increases within 12 hours after bypass in patients with poor outcomes and only minimal increases among patients with a good outcome. The differences in urinary biomarker concentration was significant at all postoperative time points for NGAL and IL-18, but only within the first 2 hours postoperatively for cystatin C. KIM-1 poorly differentiated patients with either good or poor outcomes and was, therefore, removed from further analysis.

Cutoffs to identify patients with poor outcomes were determined using receiver operating characteristic curves for NGAL, IL-18, and cystatin C (Table 2). All 3 biomarkers performed well, with NGAL having the highest area under the curve of 0.79. The time points most predictive of a poor outcome occurred for NGAL at postoperative hour 12, IL-18 at postoperative hour 6, and cystatin C at postoperative hour 0 (Table 3). Of note, all 3 biomarkers showed better negative than positive predictive values. Specifically, only 3 (9%) of 32 infants with a good outcome had an elevated

FIGURE 1. Biomarker profiles in infants undergoing cardiopulmonary bypass. Urinary concentrations of neutrophil gelatinase-associated lipocalin (NGAL) (A), interleukin 18 (IL-18) (B), cystatin C (Cys C) (C), and kidney injury molecule-1 (KIM-1) (D) were determined by enzyme-linked immunosorbent assay as described in the Methods section. Data are presented as median values in the good outcome (gray dotted line) versus poor outcome (solid black line) groups. Error bars indicate interquartile range (25th-75th percentile). * $P < .05$.

NGAL at postoperative hours 6 and 12, 1 (3%) had an elevated IL-18 at postoperative hour 6, and 4 (13%) had elevated cystatin C at postoperative hour 2.

Having multiple elevated biomarkers on arrival to the ICU (postoperative hour 0) was highly predictive of a poor outcome (Table 3). Patients with both elevated NGAL and IL-18 had a nearly 20-fold increased risk for a poor outcome and patients with elevated NGAL, IL-18, and cystatin C had a 24-fold increased risk. As with the single biomarkers, the negative predictive value of having multiple biomarkers below threshold was high.

Analysis of the NIRS data indicated that infants with a poor outcome spent more cumulative time with rSO_2 below 50% than did those with good outcomes (Table 4,

Figure E1). There were significant differences in cumulative time below 50% starting at postoperative hour 2, and after 24 hours of monitoring, poor outcome infants spent nearly an hour more time below 50% than did those infants who had a good outcome (1-2 minutes). Comparing patients with single-ventricle versus biventricular physiology, we found no difference in the time spent with NIRS rSO_2 below 50% through the first 12 hours postoperatively, although a difference did appear by the end of the NIRS monitoring period (Table E1). Examining the ability of NIRS to correlate with markers of kidney injury, we examined the distribution of low NIRS rSO_2 and the presence of AKI, as defined by meeting AKIN stage 1 (Table E2), or urinary biomarkers (Table E3). We found that there was no association

TABLE 2. Biomarker optimal cutoff values for prediction of a poor outcome

Biomarker	Optimal cutoff value (ng/mL)	AUC	Sensitivity	Specificity	Positive predictive value	Negative predictive value
NGAL	76	0.79	0.64	0.87	0.72	0.83
IL-18	0.8	0.76	0.59	0.86	0.68	0.80
Cystatin C	179	0.69	0.51	0.79	0.55	0.76

AUC, Area under the receiver operating characteristic curve; NGAL, neutrophil gelatinase-associated lipocalin; IL-18, interleukin 18.

