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Fluid Overload is Associated with Late Poor Outcomes in Neonates Following Cardiac Surgery

Nicole S Wilder, MD, FAAP[1], **Sunkyung Yu, MS**[2], **Janet E Donohue, MPH**[2], **Caren S Goldberg, MD, FACC**[2], and **Neal B Blatt, MD, PhD, FAAP, FASN**[3]

[1]Department of Anesthesiology, University of Michigan Health Systems, C.S. Mott Children's Hospital, Ann Arbor, MI

[2]Department of Pediatric Cardiology, University of Michigan Health Systems, C.S. Mott Children's Hospital, Ann Arbor, MI

[3]Department of Pediatric Nephrology, University of Michigan Health Systems, C.S. Mott Children's Hospital, Ann Arbor, MI

Abstract

Objective—Acute kidney injury (AKI) is a severe complication of cardiac surgery associated with increased morbidity and mortality, yet AKI classification for neonates remains challenging. We characterized patterns of post-operative fluid overload (FO) as a surrogate marker for AKI and as a risk factor of poor post-operative outcomes in neonates undergoing cardiac surgery.

Design—Retrospective cohort study.

Setting—Single, congenital heart center destination program.

Patients—435 neonates undergoing cardiac surgery with cardiopulmonary bypass from January 2006 through December 2010.

Interventions—None

Measurements and Main Results—Demographics, diagnosis, and perioperative clinical variables were collected, including daily weights and serum creatinine (S_{Cr}) levels. A composite poor clinical outcome (death, need for renal replacement therapy (RRT), or extracorporeal life support (ECLS) within 30 post-operative days) was considered the primary outcome measure. Twenty-one neonates (5%) had a composite poor outcome with 7 (2%) requiring RRT, 8 (2%) requiring ECLS, and 14 (3%) dying between 3 and 30 days post-surgery. Neonates with a composite poor outcome had significantly higher maximum FO (>20%) and were slower to diuresе. A receiver-operating characteristic curve determined that FO ≥ 16% and S_{Cr} ≥ 0.9 on post-operative day 3 were the optimal cutoffs for significant discrimination on the primary outcome (area under the curve = 0.71 and 0.76, respectively). In multivariable analysis, FO ≥ 16% (adjusted odds ratio [AOR] = 3.7) and S_{Cr} ≥ 0.9 (AOR = 6.6) on post-operative day 3 remained an independent risk factor for poor outcome. FO ≥ 16% was also significantly associated with cardiac

*Corresponding author: Nicole S. Wilder, M.D., University of Michigan Department of Anesthesiology, 4-911 C.S. Mott Children's Hospital, 1540 E. Hospital Drive, SPC 4245, Ann Arbor, MI 48109-4245, nicowild@umich.edu.

arrest requiring cardiopulmonary resuscitation, prolonged intensive care unit stay, and chest re-exploration.

Conclusions—This study highlights the importance of monitoring fluid balance in the neonatal cardiac surgical population, and suggests that daily FO, a readily-available, non-invasive marker of renal function, may be a sensitive and specific predictor of adverse outcomes.

Keywords

Fluid Overload; Infant; Newborn; Creatinine; Cardiac Surgical Procedures; Acute Kidney Injury

INTRODUCTION

Acute kidney injury (AKI) is a well-recognized and potentially serious complication of pediatric cardiac surgery, affecting 10–45% of operative patients (1–6). Several published studies have identified risk factors for development of cardiac surgery-associated AKI (CS-AKI) including duration of cardiopulmonary bypass (CPB), age, Risk Adjusted Classification of Congenital Heart Surgery (RACHS-1) score, post-operative hypotension and vasopressor requirement (2, 4–6). Standardization of AKI definitions over the past 10 years with the introduction of Risk, Injury, Failure, Loss, and End-Stage Kidney Disease (RIFLE) (7), pediatric modified RIFLE (pRIFLE) (8) and Acute Kidney Injury Network (AKIN) (9) scoring has allowed for valuable comparisons among studies, contributing to our improved understanding of the epidemiology of AKI (10). The AKIN definition was employed in two recent studies of neonates undergoing biventricular cardiac surgery which found the incidence of CS-AKI to be 62%–64% (11, 12).

The use of serum creatinine (S_{Cr}) or urine output (UO) to establish AKI in neonates may be problematic for several reasons. First, it is widely recognized that a rise in S_{Cr} may lag by several days following the initial insult. Also, few neonates were included in the pediatric modified RIFLE study (8, 13). Neonates experience rapid changes in glomerular filtration rate (GFR) dependent on level of prematurity and post-natal age (14). In the first few days of life, S_{Cr} may be reflective of maternal renal function (15) and over half of documented neonatal AKI cases are non-oliguric (16).

