Original Article

Risk factors and outcomes associated with acute kidney injury following extracardiac total cavopulmonary connection: a retrospective observational study

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Background: Total cavopulmonary connection (TCPC) is an important operation for the treatment of complex congenital heart disease. Epidemiology and outcomes for pediatric patients with acute kidney injury (AKI) following extracardiac TCPC have not been well documented. This study investigates the prevalence, risk factors, and outcomes of AKI in children after extracardiac TCPC surgery.

Methods: We retrospectively evaluated patients (age at surgery <18 years) who underwent extracardiac TCPC surgery between January 2008 and January 2020 in the Pediatric Cardiac Surgical Center of Fuwai Hospital, Beijing, China. AKI was defined according to the pediatric-modified risk, injury, failure, loss of function, and end-stage renal disease criteria.

Results: A total of 377 pediatric patients were included in this study; 123 patients (32.6%) had some degree of AKI. Among the patients with AKI, 101 (82.1%) were diagnosed with AKI-risk (AKI-R), while 22 (17.9%) were diagnosed with acute kidney injury/failure (AKI/F) (16 with AKI, and 6 with AKF). Preoperative estimated creatinine clearance (OR: 1.039, 95% CI: 1.024–1.055, P<0.001), neutrophil-to-lymphocyte ratio (OR: 1.208, 95% CI: 1.128–1.294, P<0.001), and renal perfusion pressure (OR: 0.962, 95% CI: 0.938–0.986, P=0.002) on postoperative day (POD) 0 were significantly associated with AKI after TCPC. Having previously undergone a bidirectional Glenn was significantly associated with the severity of postoperative AKI (OR: 0.253, 95% CI: 0.088–0.731, P=0.011). Furthermore, AKI was associated with prolonged mechanical ventilation time, prolonged intensive care unit stay, and composite adverse outcome. Compared with non-AKI patients, the 10-year survival rate of patients with severe AKI was significantly lower (95.5% *vs.* 65.9%, P=0.009).

Conclusions: Although the incidence of AKI was high in patients undergoing TCPC surgery, most cases were AKI-R. Severe AKI was significantly associated with early adverse outcomes and poor long-term survival.

Keywords: Acute kidney injury (AKI); extracardiac total cavopulmonary connection (extracardiac TCPC); pediatrics

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Introduction

With increasing refinements of surgical techniques and perioperative management, total cavopulmonary connection (TCPC) has become an important operation for the treatment of complex congenital heart disease. Systemic venous blood enters the pulmonary circulation by bypassing the right ventricle through an artificial conduit in order to correct hypoxia caused by the mixing of oxygenated and deoxygenated blood in the single ventricle (1). Patients undergoing TCPC operations are vulnerable to postoperative acute kidney injury (AKI). Alterations in physiology due to the incorporation of the vena cava into pulmonary arteries result in systemic venous hypertension and low cardiac output, and is related to a decrease in glomerular filtration rate (2,3).

However, studies evaluating the incidence and clinical outcomes of AKI in children following extracardiac TCPC are limited. Esch *et al.* (4) reported that preoperative atrioventricular valve regurgitation, pulmonary vascular resistance, cardiopulmonary bypass (CPB) time, postoperative renal perfusion, and peak inotrope score on the day of surgery were independent risk factors for postoperative AKI in children undergoing Fontan procedures (mainly lateral tunnel-type). In addition, Algaze *et al.* explored AKI associations in a cohort of purely extracardiac Fontan patients with or without the support of CPB (5). In our center, most patients received extracardiac TCPC under CPB, either with or without an aortic x-clamp. The extracardiac conduit TCPC better prevents late occurrence of postoperative arrhythmia and simplifies the operation, compared to the lateral tunnel procedure (6).

This study investigates the incidence and risk factors for the development of AKI in patients undergoing on-pump extracardiac TCPC, and the influence of AKI on postoperative clinical outcomes. We present the following article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-21-474/rc).

Methods

Study design and patient selection

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Fuwai Hospital (No. 2014-600) and individual consent for this retrospective analysis was waived. The medical records of consecutive patients (age at surgery <18 years) who had extracardiac TCPC surgery in the Pediatric Cardiac Surgical Center of Fuwai Hospital between January 2008 and January 2020 were reviewed. Exclusion criteria were: (I) preoperative serum creatinine ≥69.7 μmol/L, which is usually considered as the maximum normal range of serum creatinine in children (7), or received preoperative renal replacement therapy; (II) incomplete data of perioperative serum creatinine; (III) off-pump surgery; (IV) TCPC failure (patients who underwent TCPC surgery but failed to tolerance the anatomic change and ended with reoperation to other palliative connection) within 3 days after surgery; (V) patients with preoperative infection; (VI) primary hematological or immunological disease; (VII) patients with preoperative antibiotic administration after hospital admission.

