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Cardiac biomarkers associated with hospital length of stay after pediatric congenital heart surgery

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Abstract

Background: Prolonged hospital length of stay after congenital heart surgery is a significant cost burden and associated with post-operative morbidity. Our goal was to evaluate the association between pre- and post-operative biomarker levels and in-hospital length of stay for children after congenital heart surgery.

Methods: We enrolled patients <18 years of age who underwent at least 1 congenital heart operation at Johns Hopkins Hospital from 2010–2014. Blood samples were collected before the index operation and at the end of the bypass. ST2 and NT-proBNP measurements were evaluated as log-transformed, median and tercile cutpoints. We evaluated the association between pre- and postoperative NT-proBNP and ST2 measurements with in-hospital postoperative length of stay using multivariate logistic regression. We adjusted for covariates used in the Society of Thoracic Surgeons Congenital Heart Surgery Mortality Risk Model.

Results: In our cohort, 45% of our patients had an in-hospital postoperative length of stay longer than the median. Before adjustment, preoperative NT-proBNP above the population median and the highest tercile exhibited a significantly longer in-hospital length of stay. After adjustment for covariates in the risk model, pre- and post-operative ST2 and NT-proBNP demonstrated a significantly longer length of stay.

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Conclusions: Peri-operative ST2 and NT-proBNP had a significant association with increased postoperative in-hospital length of stay before and after adjustment. ST2 in particular could be used to guide an earlier assessment of patient risk for complications which may lead to adverse outcomes.

Keywords

pediatric congenital heart disease; biomarkers; prediction; outcomes; postoperative care

Approximately one-quarter of the 40,000 children born with congenital heart disease (CHD) annually in the United States require intervention in their first year of life[1]. In adults with CHD, a prolonged length of stay is associated with a more complex congenital heart repair[2]. At hospitals which performed <10 pediatric congenital heart operations annually, there is significantly longer length of stay than those who performed >10 annually[3]. In the United States, it costs an average of $79,011 for these postoperative stays, and CHD has the highest total cost of birth defect categories evaluated by the Centers for Disease Control and Prevention[4]. Prolonged postoperative hospital stay can place significant financial pressure on a household and the health care system[5]. Estimating risk factors associated with prolonged in-hospital length of stay is critical to tailoring interventions for children to improve their quality of care and for reducing the cost of surgery[6]. Longer in-hospital stays after operations can be attributed to reasons such as complications during surgery, additional time needed for screening/surveillance, social/family considerations, or an increased risk of morbidity or mortality after discharge[7].

Recent research suggests that cardiac biomarkers play a role in the prediction of adverse outcomes of congenital heart operations[8]. The FDA approved cardiac biomarkers N-terminal pro-brain natriuretic peptide (NT-proBNP) and ST2 are widely recognized as having prognostic utility in adult heart failure evaluation, yet the clinical application in pediatric cardiac surgery is not well understood. Preliminary evidence suggests that cardiac biomarkers can help identify pediatric patients at high risk for longer postoperative length of stay following congenital heart surgery.

ST2 is a member of the Interleukin 1 (IL-1) receptor family and plays a significant role in the inflammatory and autoimmune responses that take place within the body[9,10]. Specifically, in the heart, ST2 expression is induced in both cardiac myocytes and fibroblasts by biomechanical strain injury or angiotensin. Therefore, elevated levels of ST2 present as a response to myocardial stress, such as myocardial ischemia, neurohormonal activation or mechanical overload. NT-proBNP is a biomarker released from the myocytes as a reaction to cardiac chamber dilation, wall stress, or pressure overload[11]. In adults, NT-proBNP is a significant 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[12].

The relative utility of ST2 and NT-proBNP in predicting prolonged length of stay after pediatric congenital heart surgery has not been investigated. We sought to evaluate the novel clinical utility of biomarkers to identify children with an increased risk of a longer in-hospital stay after pediatric congenital heart surgery.