There has been increasing recognition in other patient populations, particularly those requiring renal replacement therapy (RRT), that fluid overload (FO) is associated with morbidity and mortality (17–22). Most studies focus on the level of FO at the time of continuous RRT initiation; however two recent small pediatric studies demonstrated an association between early post-operative FO and worse outcomes following cardiac surgery (23, 24). Data from these studies has prompted clinician awareness of FO as a readily-available, non-invasive marker of renal function.

In this study, we sought to characterize the pattern of post-operative FO and evaluate the degree of FO, a surrogate marker for AKI, as a predictor of poor post-operative outcomes in a large cohort of neonates undergoing cardiac surgery with CPB.

MATERIALS AND METHODS

Study Population

A retrospective cohort study of all neonates (≤ 30 days old) who underwent cardiac surgery with CPB from January 2006 through December 2010 at the University of Michigan Congenital Heart Center was performed. Neonates with a history of previous sternotomy or extracorporeal life support (ECLS) had a higher likelihood of pre-operative renal injury and were thus excluded. This study was approved by the University of Michigan Health System Institutional Review Board.

Data Collection

Subjects were identified using an electronic perfusion database containing all patients undergoing CPB at this institution. Each medical record including demographic, clinical and laboratory data was reviewed. Demographic data included gestational age, age at time of surgery, gender, pre-operative weight, and planned surgical intervention. Prematurity was defined as gestational age less than 37 weeks. Surgical complexity was assigned according to the RACHS-1 consensus based scoring system (25). Additional clinical data included cardiac diagnosis, single-ventricle status, pre-operative S_{Cr} level, laboratory values, pre-operative inotropic support, pre-operative and post-operative mechanical ventilation, intra-operative data including duration of CPB, daily weights through post-operative day (POD) 7, need for RRT or ECLS. The most common indication for ECLS is failure to wean from CPB, followed by other indications such as combined respiratory/cardiac failure, low cardiac output syndrome, pulmonary hypertension, shunt occlusion, and respiratory failure.

All patients received routine standard of care in a dedicated cardiac surgery intensive care unit (ICU) during the study period which included the use of dextrose-containing crystalloid solutions (75–100 mL/kg/day) during the first 24–48 hours post-operatively, followed by the initiation of total parenteral nutrition. Bolus furosemide (1 mg/kg/dose q6h) was initiated within the first 24 hours post-operatively. Diruetic dosing was subsequently adjusted by the cardiac intensivist with the goal of achieving a daily net negative fluid balance by post-operative day 3. Indications for RRT included worsening fluid overload, azotemia, uncontrolled metabolic acidosis, and/or electrolyte abnormalities. The decision to initiation RRT was left to the consulting pediatric nephrologist in consultation with the patient's primary cardiac surgeon and cardiac intensivist.

AKI Classification and FO Calculation

AKI classification was calculated based on the peak S_{Cr} any time within the first 72 post-operative hours using the proposed neonatal modification of the AKIN criteria (26). The baseline S_{Cr} level for each neonate was defined as the most recent S_{Cr} level measured prior to surgery. Weight based daily FO was defined as: [(Daily weight) – (Pre-operative weight)] / (Pre-operative weight) × 100 (27).

Patient Outcomes

Due to relatively low rates of RRT and death, a composite poor clinical outcome was used as primary outcome for analysis, including any of the following: death, need for RRT, or need for ECLS within 30 days of surgery. FO and S_{Cr} levels were determined daily for the first 7 PODs. Any patient who experienced a composite poor outcome within the first 48 post-operative hours was excluded from the risk factor analysis due to inability to calculate FO and document S_{Cr} level on POD 3. Secondary outcome measures including ICU length of stay (days), cardiac arrest requiring cardiopulmonary resuscitation (CPR), neurologic injury (stroke or seizure) and re-exploration of chest were also examined.

Statistical Methods

Data are presented as frequency (percentage) for categorical variables and median (interquartile range [IQR]) or mean ± standard deviation, as appropriate, for continuous variables. Demographics, clinical characteristics, and other clinical outcomes between neonates with and without a composite poor outcome were compared using Chi-square tests or Fisher's exact tests for categorical variables, and t-test or Wilcoxon rank sum tests for continuous variables. Using receiver-operating characteristic (ROC) curves, the areas under the curves (AUCs) of each the first seven PODs were compared to determine the most predictive time point for poor outcome. The optimal cutoffs of FO and S_{Cr} on the selected POD for predicting poor outcome were then determined based on sensitivity and specificity from each ROC curve. To evaluate independent relations of FO and S_{Cr} (dichotomized by their optimal cutoffs) with poor outcome, a multivariable logistic regression was used, controlling for other variables significantly associated with a poor outcome in the univariate analysis ($p < 0.05$). Unadjusted odds ratios and adjusted odds ratio with their 95% confidence intervals were reported. All analyses were performed using SAS Version 9.3 (SAS Institute Inc., Cary, NC), with statistical significance set at $p < 0.05$ using a two-sided test.