Data collection and variable definition

Perioperative variables including demographic characteristics, cardiac morphology, echocardiographic parameters, cardiac catheterization hemodynamics, intraoperative records, and postoperative data were reviewed for all patients. Baseline blood laboratory parameters 48 h before, or the latest preoperative time were collected. All patients were routinely performed postoperative blood biochemical examination on the first day morning after ICU admission. Postoperative peak serum creatinine levels between postoperative day (POD) 1 and 3 were documented to determine postoperative estimated creatinine clearance (eCCL). The approach of creatinine measurement is standard. Postoperative clinical data included central venous pressure, mean arterial pressure, vasoactive drug dosage, and routine blood examination data on POD0. The hemodynamic data were recorded every hour through bedside monitoring in ICU. We collected the first measurements of hemodynamic data as the POD0 values.

AKI was defined using the pediatric-modified risk, injury, failure, loss of function, and end-stage renal disease (pRIFLE) criteria, and patients with AKI were divided into three stages: acute kidney injury-risk (AKI-R, eCCL decreased by 25%), acute kidney injury-injury (AKI-I, eCCL decreased by 50%), and acute kidney injury-failure (AKI-F, eCCL decreased by 75% or <35 mL/min/1.73 m^2). Postoperative urine output was not used to estimate AKI since diuretics were routinely used after cardiac surgery. As in previous studies, AKI-I and AKI-F stages were considered severe AKI. The patients were divided into three groups: non-AKI, AKI-R, and AKI/F. eCCL was calculated using the modified Schwartz formula (8): eCCL = k × body length (cm)/serum creatinine value (mg/dL), with a k coefficient of 0.55 for children 2–12 years old, and 0.7 for children 12–18. Renal perfusion pressure was calculated by the following equation: mean arterial pressure (mmHg) – central venous pressure (mmHg) (2). Vasoactive-inotropic score was calculated as: dopamine (μg/kg/min) + dobutamine (μg/kg/min) + 10 × milrinone (μg/kg/min) + 100 × epinephrine (μg/kg/min) + 100 × norepinephrine (μg/kg/min) + 10,000 × vasopressin (U/kg/min). Inotrope score was calculated as: dopamine (μg/kg/min) + dobutamine (μg/kg/min) + 100 × epinephrine (μg/kg/min) (9). The neutrophil-to-lymphocyte ratio (NLR) was calculated from the whole blood count: NLR = absolute count of neutrophil (×10^9/L)/absolute count of lymphocyte (×10^9/L).

Clinical outcomes

The primary clinical outcome in our cohort was the incidence of AKI after extra-cardiac TCPC operation. Early outcomes included prolonged mechanical ventilation (>81 h, 90^{th} percentile), prolonged intensive care unit (ICU) stay (>10 days, 90^{th} percentile), in-hospital mortality, infection, pleural effusion, ascites, re-intubation, extracorporeal membrane oxygenation, and arrhythmia. Major adverse outcomes were defined as a composite of events including death, extracorporeal membrane oxygenation, re-intubation, and re-admission to ICU.

Statistical analysis

Continuous variables are presented as means and standard deviation if the distribution was approximately symmetrical, and compared using the one-way ANOVA test; otherwise, median and interquartile range are presented along with the Kruskal-Wallis H test. Categorical variables are presented as frequencies and percentages. The χ^2 test and Fisher's exact test were used for categorical variables. Pairwise comparisons were performed among the three groups. The significance level (α level) was adjusted according to the Bonferroni method to reduce the risk of type I errors (P<0.017). Univariable and multivariable logistic regression models were performed to investigate the association between AKI, different risk factors and complications. Variables with P≤0.15, and those factors of clinical significance in the univariable analysis were incorporated in the multivariable logistic regression model. In addition, multiple ordinal logistic regression was performed to determine those factors associated with severity of AKI. Spearman correlation coefficients were used to assess the relationships between NLR and parameters of renal function. The time-related survival was estimated using the Kaplan-Meier method and compared by the log-rank test. All statistical analyses were performed by SPSS 26.0 software (SPSS Inc., Chicago, IL, USA) and MedCalc 18.2. All tests were two-sided, and P values <0.05 were considered significant.