Patients and Methods

Pediatric Cohort

We performed a retrospective analysis of a prospective cohort study 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 was collected. The cohort was limited to patients with biomarker information collected in association with the initial cardiac operation for each admission (index operation; N = 174). We excluded patients with unknown prematurity status, patients weighing 2.5 kg or less, and patients age 18 years or older. We restricted our cohort to patients who had at least one preoperative and one postoperative biomarker measurement (N=162)[8]. The Committee for the Protection of Human Subjects at Dartmouth College and Johns Hopkins University (Institutional Review Board) approved this study for the prospective cohort with parental consent.

Sample Collection

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, Gaithersburg, MD) using commercial antibodies and calibrators (R&D Systems, Minneapolis, MN) as previously described[13,14].

Main Outcome

The outcome variable was postoperative in-hospital length of stay. This stay was measured in days and started the day after the index operation occurred. We elected to evaluate the outcome by dichotomizing length of stay by the median (7 days) for the entire cohort, regardless of surgical severity.

Data Collected from the Index Operation

Multivariable logistic regression analysis was used to assess the association between the preoperative and postoperative continuous, log continuous, median, and tercile cut-points. These analyses were adjusted based on covariates in the Society of Thoracic Surgeons Congenital Heart Surgery Database (STS-CHSD) Mortality Risk Model[6]. Risk factors in the model include age at surgery (in days) at surgery, weight (by kilograms), any prior cardiothoracic operation (yes/no), any non-cardiac congenital anatomic abnormality (yes/no), any chromosomal abnormality or syndrome (yes/no), presence of any clinical preoperative risk factors, operationalized as 5 different count variables listed on the footer of Table 1. Given the limited number of outcome events, we aggregated all preoperative risk factors and dichotomized based on the presence of none or ≥ 1.

Statistical Analysis

Patient, clinical and procedural characteristics were compared by in-hospital length of stay using descriptive statistics. Differences in risk factors were compared using Pearson's chi-square tests; continuous variables were compared with two-sample t-tests. Patients were

arranged by preoperative and postoperative biomarker levels above and below the population median. Similarly, patients were equally distributed into equal sized terciles for each of the biomarkers. Indicator variables were created for each of the terciles and median values.

Results

As shown in Table 1, among those in our cohort, the median age was 281 days (range 2 days-17 years) and the median weight was 8.4kg (range 2.7kg to 106kg). There was a slight male predominance within our cohort (59.9% to 40.1%). The minority of our cohort had at least one preoperative risk factor (N=26), while the majority of our cohort had a prior cardiovascular operation (N=129). The median length of stay after congenital heart surgery was 7 days with a range of 3–148 days.

Preoperative and Postoperative ST2 and In-hospital Length of Stay

Before adjustment, preoperative ST2 values above the median and the highest tercile were significantly associated with longer in-hospital length of stay after heart surgery (OR: 4.56; 95% CI: 2.34–8.87; OR: 5.17; 95% CI: 2.28–11.73, respectively). After adjustment, ST2 median and tercile values demonstrated a significant relationship with above average length of stay (OR: 3.60; 95% CI: 1.67–7.74; OR: 3.38; 1.32–8.67 (Table 2).

Before adjustment, postoperative ST2 values above the median and the highest tercile were significantly associated with longer in-hospital length of stay after heart surgery (OR: 3.64; 95% CI: 1.89–6.98; OR: 5.64; 95% CI: 2.47–12.88, respectively). After adjustment, there was a lower but still significant risk of an above average length of stay for the median and highest tercile (OR: 2.55; 95% CI: 1.21–5.33; OR: 3.39; 95% CI: 1.31–8.79) (Table 2).

Preoperative and Postoperative NT-Probnp and In-hospital Length of Stay

Before adjustment, preoperative NT-proBNP values above the median and the highest tercile were significantly associated with longer in-hospital length of stay after heart surgery (OR: 2.63; 95% CI: 1.39–4.97; OR: 4.35; 95% CI: 2.47–12.88, respectively). After adjustment, NT-proBNP median and tercile values demonstrated a significant relationship with above average length of stay (OR:1.67; 95% CI: 0.78–3.57; OR: 3.87; 95% CI:1.48–10.10) (Table 2).

