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Novel Biomarkers Improves Prediction of 365-day Readmission after Pediatric Congenital Heart Surgery

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Abstract

Objective: To evaluate the association between preoperative biomarker levels and 365-day readmission or mortality after pediatric congenital heart surgery.

Methods: Children aged 18 years or younger undergoing congenital heart surgery (n=145) at Johns Hopkins Hospital from 2010–2014 were enrolled in the prospective cohort. Novel biomarkers ST2, Galectin-3, NT-proBNP, and GFAP were measured. The composite study endpoint was unplanned readmission within 365 days following discharge or mortality either in-hospital during the surgical admission or within 365 days after discharge. A clinical model based on covariates used in the STS Congenital Heart Surgery Database Mortality Risk Model and an

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Classifications: pediatric congenital heart disease; biomarkers; prediction; readmission

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augmented model using the clinical model in conjunction with a novel biomarker panel were evaluated.

Results: Readmission or mortality within 365-days of surgery occurred among 39 (27%) pediatric patients. The clinical model alone resulted in a c-statistic of 0.719 (95% CI:0.63 – 0.81). The clinical model in conjunction with the log-transformed biomarkers improved the c-statistic to 0.805 (95% CI:0.73 – 0.88). The addition of biomarkers resulted in a significant improvement to the clinical model alone (p value: 0.035).

Conclusions: Novel biomarkers may add predictive value when assessing the likelihood of 365-day readmission or mortality after pediatric congenital heart surgery. After adjusting for clinical and novel biomarkers, pre- and post-operative ST2 remained associated with 365-day readmission or mortality. The current STS clinical congenital mortality risk model can be applied to identify children with increased risk of repeat hospitalizations and post-discharge mortality and may inform preventative care interventions that aim to reduce these adverse events.

Classifications:

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INTRODUCTION

Readmission after operations for congenital heart conditions has significant implications for patient care. Readmission rates for congenital heart surgery vary between 8.7% and 15%.[1, 2] Outcomes after operations for congenital cardiac conditions have improved significantly in terms of mortality over the past two decades. The most recent mortality rate for all congenital heart surgical procedures is 3.5%.[3] In recent years, focus has started to center on improvement in quality of care, which encompasses morbidity and readmissions.[4] Beyond their financial impact, readmissions may further increase the psychosocial burdens, financial distress, and overall life disruption for pediatric patients and their families.[5–7]

Novel biomarkers, such as ST2 and galectin-3, may have potential use either alone or as part of a multi-marker strategy to predict readmissions. ST2, a member of the interleukin-1 receptor family, has been linked to the development of cardiac fibrosis, hypertrophy, and ventricular dysfunction and has emerged as a novel cardiovascular biomarker.[8, 9] Galectin-3 plays a central regulatory role in several biological and pathological disease processes. Both ST2 and galectin-3 have been demonstrated to independently predict death in HF.[10, 11] Other biomarkers that may improve risk prediction include N-terminal prohormone brain natriuretic peptide (NT-proBNP) and Glial fibrillary acidic protein (GFAP). In the adult population, NT-proBNP is a well-established marker of long-term mortality in patients with stable coronary disease and provides prognostic information beyond conventional cardiovascular risk factors.[12] Recent studies have identified GFAP as an early marker of brain injury among children undergoing surgery for congenital heart defects.[13–15]

To reduce unplanned readmission, prediction models have been developed to aid clinicians in identifying those at greatest risk of adverse events.[16] However there has been little

emphasis on prediction of readmission following congenital heart surgery in children, particularly with assessment of biomarkers compare to clinical models alone.[17, 18] The goal of this study was to evaluate the relationship between novel cardiac biomarkers and one-year unplanned hospital readmission or death among children undergoing congenital heart surgery.