RESULTS

Study Cohort

During the study period, 523 neonates underwent cardiac surgery with CPB, 20 of which were excluded due to a history of previous sternotomy or ECLS (Figure 1). Since FO and S_{Cr} on POD 3 were determined to be optimal for predicting poor outcome based on the AUCs from the ROC curves, an additional 68 neonates (13%) were excluded from analysis because they died (n=10), required RRT (n=6), or were placed on ECLS (n=53) within 48 post-operative hours. The remaining 435 neonates were included in the analysis.

Of note, the majority of neonates were of term gestation with only 47 (11%) born prior to 37 weeks gestational age (Table 1). At the time of cardiac surgery, the neonates had a median age of 7 days and a mean weight of 3.2 kg. The median baseline S_{Cr} level for the entire cohort was 0.5 mg/dL. Pre-operative mechanical ventilation was required in 207 (48%) neonates and 132 (30%) required pre-operative inotropic support. One hundred, seventy-three neonates (40%) had functional single ventricle physiology, 124 (29%) were RACHS-1 category 5 or 6, and 107 (25%) had hypoplastic left heart syndrome (HLHS). Two hundred forty-one neonates (55%) underwent deep hypothermic circulatory arrest (DHCA) for aortic arch reconstruction. On POD 3, the median FO was 10% (IQR 3.3–18.4), median S_{Cr} level was 0.6 mg/dL (IQR 0.5–0.9), and the median peak S_{Cr} level during the first 72 post-operative hours was 0.8 mg/dL (IQR 0.7–1.0).

Incidence of and Factors Associated with a Poor Outcome

Twenty-one neonates (5%) experienced a poor outcome during POD 3–30. Neonates with a poor outcome were more likely to be ≤ 3 days of age at surgery, have single ventricle physiology (62% vs. 39%; p = 0.03) and more frequently require DHCA (76% vs. 54%; p = 0.049) compared to those without a poor outcome. Percentage of FO measured on POD 3 was significantly higher in neonates who experienced a poor outcome (18.6% vs. 9.7%; p = 0.002). Likewise, neonates with a poor outcome had a higher S_{Cr} level on POD 3 (1.0 mg/dL vs. 0.6 mg/dL; p < 0.0001) and a higher peak S_{Cr} level during the first 72 post-operative hours (1.1 mg/dL vs. 0.8 mg/dL; p < 0.001). Gender, RACHS-1 score, prematurity, pre-operative weight, and pre-operative S_{Cr} level were not associated with having a poor outcome. While degree of FO peaked on POD 2 in both cohorts, neonates with a poor outcome reached a higher level of FO (median 23% vs. 17%, p = 0.05) and took significantly longer to achieve negative fluid balance (data not shown).

Predictive Ability of Fluid Overload and Serum Creatinine

ROC curves for each post-operative time point of FO and S_{Cr} measurement determined the optimal cut-off values of 16% for FO (AUC = 0.71) and 0.9 mg/dL for S_{Cr} (AUC = 0.76) on POD 3, each with a negative predictive value of 98% (Figures 2 and 3). Unadjusted OR of poor outcome using the optimal cut-off value FO ≥ 16% was 4.8 (95% CI, 1.9–12.9). Factors significantly differed between the neonates with and without a poor outcome from univariate analysis (p < 0.05) were included in the multivariable model: age at surgery ≤ 3 days, POD 3 FO ≥ 16%, S_{Cr} ≥ 0.9 mg/dL, single ventricle, and use of DHCA. Due to its strong correlation with single ventricle physiology (Chi-square statistic = 208, p < 0.0001), HLHS was not included in the multivariable analysis. Multivariable logistic regression demonstrates that age at surgery of ≤ 3 days, POD 3 FO ≥ 16% and S_{Cr} level ≥ 0.9 mg/dL still remained independently associated with having a poor outcome, controlling for single ventricle physiology and use of DHCA (Table 2).

Applying the neonatal modified AKIN criteria to our population, 308 (71%) developed CS-AKI, which was not associated with poor outcome (AUC = 0.58, Table 3).

Secondary Clinical Outcomes in Neonates following Cardiac Surgery

Neonates with FO ≥ 16% had longer median length of stay both in the ICU (11 days vs. 7 days, p<.0001) and the hospital (20 days vs. 15 days, p<.0001). They were also more likely to experience a cardiac arrest requiring CPR (15% vs. 4%, p<.0001), develop thrombosis (10% vs. 4%, p=0.01), or require re-exploration of the chest (27% vs. 7%, p<.0001) (Table 4). For the patients who did not experience a composite poor outcome on POD 3–30, those with FO ≥ 16% had a higher proportion of death than those with FO < 16% (17% vs. 8%, p=0.01). Similarly, those with S_{Cr} ≥ 0.9 had a higher proportion of death than those with low S_{Cr} < 0.9 (15% vs. 10%, p=0.13).