Before adjustment, postoperative NT-proBNP values above the median and the highest tercile were significantly associated with above average length of stay after heart surgery (OR: 2.37; 95% CI: 1.26–4.46; OR: 4.35; 95% CI: 1.94–9.75, respectively). After adjustment, there was significant odds of above average stay for the highest pre and postoperative tercile (OR: 3.87; 95% CI: 1.48 – 10.10, OR: 2.90; 95% CI: 1.17–7.17) (Table 2).

Comment

In pre-and postoperative ST2 and NT-proBNP, we found a significant association with increased in-hospital length of stay following congenital heart surgery (Figure 1). This association was determined based on the multivariate logistic regression analysis for the

median and third tercile cutpoints. In postoperative NT-proBNP after adjustment, there was significant odds of longer length of stay for the highest tercile (OR: 2.90; 95% CI: 1.17–7.17) (Table 2). For pre and postoperative ST2, we found a 3.4-times higher odds of a longer in-hospital length of stay (Table 2).

Biomarkers are routinely collected substances that signal a process taking place within an individual[15]. Biomarkers have been used in the past to evaluate 30-day readmission or mortality results after pediatric congenital heart surgery[16]. While ST2 and NT-proBNP have been demonstrated to have prognostic utility in the adult population, the clinical application in pediatric cardiac care is novel.

We have previously analyzed the utility of cardiac biomarkers in predicting a variety of postoperative outcomes following congenital heart surgery. We found that NT-proBNP was not associated with 365-day unplanned readmission or death, but pre- and postoperative ST2 was significantly associated with 365-day unplanned readmission or death[8]. Additionally, we found that pre and post-operative ST2 was associated with unplanned 30-day readmission or death, while NT-proBNP was not useful in predicting 30-day readmission or death[17]. This evaluation of the utility of length of stay provides new insight to our team's guidance on the use of biomarkers, and especially the utility of ST2, using an outcome variable with limited literature surrounding it.

Elevated postoperative NT-proBNP levels have shown to be associated with a longer hospital stay after superior cavopulmonary connection surgery[18]. Changes in body composition occur in children with CHD, and NT-proBNP has been observed as an indicator of myocardial stress for children who do not receive proper nutrition[19] Unlike NT-proBNP, ST2 is not cardiac specific, and has been shown in a noncardiac intensive care unit (ICU) population that high ST2 levels, were associated with a longer ICU and hospital stay[20]. Additionally, among ICU patients, ST2 demonstrated the ability to predict 90-day mortality[20].

Elevated biomarker levels represent the regulation of the inflammatory and autoimmune response in the body[21,22]. Specifically in the heart, ST2 is expressed in both cardiomyocytes and cardiac fibroblasts that induced either by biomechanical strain injury or angiotensin. Elevated levels of ST2 present as a response to myocardial stress, such as myocardial ischemia, neurohormonal activation or mechanical overload[23]. NT-proBNP is a cardiac hormone and sensitive measure of cardiac stretch and has been used in heart failure treatment and to predict outcomes in patients with congenital heart disease and pulmonary hypertension[24]. These elevated biomarker levels signal more cardiac damage following congenital heart surgery, estimating longer in-hospital length of stay.

Prolonged postoperative hospital stays are associated with complex congenital heart operations[2]. In a study of the Children's Healthcare of Atlanta hospital, 70 patients who were readmitted after congenital heart surgery "spent a total of 653 days in the hospital, 205 of which were in the ICU. Total charges generated by these readmission hospital stays were approximately $8 million."[5] This information would assist practitioners in determining the appropriate timing of surgery and assess surgical alternatives. As a result, these cardiac

biomarkers can be useful tools for risk stratification and improved patient care management with a goal of improving postoperative outcomes.

