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The Association between Cardiac Biomarker NT-proBNP and 30-day Readmission or Mortality after Pediatric Congenital Heart Surgery

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Abstract

Background: Very little is known about clinical and biomarker predictors of readmissions following pediatric congenital heart surgery. The cardiac biomarker N-terminal pro-brain natriuretic peptide (NT-proBNP) can help predict readmission in adult populations, but the estimated utility in predicting risk of readmission or mortality after pediatric congenital heart surgery has not previously been studied. Our objective was to evaluate the association between pre- and post-operative serum biomarker levels and 30-day readmission or mortality for pediatric patients undergoing congenital heart surgery.

Methods: We measured pre-and postoperative NT-proBNP levels in two prospective cohorts of 522 pediatric patients <18 years of age who underwent at least one congenital heart operation from 2007 to 2014. Blood samples were collected before and after surgery. We evaluated the association between pre- and post-operative NT-proBNP with readmission or mortality within 30 days of

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discharge, using multivariate logistic regression, adjusting for covariates based on the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Mortality Risk Model.

Results: The Johns Hopkins and TRIBE-AKI cohorts demonstrate event rates of 12.9% and 9.4%, respectively, for the composite endpoint. After adjustment for covariates in the STS congenital risk model, we did not find an association between elevated levels of NT-proBNP and increased risk of readmission or mortality following congenital heart surgery for either cohort.

Conclusions: In our two cohorts, preoperative and postoperative values of NT-proBNP were not significantly associated with readmission or mortality following pediatric congenital heart surgery. These findings will inform future studies evaluating multi-marker risk assessment models in the pediatric population.

Keywords

pediatric congenital heart disease; biomarkers; prediction; readmission

Introduction

Congenital heart disease (CHD) occurs in approximately 1% of live births.^{1–3} Approximately one-quarter of the 40,000 children born annually with CHD in the US require surgery in the first year of life.⁴ Surgical intervention for pediatric CHD carries significant risk of postoperative readmission and mortality. Approximately 10–20% of pediatric patients are readmitted after congenital heart surgery⁵ and 4.2% of surgeries result in inpatient mortality.^{6,7} A variety of risk models have been developed to assess the preoperative risk assessment of readmission and mortality for adult patients undergoing cardiac surgery, but no prediction methods have been developed for children who require surgery for CHD.

Cardiac biomarker N-terminal pro-brain natriuretic peptide (NT-proBNP) is widely recognized as an essential part of adult cardiologic evaluation, yet the clinical utility in pediatric cardiac surgery is not well understood. In a large, heterogeneous cohort of adult patients undergoing cardiac surgery, Liu et al reported that preoperative NT-proBNP levels were a valuable marker of hemodynamic and functional characteristics of the patients, as well as predicting longer ICU length of stay (LOS), in-hospital LOS and increased ventilation time.⁸ In pediatrics, the relationship is unclear. NT-proBNP is released from myocytes in response to cardiac chamber dilation and wall stress. This hemodynamic burden suggests preoperative and early postoperative levels may be predictive of readmission or mortality. Prognostic biomarkers are of increasing importance with a current focus on improving long-term outcomes and quality of life for children with CHD.^{9,10}

The relative utility of NT-proBNP in predicting outcomes following pediatric congenital heart surgery is unclear. We sought to evaluate the clinical utility of novel biomarker NT-proBNP to identify children with an increased risk of 30-day readmission or mortality after congenital heart surgery.

Methods

We performed a retrospective analysis of two prospective, longitudinal cohorts of children aged 1 month to 18 years old, undergoing at least one congenital cardiac operation. Data were compiled separately. Parallel analysis on the two cohorts was performed.

Patients Cohorts

Johns Hopkins: This is a single center cohort of 244 patients who underwent cardiac surgery, with or without cardiopulmonary bypass, at Johns Hopkins Children's Center from 2010 to 2014. Patient, procedural, and outcome data were collected. The cohort was limited to patients with biomarker information collected at the index operation (N = 174). Patients with unknown prematurity status, patients weighing 2.5 kg or less, patients aged > 18 years old were excluded. The cohort was limited to patients who had at least one preoperative and one postoperative biomarker measurement (N=162).