Results

Characteristics of patients and AKI incidence

A total of 377 patients were included in this study; 59.4% (n=224) of the cohort was male. Median age at TCPC surgery was 4.9 (3.9, 6.4) years. Palliative surgery before TCPC was performed in 259 (68.7%) patients, the majority of whom underwent bidirectional Glenn operations (96.5%; n=250). Seven patients had pulmonary artery banding (4 of 7 had bidirectional Glenn at the same time) while 9 patients had BT shunt (3 of 9 had bidirectional Glenn at the same time) before TCPC operation. Based on the pRIFLE criteria, 123 patients (32.6%) developed AKI: 82.1% (101/123) AKI-R, 13.0% (16/123) AKI-I, and 4.9% (6/123) AKI-F.

Severe AKI was diagnosed in 22 of the 123 patients with AKI.

Perioperative data of patients among different AKI severity groups

As shown in *Table 1*, patients were comparable in terms of sex, age, weight, height, and cardiac morphology (P>0.05). The AKI/F group had a significantly lower incidence of bidirectional Glenn when compared with the AKI-R group (45.5% *vs.* 73.3%, P=0.037). There were no significant differences in preoperative cardiac catheterization and echocardiographic parameters among the groups.

Patients with AKI-R or AKI/F had lower preoperative serum creatinine (P<0.001) and higher preoperative eCCL (P<0.001) than those without AKI. There were no significant differences in CPB time, aortic x-clamp time, lowest rectal temperature during CPB, and incidence of fenestration among the three groups (P>0.05). NLR levels were higher in the AKI/F and AKI-R groups than the non-AKI group on the day of ICU admission (7.9 *vs.* 8.9 *vs.* 5.4, P<0.001). In addition, the AKI/F group had significantly higher central venous pressure (15.0 *vs.* 13.0 *vs.* 12.0 mmHg, P<0.001) and lower renal perfusion pressure (39.7 *vs.* 42.8 *vs.* 46.7 mmHg, P=0.001) on POD0 than the AKI-R and non-AKI groups. Mean arterial pressure differed only between the AKI-R and non-AKI groups (55.6 *vs.* 59.0 mmHg, P=0.024) (*Table 2*).

Risk factors associated with AKI

Those variables associated with the development of AKI with P≤0.15 in univariable logistic regression analysis (preoperative eCCL, CPB time, POD0 NLR, POD0 renal perfusion pressure, and POD0 inotrope score) and with clinical significance (bidirectional Glenn before TCPC) were used to create a multiple regression model of AKI. Preoperative eCCL (OR: 1.039, 95% CI: 1.024–1.055, P<0.001), POD0 NLR (OR: 1.208, 95% CI: 1.128–1.294, P<0.001), and POD0 renal perfusion pressure (OR: 0.962, 95% CI: 0.938–0.986, P=0.002) were significantly associated with the occurrence of AKI after TCPC surgery. The multivariable model for AKI showed a good fit (Hosmer-Lemeshow test P=0.229), and the discriminating ability was good (area under the curve was 0.809). Spearman correlation analysis found that the POD0 NLR had a negative relation with postoperative eCCL (correlation coefficient =−0.237, P<0.001), and a positive relation with postoperative serum creatinine (correlation coefficient =0.368, P<0.001) (*Figure 1*). From the ordinal logistic multivariable model, previous bidirectional Glenn was significantly associated with severity of postoperative AKI (OR: 0.253, 95% CI: 0.088–0.731, P=0.011) (*Table 3*).

Early- and long-term outcomes

Table 4 shows the early- and long-term clinical outcomes after surgery. In terms of early postoperative complications, patients with AKI/F were more likely to experience prolonged mechanical ventilation duration (P<0.001), prolonged ICU stay (P=0.030), infection (P<0.001), ascites (P=0.007), extracorporeal membrane oxygenation support (P=0.001), and ventricular fibrillation (P=0.003) than those without AKI. Of the six patients who died in ICU, all had AKI (one with AKI-R, five with AKI/F). The available data for 363 patients showed a median long-term follow-up time of 4 [2, 7] years. Compared with the non-AKI group, patients with AKI-R or AKI/F had a comparable survival rate at 1-year after TCPC surgery (98.7 *vs.* 97.9% *vs.* 94.1%, P=0.392). However, the overall 10-year survival rate of patients with AKI/F was significantly lower than those without AKI (65.9% *vs.* 95.5%, P=0.009) (*Figure 2*).

Association of outcomes with AKI or severe AKI in multivariable analysis

As shown in *Table 5*, multivariable regression analysis confirmed that AKI was an independent risk factor for prolonged mechanical ventilation (OR: 4.364, 95% CI: 1.796–10.601, P=0.001) and prolonged ICU duration (OR: 2.890, 95% CI: 1.142–7.317, P=0.025). Furthermore, severe AKI was independently associated with the composite adverse outcome (OR: 5.013, 95% CI: 1.797–13.985, P=0.002).