PATIENTS AND METHODS

This is a single center prospective longitudinal cohort of 244 consecutive patients who underwent at least one congenital cardiac operation, with cardiopulmonary bypass, at Johns Hopkins Children's Center from 2010 to 2014. Patient, procedural, and outcome data were collected. The cohort was limited to children with biomarker information collected in association with the initial congenital heart surgery operation for each admission (index operation; N = 174). We excluded children with unknown prematurity status, patients weighing 2.5 kg or less, and patients that were aged > 18 years old. We restricted our cohort to patients who had at least one preoperative and one post-operative biomarker measurement (N=162). We restricted our cohort to those who had unplanned readmissions (N=145). Unplanned readmissions were independently adjudicated by two pediatric cardiologists. The Committee for the Protection of Human Subjects at Dartmouth College (Institutional Review Board) approved this study for the prospective cohort with patient/parental consent.

Biomarker Sample Collection

Pre and postoperative cardiac biomarkers ST2, Galectin-3, NT-proBNP and GFAP were the main exposures of interest in this study. 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 commercial antibodies and calibrators (R&D Systems).

Main Outcome

The composite study endpoint is unplanned readmission within 365 days following discharge or mortality either in-hospital during the surgical admission or within 365 days following discharge from the surgical admission. Readmissions were defined as the first unplanned admission within 365 days of an index hospitalization.

Readmission status and all-cause mortality data were obtained for each child by linking to state all-payers claims data, hospital chart review, and the National Death Index using Social Security numbers and date of birth.

Statistical Analysis

Patient, clinical and procedural characteristics were compared with 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-tests or Wilcoxon ranksum tests.

Multivariate logistic regression and the area under the receiver operating characteristics curve (AUROC), were utilized to explore variables to be included in the models. The two models were evaluated via AUROC, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) analyses. The discriminating ability of the regression model was determined by the AUROC and bootstrap to calculate 95% CI's around the ROC-curve.

Data from the Congenital Heart Surgery Admission

Adjustment was carried out using the Society of Thoracic Surgeons Congenital Heart Surgery Database Mortality Risk Model (STS-CHSD).[19] Risk factors in the model include age (days) 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 category[20], and presence of any clinical preoperative risk factors.[21, 22] 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.[19] 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. Detailed congenital heart surgery admission information was available in all participants.

RESULTS

Patient, clinical, and procedural characteristics by one-year readmission or mortality status can be viewed in Table 1. Among those who were readmitted, the most common procedures were complete AVC repair (4, 10%) and pulmonary valve replacement (4, 10%). In our cohort, the most common procedures were ventricular septal defect repair (17, 12%) and complete atrioventricular canal repair (10, 7%).

Biomarker panel with primary composite endpoint

In the Hopkins cohort, 39 (27%) experience the composite endpoint of mortality (N=6) or unplanned readmission (N=33) within 365-days from discharge. Children who were readmitted or died within one-year were younger, weighed less than children who were not readmitted or died, had a significantly higher likelihood of having a preoperative factor or complication and having a higher STAT score. Pre-and postoperative biomarker levels and association with readmission or mortality are listed in Table 2.

Among those who were readmitted, the average time to the first readmission was 54 days (range 2 – 313 days). The most common reasons for unplanned readmissions were respiratory and gastrointestinal complications.

The association of biomarkers and readmission or mortality are described in Table 3. We observed 2.65-greater odds of experiencing 365-day hospital readmission or mortality with

each additional unit increase in preoperative log-transformed ST2 (unadjusted OR: 2.65; 95% CI: 1.72 – 4.07) and 3.24-greater odds with postoperative log-transformed ST2 (unadjusted OR: 3.24; 95% CI: 1.45 – 3.95). After adjustment, there was 2.14-greater odds of readmission or mortality with each additional unit increase in preoperative log-transformed ST2 (adjusted OR: 2.14; 95% CI: 1.94 – 4.88) and 1.49-greater odds with postoperative log-transformed ST2 (adjusted OR: 1.49; 95% CI: 1.45 – 3.38). Additionally, we observed a significant association of unadjusted preoperative log-transformed Galectin-3 and a 2-fold increase in risk of 365-day readmission or mortality. All other biomarkers, measured pre and postoperatively, were not significantly associated with our composite endpoint.