TABLE 3. Risk of poor outcome for biomarker by threshold

Biomarker	Postop hour	Poor outcome*		P value	Odds ratio	95% CI
		Yes (n = 17)	No (n = 32)			
NGAL ≥ 76 ng/mL	0	11 (65)	7 (22)	.001	9.4	2.2, 39.0
	2	10 (59)	4 (13)	.002	9.4	2.0, 54.7
	6	9 (53)	3 (9)	.001	10.2	2.0, 72.9
	12	11 (65)	3 (9)	<.0001	18.7	3.4, 144
IL-18 ≥ 0.8 ng/mL	0	9 (53)	4 (13)	.004	9.1	1.8, 56.2
	2	11 (65)	5 (16)	.0004	11.0	2.6, 45.9
	6	5 (29)	1 (3)	.01	15.4	1.5, 813
	12	4 (24)	3 (9)	.24	2.7	0.4, 21.3
Cystatin C ≥ 179 ng/mL	0	9 (53)	8 (25)	.01	5.2	1.3, 20.1
	2	7 (41)	4 (13)	.03	4.9	1.2, 20.4
	6	8 (47)	6 (19)	.05	3.7	0.9, 17.3
	12	9 (53)	10 (31)	.11	2.7	0.8, 9.3
NGAL ≥ 76 and IL-18 ≥ 0.8	0	9 (53)	2 (6)	.0002	19.7	3.1, 233
	2	8 (47)	3 (9)	.005	8.1	1.6, 58
	6	3 (18)	1 (3)	.11	6.4	0.5, 360
	12	3 (18)	1 (3)	.12	6.2	0.5, 348
NGAL ≥ 76, IL-18 ≥ 0.8, and Cystatin C ≥ 179	0	7 (41)	1 (3)	.001	24.0	2.5, 1221
	2	6 (35)	2 (6)	.02	7.8	1.2, 90
	6	2 (12)	1 (3)	.27	4.0	0.2, 252
	12	3 (18)	1 (3)	.12	6.2	0.5, 348

CI, Confidence interval; NGAL, neutrophil gelatinase-associated lipocalin; IL-18, interleukin 18. *Data are presented as N (%).

between NIRS rSO₂ less than 50% and the presence of AKI; however, in some cases, a NIRS rSO₂ less than 50% did correlate with elevated urinary biomarkers. Owing to the small sample size, we were unable to evaluate outcomes using a combination of cumulative time below 50% and biomarker levels at the individual time points.

DISCUSSION

Biomarkers

Many recent studies have focused on the ability of renal injury biomarkers to predict AKI before a rise in S_{Cr}^{10,11,13} in a mixed-age pediatric population. We examined biomarker performance in relation to clinical outcomes in a very young population and found, similar to the findings in older patients, that within the first 12 hours of arrival to the ICU after cardiac surgery, neonates and infants with elevated urinary NGAL, IL-18, and cystatin C were more likely to have poor clinical outcomes. Importantly, to our

knowledge, the negative predictive value of these biomarkers has not been previously tested and emphasized in infants. The majority of infants with good outcomes did not have biomarker levels above the cohort-based calculated thresholds. In this study, an infant with a NGAL of less than 76 ng/mL and an IL-18 of less than 0.8 ng/mL in the first 2 hours after surgery had at least a 90% chance of a good clinical outcome. Despite our broad definition of poor outcome, the ability to predict a high likelihood of having a good outcome within only 2 hours of surgery is not only useful clinically but has implications for enrollment in interventional trials, such that patients at low risk for a poor outcome can be excluded, improving the risk/benefit ratio for an experimental intervention. This concept has also been proposed by Wong and associates,²³ who reported that the negative predictive value of serum IL-8 could be used for risk stratification before enrolment in pediatric septic shock trials.