TRIBE-AKI multi-center cohort: This is a multi-cohort study of children undergoing cardiac surgery with cardiopulmonary bypass at Cincinnati Children's Hospital, Montreal Children's Hospital, Canada, and Yale New Haven Children's Hospital from 2007 to 2010 were enrolled in the study (N=429). The cohort is limited to patients who had readmission or mortality information data (N=402). The TRIBE-AKI cohort is restricted to patients that have at least one preoperative and one postoperative biomarker measurement (N=360). Detailed methods of the Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury consortium study (TRIBE-AKI) has been previously described.¹¹ The specific biomarker data from the TRIBE-AKI cohort has not previously been evaluated with unplanned readmission.

Sample collection

Johns Hopkins cohort—Perioperative blood samples (heparinized plasma) were collected immediately prior to skin incision and at the end of bypass. Samples were processed and stored at -80°C until assayed. Biomarkers were measured by ELISA using a custom printed multiplex assay (Meso Scale Discovery) using patterned arrays and an electrochemiluminescence detection method (R&D Systems).

TRIBE-AKI multi-center cohort—Blood samples were collected at preoperative evaluations within 1 month of surgery, within 6 hours after surgery and daily for up to 5 days after surgery. Biomarkers were measured using a multiplex assay (Meso Scale Discovery), preoperatively, within 6 hours after surgery and at the last available sample prior to discharge (2–5 days after surgery).

Main Outcome

The composite study endpoint is unplanned readmission within 30 days following discharge or mortality, either in-hospital during the surgical admission or within 30 days after discharge from the surgical admission. Readmissions were defined as the first unplanned admission within 30 days of the index hospitalization where the congenital heart surgery occurred. A composite endpoint was used due to the limited number of events.

Johns Hopkins and TRIBE-AKI cohorts: Readmission status and all-cause mortality data were obtained through chart abstraction at the hospital where the congenital heart surgery occurred.

Data from the Cardiac Surgery Admission

Detailed cardiac surgery admission information was available in all participants. Preoperative characteristics, operative details and postoperative complications were defined through the Society of Thoracic Surgeons Congenital Heart Surgery Database Mortality Risk Model (STS-CHSD).¹² Risk factors in the model include age (months) at surgery, weight (kilograms), any prior cardiothoracic operation (yes/no), any non-cardiac congenital anatomic abnormality (yes/no), any chromosomal abnormality or syndrome (yes/no), STAT mortality category¹³, and presence of any clinical preoperative risk factors. Preoperative risk factors were operationalized as a count variable based on the presence of the following preoperative factors: mechanical circulatory support, persistent shock at time of operation, renal dysfunction requiring dialysis, mechanical ventilation to treat cardiorespiratory failure, and preoperative neurological deficit. Given the limited number of outcome events, we aggregated all preoperative risk factors and dichotomized based on the presence of none or >1. The STAT mortality category is a risk stratification scoring system to categorize the complexity of surgery. Higher scores reflect more complex surgeries. This method of risk stratification is a widely accepted tool for the evaluation of differences in outcomes of surgery for congenital heart disease.

The TRIBE-AKI cohort lacked data on any chromosomal abnormality or syndrome. TRIBE adjusted for all other variables in the STS-CHSD risk model.

Statistical Analysis

Patient, clinical and procedural characteristics were compared by our composite endpoint using descriptive statistics. Differences in risk factors were compared using Pearson's chi-square tests or Fisher's exact test; continuous variables were compared with two-sample t-test or Wilcoxon ranksum test. We evaluated the biomarker in log-continuous, above and below the population median and tercile forms.¹⁰ Indicator variables were created for each of the terciles and median values.

We performed multivariate logistic regression to examine the association between covariates included in the STS-CHSD model and preoperative and postoperative NT-proBNP cutpoints. STATA version 14.2 (College Station, TX) was used for Hopkins cohort and SAS version 9.3 (SAS Institute) was used for the TRIBE-AKI cohort analyses.

Results

Baseline characteristics: Johns Hopkins & TRIBE-AKI

Patient and pre-procedural characteristics are described in Table 1. Of Johns Hopkins patients, the most common procedure was ventricular septal defect repair (18, 11.1%). The most common procedure in TRIBE-AKI children was a combined procedure (160, 47%),

followed by septal defect repair (120, 35%) and inflow/outflow tract or valve procedure 62 (62, 18%).