Figure 1 illustrates the added statistically significant predictive value of pre and post-operative log-transformed biomarker panel plus the STS-CHSD clinical model (AUROC of 0.805; 95% CI: 0.73 – 0.88) compared to the clinical model alone (AUROC: 0.719; 95% CI: 0.63 – 0.81; $p = 0.036$). This finding suggests the biomarkers significantly improve the ability to discriminate between children with and without readmission or mortality at 365-days. The added predictive value of preoperative and postoperative biomarkers was supported by a NRI 0.127 (p -value: 0.316), and IDI 0.052 (p -value: 0.007) results.

COMMENT

This is the first study to examine the relationship between pre- and post-operative levels of these novel biomarkers and 365-day readmission and/or mortality after pediatric congenital heart surgery. The addition of novel and clinically available biomarkers resulted in a statistically significant improvement in the performance of our prediction model from an AUROC of 0.719 to AUROC 0.805 ($p=0.036$)

In this single-center, prospective study of pediatric patients undergoing congenital heart surgery, we found that unadjusted preoperative ST2 and Galectin-3 were strong and significant predictors of readmission and/or mortality. With each unit increase in preoperative log-transformed values of ST2 and Galectin-3, the risk of 365-day readmission and/or mortality increased by over 2-fold. We also found that unadjusted postoperative ST2 has prognostic utility in estimating risk of readmission or mortality. With each unit increase in log-transformed values of ST2, the risk of 365-day readmission and/or mortality increased by over 3-fold.

After adjusting for clinical characteristics, pre-and postoperative ST2 remained significantly associated with 365-day readmission. Soluble ST2 is a member of the interleukin-1 (IL-1) receptor family of proteins, which play an important role in the regulation of immune and inflammatory response in the body.[8, 9, 23] In the heart, ST2 has a biological role in the immunological process and is directly involved in a cardiac signaling pathway. Elevated levels of ST2 have been associated with myocardial infarction and volume overloaded hearts and may have a direct, adverse effect on kidney function.^{18,19, 50} Soluble ST2 is an emerging biomarker that has been shown to predict adverse outcomes and death in adults with established heart failure.[24]

Although NT-proBNP is a well-established adult cardiac biomarker, it was not associated with 365-day unplanned readmission or death in this study.[12] This is a meaningful finding as the biomarker function of estimating postoperative risk in adults may not be directly applicable in the pediatric population. This could be due to heart structural differences, growth and development influence on biomarker assessment, and differences in the pathogenesis of diseases.

Recent studies have identified GFAP as an early marker of brain injury among children undergoing surgery for congenital heart defects. Although related to many important poor outcomes[15, 25], it might not be associated with pediatric unplanned readmission or mortality.

There is an increasing focus to identify children at greater risk of readmission following congenital heart surgery.[3, 26–29] An improved understanding of a child's estimated risk of readmission or mortality can be valuable when determining the appropriate timing of surgery, surgical alternatives, or customized hospital discharge instructions. Kogon and colleagues identified preoperative failure to thrive, postoperative length of stay and ethnicity as significant predictors of readmission[4]. Others reported arrhythmia, post-pericardiotomy syndrome, and infectious complications were the most common readmission diagnoses,[30] or found infectious complications to be a common readmission diagnosis in children who had previously undergone Norwood palliation for hypoplastic left heart syndrome[31]. The most common variables used to determine the risk of adverse outcomes following pediatric congenital heart surgery are based on the estimated risk of mortality following surgery, as defined by STS-CHSD. In addition to clinical data, our study demonstrates adding a multi-marker panel to pediatric congenital heart disease risk models can significantly improve prediction of readmission and mortality.