DISCUSSION

This study examines the role of post-operative FO in a large cohort of patients undergoing neonatal cardiac surgery with CPB. Previous studies have demonstrated that FO > 10–20% is significantly associated with adverse outcomes in critically ill children (10, 27–28). In our study, all neonates subjected to CPB developed some degree of post-operative FO (median FO = 10%), and FO ≥ 16% was an independent risk factor for worse perioperative outcomes with a higher odds ratio than having a single ventricle or use of DHCA, (OR, 4.77 versus 2.58 or 2.69 respectively.) This parallels the Blinder study findings on the severity of AKI and odds ratio for mortality being higher than single ventricle (1). The degree of FO in our patients was much higher than reported in previous pediatric studies which included few neonatal patients. In a prospective observational study of 49 infants undergoing cardiac surgery, Hazel et al found that early post-operative FO was associated with poor outcomes in infants under 6 months of age, though FO was not a risk factor for poor outcome independent of illness severity based on RACHS-1 score or maximum vasoactive inotropic support (23). Hassinger and colleagues performed a secondary analysis on 98 pediatric cardiac surgery patients aged 2 weeks to 18 years, and found that early post-operative FO (> 5% up to midnight of POD 1) was independently associated with worse post-operative outcomes (24).

The search for a neonatal definition of AKI remains a challenge for the research community. Ricci and Ronco examined the S_{Cr} and UO components of the RIFLE and pRIFLE criteria noting that UO is one of the earliest clinical signs of acute renal injury and S_{Cr} alone may underestimate the severity of AKI due to its delayed increase in the setting of rapidly evolving AKI [29]. Morgan and colleagues examined risk factors for outcomes of CS-AKI in neonates undergoing biventricular cardiac surgery using a modified version of the AKIN S_{Cr} criteria (maximum S_{Cr} level measured at 3 time points – POD 1, POD 2–5, and POD 6+) (11). In their cohort of 264 neonates with a mean age of 17 days, CS-AKI occurred in 64% of the neonates, with 55% in AKIN stage 1, 20% in AKIN stage 2, and 25% in AKIN stage 3. Applying modified AKIN S_{Cr} criteria to our neonatal cohort resulted in a higher CS-AKI incidence of 71%, which is not surprising given the median age of our neonates was 7 days and 40% had single ventricle physiology. Although CS-AKI defined as AKIN stage 1 was not associated with poor outcomes in our study, S_{Cr} level ≥ 0.9 mg/dL was another independent risk factor for the poor outcome.

In this study, FO ≥ 16% was shown to be an independent risk factor of the composite poor outcome and is significantly associated with increased ICU length of stay, cardiac arrest requiring CPR, and re-exploration of the chest. Many factors play a role in post-cardiac surgery FO including hemodilution from CPB, fluid/ blood product administration, low oncotic pressure and capillary leak, low cardiac output, and/or impaired renal function. It is not currently clear whether preventing/treating FO would improve post-operative outcomes.

In the pediatric cardiac surgery population, peritoneal dialysis (PD) catheter implantation for abdominal decompression and dialysis access is sometimes employed. In pediatric patients on ECLS requiring continuous RRT at our institution, degree of fluid overload at RRT initiation was the most consistent predictor of survival suggesting that the prevention of significant FO is likely to be more effective at improving outcomes than attempting fluid removal once significant FO is established (30).

Management of volume status in neonates following cardiac surgery is complex and the role of diuretics is controversial. In a prospective trial, Ricci et al randomized infants with congenital heart disease to receive either furosemide or ethacrynic acid following elective cardiac surgery. They found that ethacrynic acid was slightly more effective at augmenting urine output without any significant differences in post-operative serum creatinine or incidence of AKI (based on pRIFLE) (31). In a study of 30 pediatric patients with congestive heart failure already receiving inotropic and diuretic therapy, administration of synthetic B-type natriuretic peptide resulted in improved diuresis without significant increase in S_{Cr} (32). A single-center randomized double-blind controlled trial of 80 infants undergoing biventricular cardiac surgery compared high-dose fenoldopam treatment with placebo during CPB and found decreased urinary levels of neutrophil gelatinase-associated lipocaline and cystatin C, reduced the use of diuretics and vasodilators during CPB, and a trend towards lower AKI incidence (50% vs. 72%, p = 0.08) (33). Michael and colleagues have suggested that aggressive use of diuretics and early initiation of RRT to prevent worsening of FO may improve survival of pediatric stem-cell transplant recipients (34). In a meta-analysis of 9 RCTs including 849 adult patients, furosemide was not associated with any significant clinical benefits in the prevention and treatment of acute renal failure (35). Using data from the Fluid and Catheter Treatment Trial, a multicenter, RCT evaluating a conservative versus liberal fluid-management strategy in 1,000 patients with acute lung injury, Grams et al found that post-AKI fluid balance was significantly associated with 60-day mortality and higher post-AKI furosemide doses had a protective effect on mortality but no significant effect after adjustment for post-AKI fluid balance (36).