We observed a significant difference between surgery severity and risk of experiencing the composite endpoint for both cohorts. In the Hopkins cohort, 43% were STAT 1, 27% STAT 2, 11% STAT 3, 9% STAT 4 and 6% STAT 5 ($p=0.031$). In the TRIBE-AKI multi-center cohort, 44% were STAT 1, 32% STAT 2, 14% STAT 3, 9% STAT 4 and 1% STAT 5 ($p=0.035$).

Biomarkers with primary composite endpoint

In the Hopkins cohort, 21 (12.9%) patients experienced the composite endpoint of mortality ($N=3$) or readmission ($N=18$) within 30-days from discharge. In the TRIBE-AKI multi-center cohort, 34 (9.4%) patients experienced the composite endpoint of mortality ($N=4$) or readmission ($N=30$) within 30-days from discharge. Pre- and postoperative biomarker levels and the association with readmission or mortality are listed in Table 2.

Preoperative NT-proBNP

Johns Hopkins cohort: Before adjustment, preoperative NT-proBNP values above the median and the highest tercile were not significantly associated with readmission or mortality after heart surgery (OR: 1.28, 95% CI: 0.43 – 3.78; OR: 1.48, 95% CI: 0.46 – 4.80, respectively). After adjustment, NT-proBNP tercile values did not show a significant relationship with readmission or mortality (Table 3).

TRIBE-AKI multi-center cohort: Before adjustment, preoperative NT-proBNP values above the median and the highest tercile were not significantly associated with readmission or mortality after heart surgery (OR: 0.93 (0.43 – 1.99); OR: 1.42, 95% CI: 0.055 – 3.70, respectively). After adjustment, NT-proBNP tercile values did not show a significant relationship with readmission or mortality.

Postoperative NT-proBNP

Johns Hopkins cohort: Unadjusted postoperative NT-proBNP median and highest terciles, compared to the lowest tercile, were not significantly associated with 30-day readmission or mortality (OR: 1.86, 95% CI: 0.64 – 5.37; OR: 1.50, 95% CI: 0.44 – 5.12, respectively). After adjustment, there was no association between elevated levels of NT-proBNP and increased risk of 30-day readmission or mortality (OR: 2.71, 95% CI: 0.65 – 11.29).

TRIBE-AKI multi-center cohort: Before adjustment, postoperative NT-proBNP median and tercile values, measured 0–6 hours after surgery, were not significantly associated with readmission or mortality (OR: 1.49, 95% CI: 0.61 – 3.66; OR: 1.12, 95% CI: 0.44 – 2.89). Unadjusted postoperative values measured immediately before discharge demonstrated a protective effect at the median tercile, compared to lowest tercile (OR: 0.25, 95% CI: 0.07 – 0.91). All other unadjusted postoperative values measured immediately prior to discharge were not significant. After adjustment, all postoperative NT-proBNP values did not show a significant relationship with readmission or mortality.

Discussion

To our knowledge, this is the first study to evaluate the predictive value of NT-proBNP on 30-day readmission or mortality in pediatric congenital heart surgery. We analyzed multiple pediatric cohorts with the two of the largest congenital heart surgery biorepositories in the world. For the Hopkins and TRIBE-AKI cohorts, there was no association between pre- or postoperative NT-proBNP levels and risk of readmission or mortality, after adjusting for clinical risk factors.

Cardiac biomarkers, especially BNP and NT-proBNP, are routinely used in adult cardiologic evaluation.^{14,15} Both peptides are established as independent predictors of survival after acute coronary syndromes and ischemic heart failure in adult patients.^{16,17} In adult patients undergoing cardiac surgery, particularly coronary artery bypass grafting (CABG), both preoperative and postoperative elevated BNP levels were found to be associated with increases in hospitalization time, complication rates and mortality.¹⁸ For adult CABG patients, studies have found associations between elevated levels of preoperative NT-proBNP and postoperative mortality, prompting the inclusion of NT-proBNP in adult predictive models for readmission or mortality. NT-ProBNP has also been shown to predict postoperative survival in patients with aortic stenosis, in-hospital mortality in patients with heart failure, all-cause mortality within 30 days of discharge after non-cardiac surgery, and all-cause mortality in adults with congenital heart disease.^{19–22}