Limitations

There are several important limitations to our study. We initially applied covariates from the contemporary version of the STS-CHSD mortality risk model in our risk adjustment.[19, 32] Due to the limited number of events in our cohort, we were unable to adjust for all covariates in the STS-CHSD model. We aggregated preoperative clinical factors (mechanical circulatory support, persistent shock at time of operation, renal dysfunction requiring dialysis, mechanical ventilation to treat cardiorespiratory failure, and preoperative neurological deficit). Second, the occurrence of our composite endpoint was dominated by readmission, which occurred more frequently than mortality. Third, we included only patients for whom both pre-and post-operative samples had been collected. It is possible that this approach may lead to sampling bias if biomarker collection was associated with congenital heart disease severity. Fourth, we only counted same-center readmissions in our analysis. It is possible that we have undercounted total readmissions. Finally, this is single center prospective study where the study population could be more homogeneous than a multi-center study.

Future research

Our novel research demonstrates cardiac biomarkers should be used to improve risk stratification for readmission or mortality following congenital heart surgery. We recommend surgical teams include the clinical variables and biomarkers available to them in the model to identify the risk of readmission or death for each patient prior to discharge. Improved readmission risk models can provide surgeons, caregivers, and primary care providers a transitional care plan that is tailored to each individual patient to mitigate major adverse events and readmission. To do so, we should bring together collaborations of biorepositories in congenital heart surgery to evaluate new biomarker candidates for predicting readmission and mortality with external validation.

CONCLUSIONS

Our findings suggest that novel cardiac biomarkers can be used to identify children at increased risk of readmission or mortality after pediatric congenital heart surgery. These findings may inform preventative care interventions that aim to reduce these adverse events. Clinical application of novel biomarkers is valuable when determining the appropriate timing of surgery, surgical alternatives, operative care strategies, discharge protocols and follow-up care. Exploration of other biomarkers that signal survival or readmission prediction, along with multiple post-operative measurement periods, is warranted.

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Figure 1.
AUROC curve for the clinical risk model with and without pre-and postoperative log-transformed biomarkers

Table 1.

Patient characteristics

Risk Factors	N = (145)	No readmission or mortality N = 106(%)	Readmission or mortality N = 39 (%)	p value
Age group				
Neonates	13	9 (69.2)	4 (30.8)	0.042
Infants	52	32 (61.5)	20 (38.5)	
Children	80	65 (81.3)	15 (18.7)	
Age, by month (median, IQR)		34.8 (5.2, 80.6)	7.4(4.1,48.7)	0.107
Gender				
Female	54	36 (66.7)	18 (33.3)	0.178
Male	91	70 (76.9)	21 (23.1)	
Weight				
>10 th percentile	130	101 (77.7)	29 (22.3)	0.026
<10 th percentile	15	5 (33.3)	10 (66.7)	
Weight, by kg (median, IQR)		12.3(6,21)	7.5(5.2, 16.1)	0.147
Prematurity among neonates and infants				
No	127	93 (73.2)	34 (26.8)	0.928
Yes	18	13 (72.2)	5 (27.8)	
STAT Level				
1	60	52 (88.7)	8 (13.3)	0.010
2	37	24 (64.9)	13 (35.1)	
3	22	16(72.7)	6 (27.3)	
4	16	7 (43.8)	9 (56.2)	
5	8	5 (62.5)	3 (37.5)	
Missing	2	2 (100.0)	0 (0.0)	
Prior cardiothoracic operation				
No	133	98 (73.7)	35 (26,3)	0.600
Yes	12	8 (66.7)	4 (33.3)	
Any non cardiac congenital anatomic abnormality				
No	125	93 (74.4)	32 (25.6)	0.379
Yes	20	13 (65.0)	7 (35.0)	
Chromosomal abnormality or syndrome				
No	104	78 (75.0)	26 (25.0)	0.412
Yes	41	28 (68.3)	13 (31.7)	
Any preoperative factor				
No	124	93 (75.0)	31 (25.0)	0.211
Yes	21	13 (61.9)	8 (38.1)	
Cardiopulmonary bypass time, in		123.4 (73.9)	168.3 (84.2)	0.002

Risk Factors	N = (145)	No readmission or mortality N = 106(%)	Readmission or mortality N = 39 (%)	p value
minutes (mean, SD)				
Cross clamp time, in minutes (mean, SD)		66.7 (54.3)	88.7 (71.4)	0.052

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Table 2.