Limitations

There are several limitations to the results of our study. This was a single-center study and a multicenter evaluation is needed to strengthen the evidence found here. Our study was limited by its retrospective cohort design with its inherent risk of confounding and bias. Since FO and S_{Cr} measurements on POD 3 were most predictive of poor outcome based on the ROC curves, we were forced to exclude neonates who experienced a composite poor outcome prior to POD 3. This exclusion of early poor outcomes reduced the power of our study. Although furosemide is routinely employed for the post-operative management of FO in our neonatal cardiac surgery population, the amount of diuretic administered was not incorporated into our analysis. Likewise, exposure to nephrotoxic agents was not examined and could have contributed to the development of AKI in a subset of our neonates. Degree of FO can be calculated by difference in daily weights or net fluid balance (subtracting total fluid out from total fluid in each day). We chose to employ the weight-based method which may be limited by the addition of surgical tubes and catheters during surgery, but incorporates insensible fluid losses and is easier to calculate at the bedside than the fluid balance method (23). Since FO is often the indication for initiation of RRT, the association of FO with a composite poor outcome which includes RRT may be somewhat confounded. UO data was not collected on all of the study subjects, thus AKI as calculated by the AKIN UO criteria could not be determined. Our neonates had a median age of 7 days, thus, it is likely that the pre-operative S_{Cr} levels were falsely elevated in some of the subjects due to the lingering influence of maternal creatinine. This could have led to an underestimation of the true incidence of AKI as calculated by the AKIN S_{Cr} criteria.

CONCLUSIONS

Post-operative FO is an independent risk factor for poor outcomes in neonates following cardiac surgery with CPB. Daily FO, a readily-available, non-invasive marker of renal function, may be a sensitive and specific predictor of adverse outcomes including need for ECLS, RRT, or death. Additional prospective study is warranted to determine if daily FO can be used to guide the perioperative management of this vulnerable patient population.

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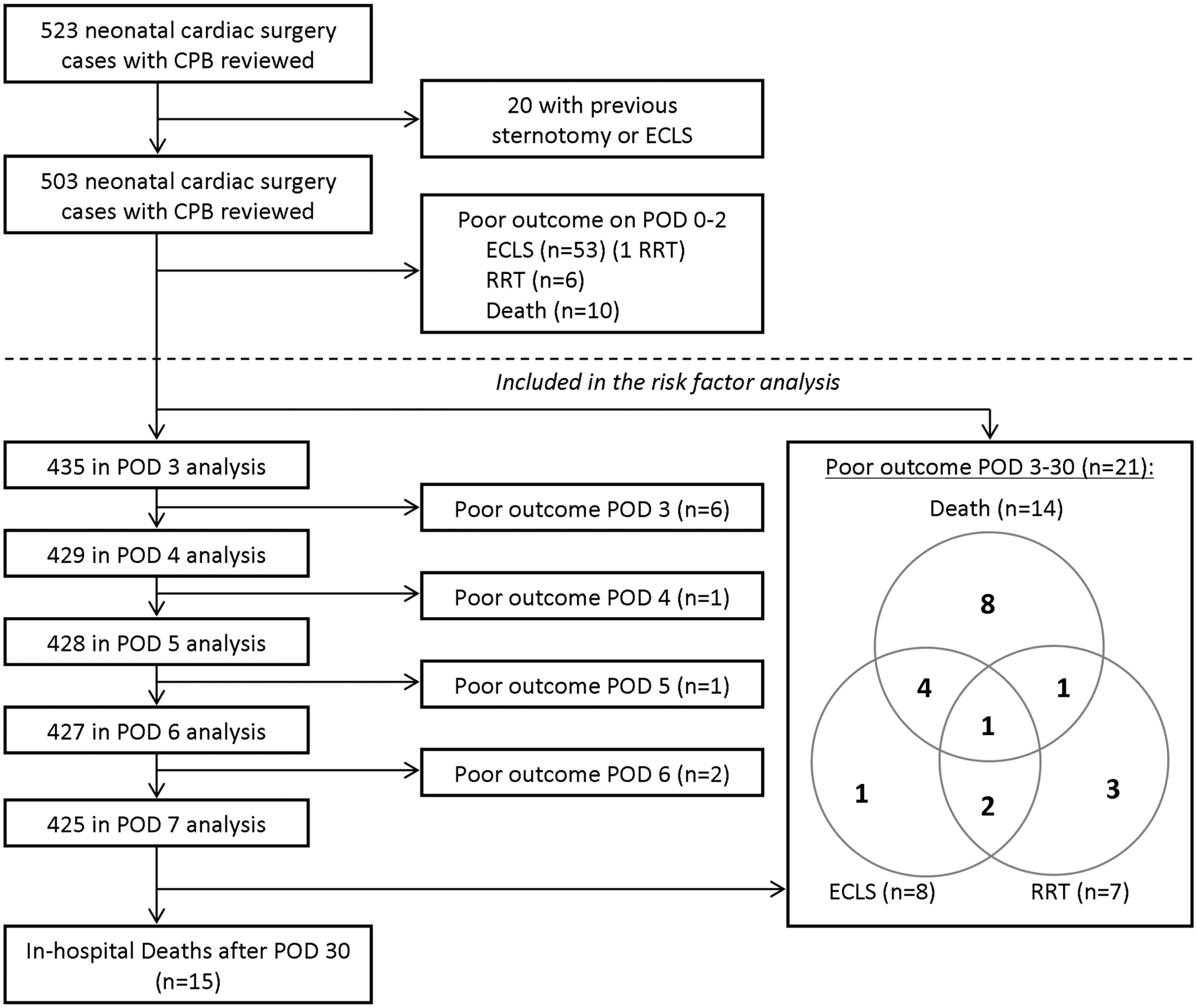