In the pediatric population, several studies have found a relationship between BNP and NT-proBNP in identifying the presence and severity of pediatric heart failure.^{14,23,24} Studies have found NT-proBNP and BNP as markers of systolic dysfunction and important predictors of the need for mechanical circulatory support, heart transplantation, and need for therapy with inotropic drugs after surgery.^{25,26} For children with heart failure, NT-proBNP has been useful to evaluate the success of treatment and the need for escalation of therapy. Studies have suggested that preoperative NT-proBNP levels are associated with postoperative complications in children who underwent low-risk open-heart surgery, including pleural effusions, sepsis, arrhythmia, and respiratory insufficiency.²³ Furthermore, it has been suggested that higher NT-proBNP concentrations correlate with ventricular dysfunction or left or right ventricular volume overload in children with CHD.²⁷ These studies demonstrate that natriuretic peptide levels rise in proportion to symptomatic severity and the degree of remodeling in diverse pediatric cardiac diseases.

The evaluation of NT-proBNP is part of a broader undertaking to evaluate multiple biomarkers and their individual or combined value in predicting 30-day readmission or mortality following cardiac surgery. While NT-proBNP is regularly used to predict readmission in adults after cardiac surgery, this biomarker does not have the same predictive value in a heterogeneous population of children who receive surgery for CHD. These findings suggest that biomarkers routinely used in the adult population may not be appropriate in pediatric clinical evaluation.

Limitations

Our findings should be interpreted in light of several limitations. First, risk adjustment was performed using the the covariates from the contemporary version of the STS-CHSD mortality risk model, which is a method of adjusting for procedural case mix. Due to the low event rate, we were not able to adjust for all of the covariates included in the risk adjustment model. Specifically, we were not able to adjust for prematurity status or the individual preoperative risk factors described in the STS CHSD model (preoperative/preprocedural mechanical circulatory support; shock, persistent at time of operation; renal dysfunction or renal failure requiring dialysis; mechanical ventilation to treat cardiorespiratory failure; and preoperative neurological deficit.) Second, the relatively small proportion of patients with our composite endpoint after congenital heart surgery may have obfuscated some of the statistical associations between the biomarkers and our model covariates. A larger sample size would have improved our power to assess the performance of NT-proBNP in the preoperative setting. Third, we included only patients for whom both pre-and postoperative samples had been collected. This approach may lead to sampling bias if biomarker collection was associated with congenital heart disease severity. Finally, there is a fair amount heterogeneity in the CHD population and this is inherent to patients with congenital heart disease. Additionally, biorepositories are exceedingly rare in pediatric congenital heart surgery due to the complexity of sample harvesting and patient/guardian consent. While we know the most prevalent types of surgical procedures in these cohorts, we don't have the statistical power to conduct a subgroup analysis.

Conclusion

This is the first study to evaluate pre-and postoperative levels of NT-proBNP and the association with increased risk of readmission or mortality after pediatric cardiac surgery. In our cohorts, we did not observe a significant association with preoperative and postoperative NT-proBNP and readmission or mortality following congenital heart surgery. The ability to predict postoperative adverse outcomes from preoperative clinical data has important implications for identifying patients who may benefit from earlier interventions after cardiac surgery. These cardiac biomarkers can be useful tools for risk stratification and improved patient care management.

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Figure 1. Johns Hopkins cohort: the association between cardiac biomarker NT-proBNP and 30-day readmission or mortality after pediatric congenital heart surgery

Figure 2.

TRIBE-AKI multi-center cohort: the association between cardiac biomarker NT-proBNP and 30-day readmission or mortality after pediatric congenital heart surgery

Table 1.