Discussion

Limited evidence exists regarding the postoperative AKI epidemiology in pediatric extra-cardiac TCPC surgery. Our study demonstrates that AKI occurred in 32.6% of this population according to the pRIFLE criteria, lower than what has been described in previous studies (4,5). After adjusting for possible confounding variables by multivariable logistic regression analysis, preoperative eCCL, POD0 NLR, and POD0 renal perfusion pressure were independent risk factors of AKI. It is worth noting that higher NLR on POD0 could increase the risk of AKI, and

Table 1 Patient characteristics

Variables	Non-AKI (n=254)	AKI-R (n=101)	AKI-I/F (n=22)	P value*
Sex, male, n (%)	152 (59.8)	58 (57.4)	14 (63.6)	0.831
Age at surgery (years)	5.0 (4.0, 6.6)	5.0 (3.8, 7.0)	3.9 (3.5, 6.3)	0.365
Weight (kg)	17.0 (15.0, 20.0)	17.0 (14.8, 20.0)	15.5 (14.0, 18.3)	0.174
Cardiac diagnosis, n (%)				
Single ventricle	93 (36.6)	44 (43.6)	9 (40.9)	0.468
Double outlet right ventricle	70 (27.6)	28 (27.7)	7 (31.8)	0.912
Tricuspid atresia	51 (20.1)	13 (12.9)	3 (13.6)	0.274
Pulmonary atresia	39 (14.6)	13 (12.9)	4 (18.2)	0.702
Complete transposition of great arteries	30 (11.8)	8 (7.9)	3 (13.6)	0.486
Congenital corrected transposition of great arteries	36 (14.2)	10 (9.9)	2 (9.1)	0.539
Ventricle morphology, n (%)				
Intermediated	163 (64.2)	61 (61.4)	12 (54.5)	0.627
Left	40 (15.7)	21 (20.8)	6 (27.3)	0.232
Right	51 (20.1)	19 (18.8)	4 (18.2)	0.974
Atrioventricular valve regurgitation, n (%)				
Mild	31 (12.2)	18 (17.8)	4 (18.2)	0.282
Moderate	15 (5.9)	7 (6.9)	1 (4.5)	0.930
Severe	3 (1.2)	1 (1.0)	0 (0.0)	1.000
Left ventricular ejection fraction (%)	62.7±6.2	63.3±5.7	62.3±7.7	0.654
Primary TCPC, n (%)	84 (33.1)	24 (23.8)	10 (45.5)	0.082
Palliative operations before TCPC, n (%)[‡]				
Bidirectional Glenn	166 (65.4)	74 (73.3)[a]	10 (45.5)[a]	0.037
PA banding	2 (0.8)	4 (4.0)	1 (4.5)	0.053
Systemic pulmonary artery shunt	6 (2.4)	2 (2.0)	1 (4.5)	0.685
Interval between Bidirectional Glenn to TCPC (years)	3.3±1.7	3.0±1.7	2.8±1.2	0.411
Cardiac catheterization at pre-TCPC				
Mean pulmonary pressure (mmHg)	13.0±4.3	12.1±3.3	12.1±2.6	0.256
Aortic systolic pressure (mmHg)	97.8±17.1	98.6±18.6	97.8±12.0	0.969
Aortic diastolic pressure (mmHg)	62.8±15.6	61.1±15.9	60.1±9.2	0.745
Central venous pressure (mmHg)	12.0 (10.0, 15.0)	12.0 (10.0, 13.3)	9.5 (7.5, 13.3)	0.720

Values are presented as means ± standard deviation, medians with interquartile range, or numbers and percentages of observations. *, P value for the comparison among three groups (the overall effect); [a], the differences between the two groups were statistically significant and P value <0.017 by Bonferroni correction; [‡], four patients underwent both Bidirectional Glenn and PA banding, while three patients underwent both Bidirectional Glenn and systemic pulmonary artery shunt. AKI, acute kidney injury; R, risk; I/F, injury/failure; TCPC, total cavopulmonary connection; PA, pulmonary artery.