Figure 1. Study cohort

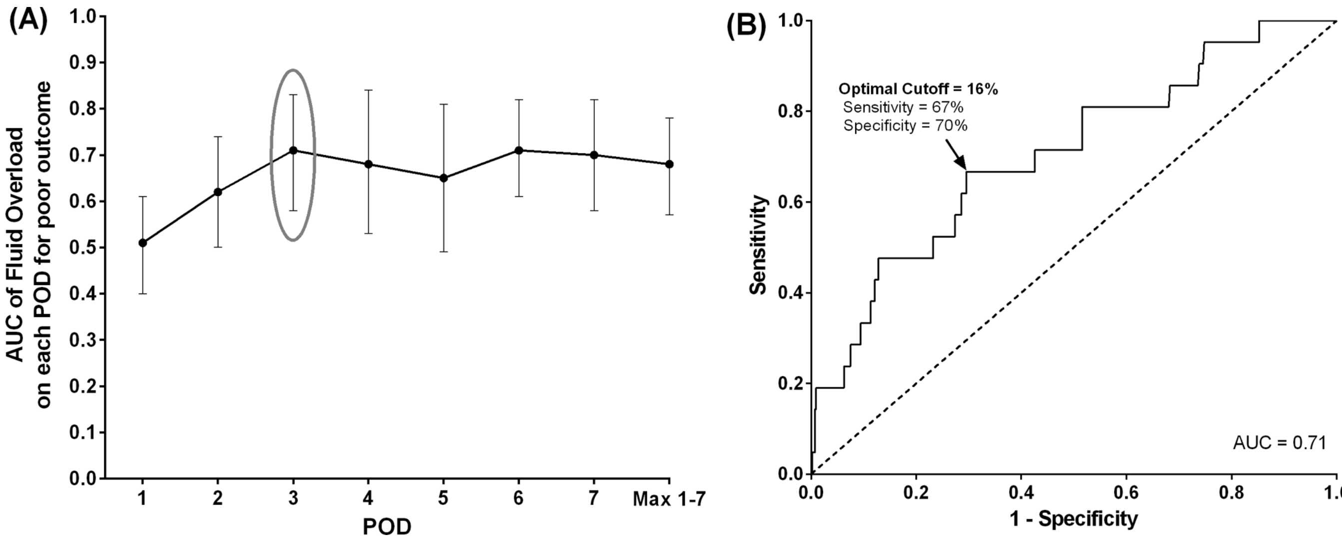

Figure 2. Fluid overload and poor composite outcome by post-operative day

(A) Area under the curve for each of the first seven PODs were compared to determine the most predictive time point for poor outcome. (B) The optimal cutoffs of FO on the selected POD for predicting poor outcome from (A) were then determined based on sensitivity and specificity from the ROC curve.