Patient characteristics

Risk Factors	Johns Hopkins				TRIBE-AKI			
	ALL (N=162)	No (N = 141)	Yes (N = 21)	p value	ALL (N= 360)	No (N= 326)	Yes (N=34)	p value
Age category								
Neonates and Infants	84	60 (42.6)	8 (38.1)		150	134 (41.1)	16 (47.0)	
Children	78	68 (48.2)	10 (47.6)	0.755	210	192 (59.0)	18 (53.0)	0.503
Age group								
Age < 2 years	87	76 (53.9)	11 (52.4)		170	153 (47.0)	17 (50.0)	
Age > 2 years	75	65 (46.1)	10 (47.6)	0.896	190	173 (53.0)	17 (50.0)	0.733
Age, by month (mean, sd) *	48 (63)	46 (59)	62 (79)	0.270	48 (55)	48 (54)	52 (67)	0.950
Gender								
Male	97	86 (62.4)	11 (52.4)	0.453	193	173 (53)	20 (59.0)	0.522
Weight								
>10 th percentile	148	130 (92.2)	18 (85.7)	0.324	163	147 (45)	16 (47)	0.826
Weight, by kg (mean, sd) *		16.7 (1.5)	25.45 (6.6)	0.059		16.9 (16.9)	16.8 (18.3)	0.788
Prematurity status by neonates or infants								
No	141	121 (85.8)	20 (95.2)	0.230	N/A			
STAT Level *†								
1	69				159	149 (46)	10 (29)	
2	43	33 (23.4)	10 (47.6)		115	99 (30)	16 (47)	
>3 or Missing	50	43 (30.5)	7 (33.3)	0.027	86	78 (24)	8 (24)	0.035
Prior cardiothoracic operation *								
No	129	118 (83.7)	11 (52.4)	0.001	202	186 (58)	16 (48)	0.123
Any non cardiac congenital anatomic abnormality *								
No	141	123 (87.2)	18 (85.7)	0.847	327	296 (91)	31 (91)	0.942
Chromosomal abnormality or syndrome *								
No	118	105 (74.5)	13 (61.9)	0.227				
Any preoperative factor *								
No	136	123 (87.2)	13 (61.9)	0.003	304	276 (88)	28 (85)	0.649
In-hospital length of stay (median, IQR)	7 (5,10)	6 (4,11)	15 (8,25)	0.717	5 (3,9)	5 (3,8)	7 (4,11)	0.057

* Variables used in the risk-adjustment, informed by the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database (STS-CHSD) Mortality Risk model.

[†] STAT categories were collapsed in this table to suppress small cell counts (<5). Non-collapsed STAT categories were included in analytic models.

N/A indicates not available in the TRIBE-AKI cohort.

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Table 2.

Pre-and postoperative biomarker levels and the association with readmission or mortality 30-days from surgery

	NT Pro BNP (ng/mL) by Readmission or Mortality at 30 days Median (IQR)									
	Johns Hopkins					TRIBE-AKI				
	Time point	ALL (n=162)	No (n=141)	Yes (n=21)	p value	Time point	ALL (n=360)	No (n=326)	Yes (n=34)	p value
PREOPERATIVE	Immediately prior to skin incision	0.42 (0.20, 1.73)	0.43 (0.20, 1.20)	0.50 (0.17, 2.0)	0.858	Pre- operatively (within 1 month)	0.39 (0.16, 1.23)	0.39 (0.16, 1.21)	0.32 (0.17, 1.59)	0.723
POSTOPERATIVE	End of bypass	0.72 (0.17, 1.45)	0.71 (0.16, 1.35)	0.77 (0.31, 2.43)	0.835	0–6 Hours post-op	0.71 (0.24, 2.83)	0.71 (0.24, 2.89)	0.79 (0.30, 2.05)	0.930
						Last sample Prior to discharge	5.18 (2.31, 11.31)	5.17 (2.35, 11.22)	8.70 (2.07, 12.94)	0.685

Table 3.