We found little diagnostic utility for KIM-1 in this study. While Han and associates¹³ found that in a cohort of children undergoing CPB, urinary KIM-1 detected AKI before S_{Cr}, they did not correlate these findings with the same clinical outcomes included in this study, other than the need for RRT. Krawczeski and associates²⁴ found that KIM-1 at 12 hours after CPB independently correlated with ventilator time after adjusting for patient age, CPB time, and RACHS-1 score. Whereas the median age of AKI patients in that study was 6 months, the mean age of the present study patients was 2 months, with a significant proportion of neonates. Further study will be needed to determine the

TABLE 4. Median cumulative time (in minutes) with NIRS saturation below 50%

NIRS saturation	Postop hours	Poor outcome		P value
		Yes (n = 10)	No (n = 31)	
<50%	2	1.0 (0.0-57.5)	0.0 (0.0-0.0)	.02
	6	3.5 (0.0-285.0)	0.0 (0.0-1.5)	.03
	12	17.2 (0.0-507.5)	0.0 (0.0-8.0)	.08
	24	59.5 (4.0-507.5)	1.5 (0.0-20.5)	.02

Data are presented as median (interquartile range, 25th percentile-75th percentile) of cumulative time spent with near-infrared spectroscopy (NIRS) saturation below 50% from the beginning of monitoring until the indicated postoperative hour.

clinical utility of KIM-1 in neonates and infants less than 6 months of age.

We also evaluated the performance of NGAL, IL-18, and cystatin C in combination and found the highest risk for a poor outcome occurred in infants with elevations in all 3 biomarkers immediately after surgery. While Parikh and coworkers¹² found that urinary NGAL and IL-18 were both strong predictors of severe AKI, defined as a 2-fold increase in S_{Cr} or need for dialysis, the combination of these 2 biomarkers minimally improved predictive power. In contrast, Krawczeski and associates²⁴ found that adding combinations of the urinary biomarkers NGAL, IL-18, KIM-1, and liver fatty acid-binding protein to a clinical model of AKI risk factors improved the predictive ability of the model in the first 24 hours after CPB. Although the concept of a biomarker “panel” is appealing, more studies are needed to determine the optimal timing and combination that maximizes predictive power. Owing to differences in organ maturity, it is possible that such a panel may be age dependent (ie, the optimal panel and marker thresholds for a child may be different from that which is most useful in a neonate or infant).

Using AKIN/KDIGO stage 1 criteria, the incidence of AKI in this study was 86%, which is higher than other contemporary infant cardiac surgical data.^{1,8,24} In addition, the presence of AKI did not distinguish between those infants with good or poor outcomes. This result is in contrast with the findings of Blinder and coworkers,⁸ who found that the presence of AKI correlated with mortality, duration of mechanical ventilation, and prolonged ICU length of stay. These differences may be due to the relatively small sample size on our cohort, the use of a composite outcome variable in this study, or the high proportion of neonates who underwent complex RACHS-1 category 5 and 6 operations.

Near-Infrared Spectroscopy

Our study found that increased time spent with NIRS rSO_2 less than 50% was associated with a poor outcome. Assuming that the NIRS probe is measuring the mixed oxygen saturation of blood in the renal parenchyma, low rSO_2 would be an indicator of poor renal oxygen delivery. Although the exact threshold below which renal injury occurs is not known, these results corroborate those of Owens and colleagues,¹⁶ who showed that rSO_2 less than 50% for more than 2 hours correlated with higher serum creatinine values and increased incidence of AKI in infants during the first 48 hours after CPB.

Our study included both single-ventricle and biventricular patients; however, there was no difference between these 2 groups in cumulative time with rSO_2 less than 50% during the first 12 postoperative hours (see Table E1). This finding is similar to the results published by Uebing and coworkers,²⁵ who found depressed cerebral oxygen

saturations immediately after CPB in neonates who underwent the Norwood and arterial switch operations and may be attributable to a post-CPB effect on renal blood flow rather than the presence or absence of a parallel circulation.

Our study was not large enough to analyze the predictive power of the combination of renal NIRS and urinary biomarkers to predict outcomes. We did, however, observe that independent of outcome, higher urinary biomarker levels correlated with lower duration of time with renal NIRS rSO_2 less than 50% (see Table E3). Although a substantial degree of renal injury occurs during CPB, it is possible that the real-time information obtained from NIRS may compliment the data obtained from urinary biomarkers, such that biomarkers would identify patients at risk for AKI on arrival to the ICU. In doing so, NIRS would provide a method for monitoring the effectiveness of postoperative interventions by trending the rSO_2 . Further study is needed to evaluate this hypothesis.