Table 2 Perioperative data among different stages of AKI

Variables	Non-AKI (n=254)	AKI-R (n=101)	AKI-I/F (n=22)	P value*
Preoperative hemoglobin (g/L)	178.2±25.7	172.1±21.4	178.5±31.0	0.108
Preoperative neutrophil (×10^9/L)	4.0±2.0	4.1±1.7	4.0±1.7	0.900
Preoperative lymphocyte (×10^9/L)	3.8±1.7	3.8±1.4	4.4±1.7	0.218
Preoperative NLR	1.0 (0.7, 1.6)	1.0 (0.7, 1.4)	0.8 (0.6, 1.4)	0.620
Preoperative serum creatinine (mg/dL)	0.47±0.10[a,b]	0.42±0.10[b]	0.38±0.09[a]	<0.001
Preoperative eCCL (mL/min/1.73 m^2)	99.1±17.7[a,b]	111.2±18.2[b]	119.5±28.9[a]	<0.001
CPB time (min)	97.0 (77.0, 124.5)	109.0 (80.0, 151.5)	110.0 (94.0, 163.5)	0.085
Cross-clamping, n (%)	69 (27.2)	26 (26.0)	4 (20.0)	0.777
Cross-clamping time (min)	67.4±30.6	78.0±35.7	59.2±23.0	0.255
Cardioplegia, n (%)				
Histidine-tryptophan-ketoglutarate solution	27 (10.6)	13 (13.0)	0 (0.0)	0.147
St. Thomas solution	42 (16.5)	13 (13.0)	4 (20.0)	0.147
Minimum rectal temperature during CPB (℃)	34.5 (33.3, 35.1)	34.3 (32.2, 35.0)	34.6 (33.4, 35.3)	0.816
Fenestration, n (%)	71 (28.0)	31 (30.7)	9 (40.9)	0.419
POD0 hemoglobin	135.7±22.4	138.3±23.0	139.6±29.1	0.509
POD0 neutrophil (×10^9/L)	11.3 (8.5, 15.0)[a,b]	14.3 (11.4, 18.0)[b]	14.5 (12.0, 18.7)[a]	<0.001
POD0 lymphocyte (×10^9/L)	2.0 (1.4, 2.8)[a]	1.5 (1.0, 2.2)[a]	1.7 (1.0, 2.6)	<0.001
POD0 neutrophil-to-lymphocyte ratio	5.4 (3.9, 8.0)[a,b]	8.9 (6.9, 12.8)[b]	7.9 (6.5, 11.7)[a]	<0.001
Postoperative peak serum creatinine (mg/dL)	0.46 (0.40, 0.52)[a]	0.62 (0.53, 0.74)[a]	0.93 (0.77, 1.38)[a]	<0.001
Postoperative eCCL (mL/min/1.73 m^2)	97.7 (86.2, 112.5)[a]	70.7 (62.9, 81.3)[a]	41.5 (27.7, 48.5)[a]	<0.001
POD0 mean arterial pressure (mmHg)	59.0±10.8[a]	55.6±10.9[a]	55.5±12.7	0.024
POD0 central venous pressure (mmHg)	12.0 (11.0, 14.0)[a]	13.0 (11.0, 14.0)[b]	15.0 (13.0, 16.5)[a,b]	<0.001
POD0 renal perfusion pressure (mmHg)	46.7±11.2[a]	42.8±11.1[a]	39.7±11.6[a]	0.001
POD0 vasoactive-inotropic score	14.0 (10.0, 19.0)	11.0 (10.0, 19.0)	17.0 (12.0, 24.2)	0.105
POD0 inotrope score	10.0 (6.0, 14.0)	11.0 (8.0, 14.0)	12.5 (8.8, 17.3)	0.045

Values are presented as means ± standard deviation, medians with interquartile range, or numbers and percentages of observations. *, P value for the comparison among three groups (the overall effect); [a,b], the differences between the two groups were statistically significant and P value <0.017 by Bonferroni correction. AKI, acute kidney injury; R, risk; I/F, injury/failure; eCCL, estimated creatinine clearance; CPB, cardiopulmonary bypass; POD, postoperative day.

has never been identified in patients who underwent TCPC operations. We also noticed that AKI was an independent risk factor for prolonged mechanical ventilation, prolonged ICU stay, and composite adverse outcome. The most important finding of this study is the significantly lower 10-year survival of patients with severe AKI.