Readmission or mortality by NT-proBNP measurements

		Range, N	N (%)	Johns Hopkins		Range, N	N (%)	TRIBE-AKI	
				Unadjusted OR (95% CI)	Adjusted* OR (95% CI)			Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
PREOPERATIVE	Log Continuous	---	21 (12.9)	1.07 (0.84 – 2.36)	0.94 (0.71 – 1.24)	...	34 (9.4)	1.09 (0.79 – 1.22)	1.04 (0.80 – 1.37)
	Below Median	0.04 – 0.42 (n=81)	10 (12.4)	1.0 (Ref)	1.0 (Ref)	0.02–0.39 (n=149)	15 (10.1)	1.0 (Ref)	1.0 (Ref)
	Above Median	0.42 – 181.58 (n=81)	11 (13.6)	1.42 (0.56 – 3.58)	1.20 (0.32 – 4.47)	0.39–99.1 (n=149)	14 (9.4)	0.93 (0.43 – 1.99)	0.77 (0.31 – 1.86)
	Tercile 1	0.04 – 0.24 (n=54)	7 (13.0)			0.02–0.23 (n=99)	8 (8.1)		
	Tercile 2	0.25 – 0.87 (n=54)	5 (9.3)	1.28 (0.43 – 3.78)	1.10 (0.26 – 4.63)	0.23–0.89 (n=100)	10 (10.0)	1.26 (0.48 – 3.35)	1.43 (0.48 – 4.22)
	Tercile 3	0.89 – 181.58 (n=54)	9 (16.7)	1.48 (0.46 – 4.80)	0.88 (0.18 – 4.31)	0.89–99.1 (n=99)	11 (11.1)	1.42 (0.55 – 3.70)	1.43 (0.46 – 4.46)
POSTOPERATIVE	Log Continuous	---	21 (12.9)	1.19 (0.97 – 1.46)	1.14 (0.86 – 1.51)	...	34 (9.4)	0.98 (0.79 – 1.22)	1.00 (0.78 – 1.29)
	Below Median	0.04 – 0.45 (n=81)	7 (8.6)	1.0 (Ref)	1.0 (Ref)	0.02–0.71 (n=153)	15 (9.8)	1.0 (Ref)	1.0 (Ref)
	Above Median	0.45 – 0.89.40 (n=81)	14 (17.3)	1.82 (0.72 – 4.60)	1.76 (0.47 – 6.64)	0.71–76.81 (n=154)	17 (11.0)	1.14 (0.55 – 2.38)	1.40 (0.60 – 3.25)
	Tercile 1	0.04 – 0.26 (n=54)	4 (7.4)			0.02–0.35 (n=102)	9 (8.8)		
	Tercile 2	0.26 – 0.89 (n=54)	7 (13.0)	1.86 (0.64 – 5.37)	2.71 (0.65 – 11.29)	0.35–1.34 (n=103)	13 (12.6)	1.49 (0.61 – 3.66)	1.50 (0.56 – 4.01)
	Tercile 3	0.94 – 89.40 (n=54)	10 (18.5)	1.50 (0.44 – 5.12)	1.07 (0.23 – 5.01)	1.34–76.81 (n=102)	10 (9.8)	1.12 (0.44 – 2.89)	1.37 (0.46 – 4.07)
IMMEDIATELY PRIOR TO DISCHARGE	Log Continuous					...	34 (9.4)	1.15 (0.82 – 1.60)	1.16 (0.78 – 1.74)
	Below Median					0.07–5.17 (n=134)	13 (9.7)	1.0 (Ref)	1.0 (Ref)
	Above Median					5.17–118.70 (n=135)	14 (10.4)	1.08 (0.49 – 2.39)	1.16 (0.45 – 2.97)
	Tercile 1					0.07–3.1 (n=89)	11 (12.4)		
	Tercile 2					3.10–8.7 (n=90)	3 (3.3)	0.25 (0.07 – 0.91)	0.25 (0.06 – 1.01)

		Range, N	N (%)	Johns Hopkins		Range, N	N (%)	TRIBE-AKI	
				Unadjusted	Adjusted*			Unadjusted	Adjusted*
				OR (95% CI)	OR (95% CI)			OR (95% CI)	OR (95% CI)
	Tercile 3					8.70–118.7 (n=90)	13 (14.4)	1.20 (0.51 – 2.84)	1.36 (0.46 – 4.07)

* Adjusted using a modified STS CHSD mortality risk model. Covariates include: age, by month; weight, by kg; STAT mortality category; any prior cardiothoracic operation; any non-cardiac congenital anatomic abnormality; any chromosomal abnormality or syndrome; and any preoperative factor. TRIBE-AKI multi-center cohort did not include any chromosomal abnormality or syndrome in their analysis.