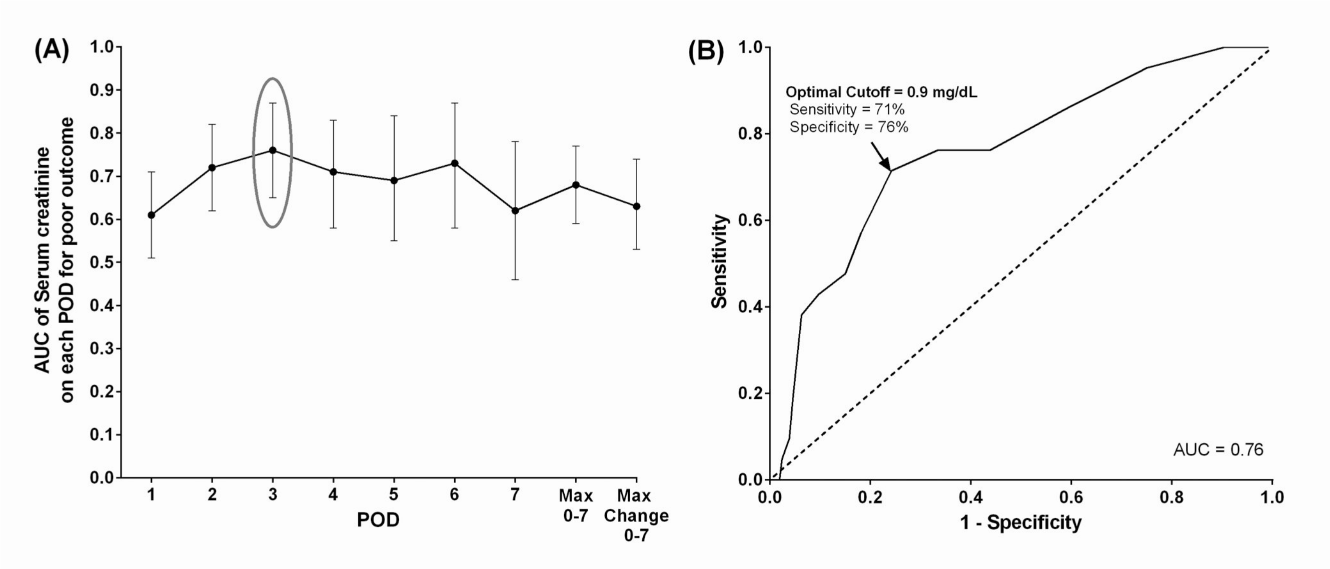

Figure 3. Serum creatinine and poor composite outcome by post-operative day

(A) Area under the curve for each of the first seven PODs were compared to determine the most predictive time point for poor outcome. (B) The optimal cutoffs of S_{Cr} on the selected POD for predicting poor outcome from (A) were then determined based on sensitivity and specificity from the ROC curve.

TABLE 1

Demographic, Surgical, and Clinical Characteristics of All Neonates Following Cardiac Surgery according to Presence or Absence of Poor Outcome

Variables	All (n = 435)	Poor outcome[a] Yes (n = 21)	Poor outcome[a] No (n = 414)	*p*
Demographics				
Male sex	262 (60.2)	10 (47.6)	252 (60.9)	0.23
Caucasian race	296 (68.0)	12 (57.1)	284 (68.6)	1.00
Age at surgery (day)	7 (5–10)	6 (3–10)	7 (5–10)	0.05
Age at surgery ≤ 3 days	43 (9.9)	8 (38.1)	35 (8.5)	< 0.001
Single ventricle	173 (39.8)	13 (61.9)	160 (38.6)	0.03
RACHS-1 score: 5 or 6	124 (28.5)	9 (42.9)	115 (27.8)	0.14[b]
Prematurity (gestational age < 37 week)	47 (10.8)	3 (14.3)	44 (10.6)	0.49
Kidney abnormality	32 (7.4)	2 (9.5)	30 (7.2)	0.67
Diagnosis: HLHS	107 (24.6)	9 (42.9)	98 (23.7)	
d-TGA	94 (21.6)	2 (9.5)	92 (22.2)	
Coarc with VSD	71(16.3)	2 (9.5)	69 (16.7)	
TOF	35 (8.0)	1 (4.8)	34 (8.2)	
Other	128 (29.4)	7 (33.3)	121 (29.2)	
Pre-Operative				
Pre-operative weight, kg	3.2 ± 0.6	3.1 ± 0.6	3.2 ± 0.6	0.28
Pre-operative S_{Cr}, mg/dL	0.5 (0.3–0.6)	0.45 (0.4–0.6)	0.5 (0.3–0.6)	0.29
Intubated	207 (47.6)	13 (61.9)	194 (46.9)	0.18
Inotropic support	132 (30.3)	8 (38.1)	124 (30.0)	0.43
Intra-Operative				
Cardiopulmonary bypass time (min)	94 (69–129)	115 (82–142)	93.5 (69–128)	0.17
Aortic cross-clamp time (min)	39 (28–58)	38 (27–55)	39 (28–58)	0.92
DHCA used	241 (55.4)	16 (76.2)	225 (54.3)	0.05
Post-Operative				
FO on POD 3 (%)	10.0 (3.3–18.4)	18.6 (9.1–30.6)	9.7 (3.0–17.6)	< 0.01
S_{Cr} on POD 3 (mg/dl)	0.6 (0.5–0.9)	1.0 (0.8–1.3)	0.6 (0.5–0.8)	< 0.0001
FO ≥ 16 % on POD 3	136 (31.3)	14 (66.7)	122 (29.5)	< 0.001
S_{Cr} ≥ 0.9 mg/dL on POD 3	115 (26.4)	15 (71.4)	100 (24.2)	< 0.0001
ICU length of stay (day)	7 (5–13)	19 (8–28)	7 (5–12)	< 0.001
Hospital length of stay (day)	17 (11–26)	20 (11–37)	16 (11–25)	0.40
Cardiac arrest requiring CPR	34 (7.8)	12 (57.1)	22 (5.3)	< 0.0001
Re-exploration of chest	57 (13.1)	10 (47.6)	47 (11.4)	< 0.0001