In our cohort, children with higher preoperative eCCL had a higher chance of developing AKI. Increased glomerular filtration could increase intraoperative exposure of renal tubules to harmful substances such as cell-free hemoglobin in the plasma, or toxic-free iron generated by blood damage (10). Additionally, children with higher preoperative eCCL may have lower muscle mass, a poor nutritional state, or fluid overload, factors also increase the risk of AKI (11). Further studies are needed to explore why higher preoperative eCCL increases the risk of AKI after pediatric cardiac surgery. In our study, we found renal perfusion pressure was also an important predictor for the

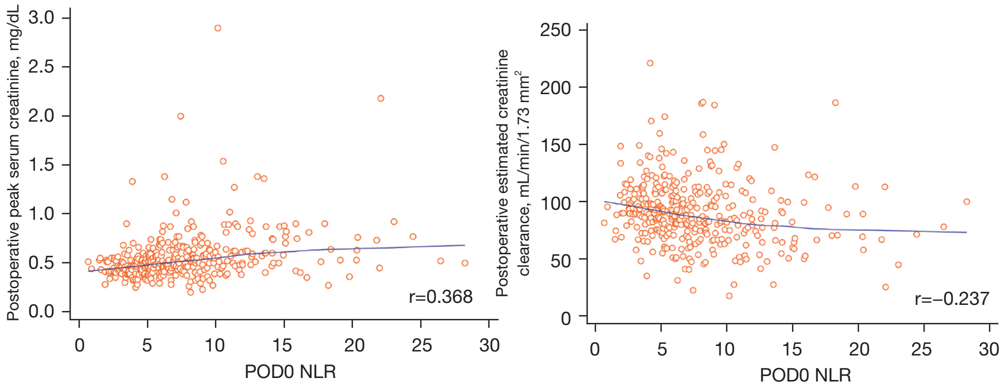

Figure 1 The relationship between POD0 NLR and postoperative renal function. POD, postoperative day; NLR, neutrophil to lymphocyte ratio.

Table 3 Multivariable logistic analysis to predict the occurrence of AKI and AKI severity

Variables	Univariable logistic regression analysis			Multivariable logistic regression analysis			Ordinal logistic regression analysis		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Male	0.947	0.612–1.468	0.809	–	–	–	–	–	–
Age (years)	0.978	0.897–1.066	0.617	–	–	–	–	–	–
Weight (kg)	1.006	0.975–1.038	0.708	–	–	–	–	–	–
Preoperative eCCL (mL/min/1.73 m^2)	1.038	1.025–1.052	<0.001*	1.039	1.024–1.055	<0.001*	1.017	0.994–1.041	0.145
Cardiopulmonary bypass time (per 10 min)	1.036	0.999–1.074	0.057	1.035	0.992–1.080	0.116	1.058	0.979–1.144	0.155
Aortic cross-clamp	0.956	0.586–1.559	0.856	–	–	–	–	–	–
Fenestration	1.242	0.779–1.980	0.362	–	–	–	–	–	–
Preoperative atrioventricular valve regurgitation									
Mild	0.879	0.329–2.346	0.797						
Moderate	1.396	0.485–4.014	0.536						
Severe	2.074	0.129–33.434	0.607						
Bidirectional Glenn before TCPC	1.142	0.721–1.808	0.572	1.405	0.803–2.459	0.234	0.253	0.088–0.731	0.011*
Preoperative mean pulmonary pressure (mmHg)	0.984	0.956–1.012	0.264	–	–	–	–	–	–
Preoperative central venous pressure (mmHg)	0.955	0.891–1.024	0.198	–	–	–	–	–	–
POD0 neutrophil-to-lymphocyte ratio	1.236	1.162–1.315	<0.001*	1.208	1.128–1.294	<0.001*	1.006	0.898–1.128	0.913
POD0 renal perfusion pressure (mmHg)	0.965	0.945–0.985	0.001*	0.962	0.938–0.986	0.002*	0.974	0.923–1.029	0.348
POD0 inotrope score	1.050	1.010–1.091	0.013*	1.014	0.965–1.066	0.577	1.021	0.938–1.110	0.636

*, P<0.05. AKI, acute kidney injury; eCCL, estimated creatinine clearance; POD, postoperative day; TCPC, total cavopulmonary connection.

Table 4 Early-term outcomes among patients with different stages of AKI, after TCPC operation

Variables	Non-AKI (n=254)	AKI-R (n=101)	AKI/F (n=22)	P value*
Mechanical ventilation time >81 h, n (%)[b]	14 (5.5)[a]	15 (15.0)[a]	17 (47.1)[a]	<0.001
Length of ICU stay >10 d, n (%)[b]	20 (7.9)[a]	13 (13.0)	5 (29.4)[a]	0.030
In-hospital death, n (%)	0 (0.0)[a]	1 (1.0)[c]	5 (22.7)[a,c]	<0.001
Infection, n (%)	20 (7.9)[a]	13 (12.9)[c]	10 (45.5)[a,c]	<0.001
Re-intubation, n (%)	9 (2.5)	5 (5.0)	1 (4.5)	0.580
Re-admission to ICU, n (%)	14 (5.5)	6 (5.9)	3 (13.6)	0.404
Pleural effusion, n (%)	48 (18.9)	27 (26.7)	8 (36.4)	0.063
Ascites, n (%)	14 (5.5)[a]	14 (13.9)[a]	4 (18.2)	0.007
Re-intubation, n (%)	9 (3.5)	5 (5.0)	1 (4.5)	0.580
Extracorporeal membrane oxygenation, n (%)	1 (0.4)[a]	1 (1.0)[c]	5 (22.7)[a,c]	<0.001
Ventricular fibrillation, n (%)	0 (0.0)[a]	0 (0.0)	2 (9.1)[a]	0.003