Pre-and postoperative biomarker means and ranges

Preoperative biomarker	Median and IQR (ng/mL)
ST2	2.12 (1.30, 3.86)
Galectin-3	15.75 (9.00, 20.15)
NT-proBNP	0.44 (0.20, 1.87)
GFAP	0.001 (0.00, 0.01)
Postoperative biomarker	
ST2	3.47 (1.98, 5.91)
Galectin-3	23.34 (14.35, 37.16)
NT-proBNP	0.45 (0.17, 1.38)
GFAP	0.073 (0.01, 0.18)

sST2: Soluble suppression of tumorigenicity 2, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, GFAP: Glial fibrillary acidic protein,

IQR: Interquartile range, ng/mL: nanogram/milliliter

Table 3.

Pre-and postoperative biomarker panel to predict 365-day readmission or mortality after pediatric congenital heart surgery

Risk factor	Unadjusted OR (95% CI)	Clinical model OR (95% CI)	Clinical model + Biomarker model OR (95% CI)
Age, in days	1.00 (0.99, 1.00)	0.99 (0.99 – 1.00)	0.99 (0.99 – 1.00)
Weight, in kg	1.02 (1.01, 1.04)	1.02 (0.98 – 1.06)	1.01 (0.97 – 1.06)
STAT category			
1	REF	REF	
2	3.52 (1.29 – 9.62) *	3.63 (1.24 – 10.64) *	3.69 (1.09 – 12.50) *
3	2.44 (0.74 – 8.07)	2.15 (0.59 – 7.86)	2.61 (0.57 – 11.94)
4	3.90 (0.78 – 19.58) *	3.34 (0.62 – 18.14) *	2.73 (0.34 – 21.75)
5	8.36 (2.43 – 28.79) *	7.44 (2.06 – 26.92) *	5.01 (1.04 – 24.12) *
Any prior operation	1.40 (0.40 – 4.94)	1.98 (0.22 – 4.38)	0.63 (0.09 – 4.48)
Any non-cardiac congenital anatomic abnormality	1.56 (0.57 – 4.27)	1.14 (0.38 – 3.43)	1.29 (0.36 – 4.64)
Chromosomal abnormality or syndrome	1.39 (0.63 – 3.08)	1.21 (0.49 – 2.97)	1.14 (0.41 – 3.17)
Any preoperative factor	1.85 (0.70 – 4.87) *	1.55 (0.50 – 4.86)	1.08 (0.28 – 4.20)
Preoperative log-transformed biomarkers			
ST2	2.65 (1.35 – 2.95) *		2.14 (1.94 – 4.88) *
Galectin-3	2.04 (1.08 – 2.86) *		1.79 (0.81 – 3.93)
GFAP	0.96 (0.92 – 1.01)		0.98 (0.91 – 1.04)
NT-proBNP	1.18 (0.98 – 1.43)		0.84 (0.56 – 1.26)
Postoperative log-transformed biomarkers			
ST2	3.24 (1.45 – 3.95) *		1.49 (1.45 – 3.38) *
Galectin-3	1.47 (0.87 – 2.49)		0.77 (0.30 – 1.94)
GFAP	1.01 (0.95 – 1.06)		1.02 (0.95 – 1.12)
NT-proBNP	1.22 (1.00 – 1.50)		1.05 (0.65 – 1.39)

OR: Odds ratio, CI: Confidence Interval, REF: Reference category, STS: Society of Thoracic Surgeons, AUC: Area under the curve, STAT: The Society of Thoracic Surgeons—European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Categories, sST2: Soluble suppression of tumorigenicity 2, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, GFAP: Glial fibrillary acidic protein

* P-value < 0.05