CONCLUSIONS

Infants under 6 months of age with elevated urinary NGAL, IL-18, and cystatin C immediately after CPB are at increased risk for poor ICU outcomes. Increased duration of renal NIRS rSO_2 less than 50% in the first 24 hours after CPB also predicts a poor clinical outcome. Importantly, infants with low urinary biomarkers within the first 2 hours after bypass are likely to have a good ICU outcome, which can help clinicians counsel families. These findings also underscore the potential utility of urinary AKI biomarkers in identifying infants at risk for poor outcomes, which can aid in the development of prospective trials. Further studies are needed to determine whether a panel of renal injury biomarkers and renal NIRS can be used together and in the postoperative management of infants after surgery for congenital heart disease.

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FIGURE E1. Cumulative time with low renal near infrared spectroscopy regional oxyhemoglobin saturation (rSO_2). Median cumulative time spent with rSO_2 less than 50% in the good outcome (gray squares) versus poor outcome (black circles) groups.

TABLE E1. Comparison of cumulative time (in minutes) with NIRS saturation below 50% between single- and biventricular circulations

NIRS		Single (n = 7)	Two (n = 34)	P value
saturation	Postop hours			
<50%	2	0 (0, 60)	0 (0, 60)	.20
	6	0 (0, 286.5)	0 (0, 294)	.50
	12	9 (0, 646.5)	0 (0, 654)	.12
	24	89.5 (9.5, 1327)	1.5 (0, 1356)	.01

Data are presented as median (range, minimum-maximum). P value from Wilcoxon rank sum test. NIRS, Near-infrared spectroscopy.

TABLE E2. Relationship of cumulative time (in minutes) with NIRS saturation below 50% with AKI by AKIN categorization

NIRS saturation	Postop hours	AKI		P value
		Yes (n = 34)	No (n = 7)	
<50%	2	0 (0, 2)	0 (0, 0)	.39
	6	0 (0, 5.5)	0 (0, 0)	.17
	12	1.5 (0, 102)	0 (0, 4)	.14
	24	2.5 (0, 127)	9.5 (0, 25)	.96

Data are presented as median (interquartile range; 25th percentile, 75th percentile). P value from Wilcoxon rank sum test. NIRS, Near-infrared spectroscopy; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network.

TABLE E3. Relationship of cumulative time (in minutes) with NIRS saturation below 50% with each biomarker

NIRS saturation	Postop hours	NGAL		P value
		≥76	<76	
<50%	2	0.75 (0, 3.75)	0 (0, 0)	.02
	6	2.25 (0, 168)	0 (0, 1.5)	.045
	12	4.75 (0, 507.5)	0.25 (0, 9)	.30
	24	137.75 (14, 416.75)	2 (0, 29.5)	.07

NIRS saturation	Postop hours	IL-18		P value
		≥0.8	<0.8	
<50%	2	0 (0, 2)	0 (0, 0)	.35
	6	226.5 (84, 285.75)	0 (0, 1.5)	.02
	12	304.75 (4, 527)	0 (0, 8)	.03
	24	583	3 (0, 59.5)	.13

NIRS saturation	Postop hours	Cystatin C		P value
		≥179	<179	
<50%	2	4.5 (0, 2)	0 (0, 0)	.045
	6	0 (0, 3)	0 (0, 4.5)	.96
	12	5.25 (0, 304.75)	0 (0, 7)	.08
	24	109.5 (1.5, 399.5)	3 (0, 29.5)	.42

Data are presented as median (interquartile range; 25th percentile, 75th percentile). P value from Wilcoxon rank sum test. NIRS, Near-infrared spectroscopy; NGAL, neutrophil gelatinase-associated lipocalin; IL-18, interleukin 18.