*, P value for the comparison among three groups (the overall effect); [a,c], the differences between the groups were statistically significant and P value <0.017 by Bonferroni correction; [b], one patient in AKI-stage 1 group and five patients in stage 2&3 were not followed up because of in-hospital death. AKI, acute kidney injury; TCPC, total cavopulmonary connection; R, risk; I/F, injury/failure; ICU, intensive care unit.

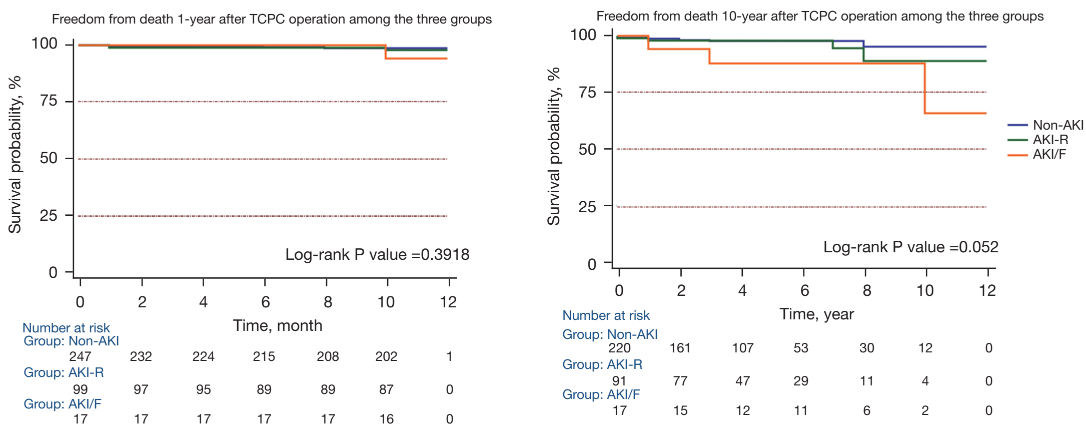

Figure 2 Comparing the 1- and 10-year survival rates among patients with different stages of AKI after TCPC operation. AKI-R, acute kidney injury-risk; AKI/F, acute kidney injury/failure; TCPC, total cavopulmonary connect.

occurrence of AKI, consistent with the previous reports from Esch *et al.* and Algaze *et al.* (4,5). Compared with non-AKI patients, the postoperative renal perfusion pressure of patients with severe AKI was significantly lower. In terms of inotropic support, we found that the inotropic score on POD 0 were comparable in different stages of AKI. However, compared to patients without AKI, the inotrope requirement on POD 1 to POD 3 were significantly higher in those with AKI, indicating that AKI patients may require more support with inotropes to support a higher MAP and increase renal perfusion pressure. The management of renal perfusion pressure is a complex problem, especially after cardiac surgery and the ability to improve renal perfusion pressure by enhancing rhe inotrope requirement was limited (12).

In our study, 111 patients (29.4%) underwent fenestration during TCPC. Some studies considered that fenestration could reduce drainage from chest tubes and duration of hospitalization because of the lower extra-cardiac conduit pressure and larger cardiac output in the

Table 5 Multivariable analyses of postoperative AKI for adverse in-hospital outcome

Variables	OR	95% CI	P value
Prolonged mechanical ventilation			
AKI	4.364	1.796–10.601	0.001
CPB duration (per 10 minutes)	1.023	0.956–1.095	0.512
Intraoperative blood loss (mL/kg)	1.130	1.066–1.197	<0.001
Aortic across-clamp time (minutes)	1.009	0.998–1.020	0.128
Prolonged ICU stay			
AKI	2.890	1.142–7.317	0.025
CPB duration (per 10 minutes)	1.031	0.989–1.075	0.773
Intraoperative blood loss (mL/kg)	1.096	1.037–1.158	0.001
POD0 vasoactive-inotropic score	1.021	1.005–1.037	0.011
Composite adverse outcome			
AKI/F	5.013	1.797–13.985	0.002
CPB duration (per 10 minutes)	1.033	0.983–1.086	0.202
Age (years)	1.022	0.877–1.192	0.778