Coarc = coarctation of the aorta, CPR = cardiopulmonary resuscitation, DHCA = deep hypothermic circulatory arrest, d-TGA = d-transposition of great arteries, FO = fluid overload, HLHS = hypoplastic left heart syndrome, ICU = intensive care unit, POD = post-operative day, RACHS-1 = risk adjustment for congenital heart surgery, S_{Cr}= serum creatinine, TOF = tetralogy of Fallot, VSD = ventricular septal defect.

For categorical variables, data are presented as N (% of outcome category)

[a]Composite poor outcome includes renal replacement therapy, extracorporeal life support or death on POD 3–30.

[b]Comparison was made as RACHS-1 category 1 to 4 vs. 5 or 6 and p-value was from Chi-square test.

TABLE 2

Odds of Having a Poor Outcome[a] in Neonates Following Cardiac Surgery

	Unadjusted			Adjusted		
Variables	OR	95% CI	p[b]	AOR	95% CI	p[c]
Age at surgery ≤ 3 days	6.61	2.45, 17.1	<0.001	5.66	1.93, 16.6	<0.01
Single ventricle	2.58	1.06, 6.65	0.03	2.74	0.96, 7.81	0.06
DHCA used	2.69	1.03, 8.34	0.05	2.67	0.85, 8.36	0.09
FO on POD 3 ≥ 16%	4.77	1.94, 12.9	<0.001	3.74	1.33, 10.5	0.01
S_{Cr} on POD 3 ≥ 0.9 mg/dL	7.83	3.09, 22.4	<0.0001	6.59	2.27, 19.1	<0.001

AOR = adjusted odds ratio, CI = confidence interval, DHCA = deep hypothermic circulatory arrest, FO = fluid overload, OR = unadjusted odds ratio, POD = post-operative day, S_{Cr} = serum creatinine.

[a] Composite poor outcome includes renal replacement therapy, extracorporeal life support or death on POD 3–30.

[b] P-value from univariate logistic regression.

[c] P-value from multivariable logistic regression.

TABLE 3

Maximum AKIN Stage During First Three Post-operative Days

Variables	All (n = 435)	Poor outcome[a] Yes (n = 21)	Poor outcome[a] No (n = 414)	OR[b]	95% CI	*p*
No AKI	127 (29.2)	3 (14.3)	124 (30.0)			
Stage I	116 (26.7)	6 (28.6)	110 (26.6)	2.25	0.55,9.23	0.26
Stage II	114 (26.2)	5 (23.8)	109 (26.3)	1.90	0.44,8.12	0.39
Stage III	78 (17.9)	7 (33.3)	71 (17.1)	4.08	1.02,16.3	0.047

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; CI, confidence ratio; OR, odds ratio.

Data are presented as N (% of outcome category)

[a]Composite poor outcome includes renal replacement therapy, extracorporeal life support or death on POD 3–30.

[b]Comparison was made as No AKI vs. AKI (Stage I, II, or III) and p-value was from Fisher's exact test.

TABLE 4

Association of Fluid Overload and Serum Creatinine on POD 3 with other Clinical Outcomes in Neonates following Cardiac Surgery (n=435)

	Fluid Overload on POD 3			Serum Creatinine on POD 3		
Characteristics	**≥ 16% (n=136)**	**< 16% (n=298)**	**p[a]**	**≥ 0.9 mg/dl (n=115)**	**< 0.9 mg/dl (n=319)**	**p[a]**
ICU length of stay	11 (7–18)	7 (5–10)	<0.0001	10 (6–17)	7 (5–11)	<0.0001
Hospital length of stay	20 (15–31)	15 (10–24)	<0.0001	19 (12–36)	16 (11–25)	0.02
Cardiac arrest requiring CPR	21 (15.4)	13 (4.4)	<0.0001	17 (14.8)	17 (5.3)	0.001
Thrombosis	14 (10.3)	11 (3.7)	0.01	8 (7.0)	17 (5.3)	0.52
Re-exploration of the chest	37 (27.2)	20 (6.7)	<0.0001	19 (16.5)	38 (11.9)	0.21

Abbreviations: CPR, cardiopulmonary resuscitation; ICU, intensive care unit; POD = post-operative day.

Data are presented as N (%) for categorical variables and Median (25th percentile – 75th percentile) for continuous variables.

[a]P-value from Chi-square test for categorical variables and Wilcoxon Rank Sum test for continuous variables.