AKI, acute kidney injury; I/F, injury/failure; CPB, cardiopulmonary bypass; ICU, intensive care unit; POD, postoperative day.

early postoperative period, where some others studies found no significant difference of perioperative data between patients with and without fenestration in TCPC operation. These different opinions also influenced the surgeons' operation procedures in our center. Our results showed no significant differences in postoperative mean arterial pressure, central venous pressure, and renal perfusion pressure between patients with and without fenestration, but this kind of right-to-left shunting could alleviate the sudden changes in hemodynamics induced by crying, asphyxia, or airway obstruction after operation. Although we did not find any association between fenestration and AKI, Fan *et al.* (13) reported that for patients undergoing high-risk TCPC, intraoperative fenestration was beneficial for reducing postoperative chest tube drainage volume and duration, consistent with our results.

For the AKI patients in our cohort, the proportion of receiving bidirectional Glenn before TCPC was lower in severe AKI patients, and indicates that a bidirectional Glenn before TCPC decreases AKI severity, something which has not been reported. Staged palliation with a bidirectional Glenn and subsequent TCPC is a common treatment strategy in patients with functional single ventricle, and has the advantages of improving oxygen saturations and further reducing the volume load. While these favorable effects of the bidirectional Glenn can improve pulmonary hemodynamics, the influence on kidney function and association with AKI remain unclear. Hypoxemia may induce hyperviscosity due to secondary erythrocytosis, leading to glomerular blood flow and pathological glomerular changes (2). The mechanism by which a bidirectional Glenn decreased the risk of severe AKI may be due to palliation improving oxygen saturation and decreasing blood viscosity, thereby attenuating pathological glomerular changes (14).

Another major finding of our study was that POD0 NLR was associated with AKI. The relationship between postoperative NLR and AKI has been evaluated in cardiac surgery and septic shock (15,16). As an indicator of inflammatory response, NLR is a common clinical index, and is easily obtained from a routine blood test. Furthermore, it has been shown to predict mortality and major adverse events after cardiac surgery (17-19). Recently, Manuel *et al.* (20) found an association between a high preoperative NLR and severe AKI after tetralogy of Fallot repair. We did not find any differences in preoperative NLR among different stages of AKI after TCPC operation. The inflammatory levels were comparable in patients before surgery. In our study, the negative correlation of POD0 NLR with postoperative eCCL, and the positive correlation with postoperative serum creatinine also indirectly indicate that the NLR plays an important role in the prediction of AKI. Unlike other inflammatory markers such as TNF-a and IL-6, NLR is a convenient and low-cost biomarker that could be used for AKI prediction.

Consistent with other studies of AKI after pediatric cardiac surgery, AKI was an independent risk factor of prolonged ICU stay and mechanical ventilation in our cohort (11,21,22). AKI was also shown to be independently associated with increased mortality in children (23-25). In this study, early-term mortality after TCPC was 1.6% (6/377), and patients with severe AKI had higher in-hospital mortality and other complications than those without AKI. The follow-up results of our study showed that the 10-year survival was significantly lower in severe AKI patients. Although most AKI cases after TCPC were mild and had a favorable prognosis, the early and long-term clinical outcomes of patients with severe AKI are poor. Early postoperative identification and intervention are important steps to improve the outcomes of patients with severe AKI.

This study had several limitations. Since this was a single-center retrospective study, the patient selection criteria are not completely random, and the inherent bias associated with a retrospective study exists. A multicenter study or random controlled trial needs to be carried out to further evaluate the results of our study. Secondly, only a biochemical test was used to assess kidney function. Since serum creatinine levels were not measured in most patients after discharge from ICU, the recovery time from AKI could not be exactly determined. Furthermore, our limited examination data were not enough to evaluate long-term kidney function after discharge from the hospital. Finally, although we found several risk factors for AKI after TCPC, we could not conclude that modifying any factor would improve patient outcome.

In conclusion, the incidence of AKI was high in patients undergoing TCPC surgery, but most cases were AKI-R. Preoperative eCCL, NLR and renal perfusion pressure on POD0 were independently associated with AKI. Bidirectional Glenn procedures were found to be associated with AKI severity. Although there were no significant differences in 1-year survival rates between patients with and without AKI, severe AKI was significantly associated with early adverse outcomes and poor long-term survival.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Fuwai Hospital (No. 2014-600) and individual consent for this retrospective analysis was waived.

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