Limitations

This study has a few limitations. First, risk adjustment was initially performed using the covariates from the contemporary version of the STS-CHSD mortality risk model, which is a method of adjusting for clinical and 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, a larger sample size would have improved our power to assess the performance of ST2 and NT-proBNP in the preoperative setting. Third, we included only patients for whom both pre-and post-operative samples had been collected. This approach may lead to sampling bias if biomarker collection was associated with congenital heart disease severity.

Conclusion

We found an association between elevated NT-proBNP and ST2 and an increased risk of longer postoperative hospital length of stay. 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 biomarkers can be useful tools for risk stratification and improved patient care management. More research on the utility of cardiac biomarker levels as an indicator for potential postoperative complications will equip surgeons with information necessary to decrease adverse outcomes.

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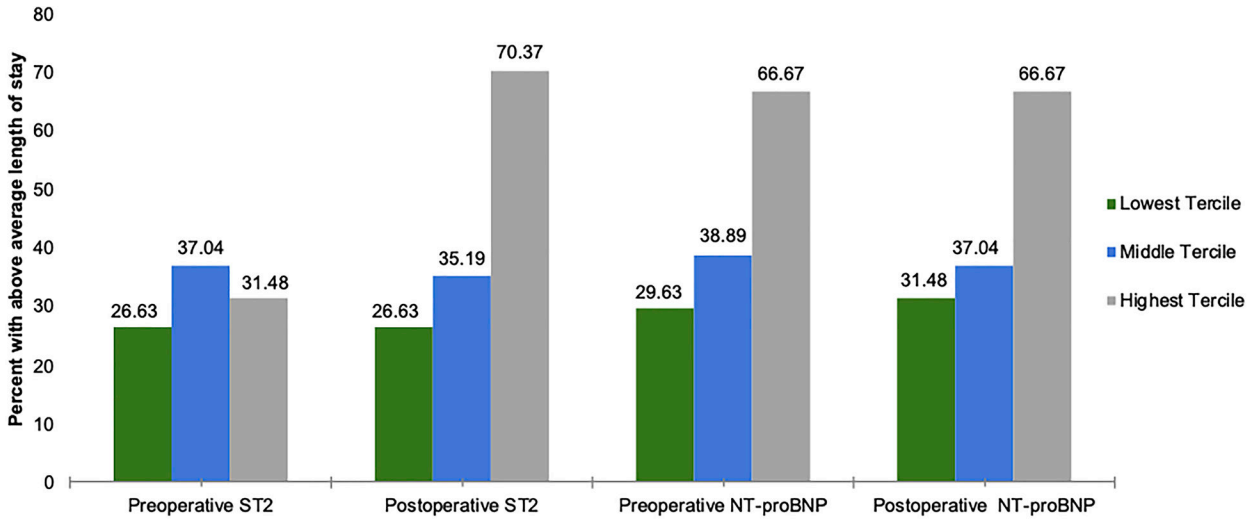

Figure 1:

There is a significant association between pre-and postoperative ST2 and NT-proBNP and above average in-hospital length of stay following congenital heart surgery Before and after adjustments, we observe a stepwise association of above average in hospital length of stay for postoperative ST2 & NT-proBNP as well as preoperative NT-proBNP.

Table 1:

Patient characteristics

Risk Factor	N=162	Length of Stay over 7 days N=73(%)	Length of Stay under 7 days N=89(%)	P-value
Age group				
Neonates	68	28(38.36)	40(44.94)	
Infants	78	31(42.47)	47(52.81)	
Children	16	14(19.18)	2(2.25)	0.002
Age (days)	1477.253	1215.849	1691.663	0.059
Weight (kg)	17.799	14.618	20.409	0.033
Gender				
Male	97	39(53.42)	58(65.17)	
Female	65	34(46.58)	31(34.83)	0.129
Prematurity				
No	141	63(86.30)	78(87.64)	
Yes	21	10(13.70)	11(12.36)	0.801
Stat Level				
1	69	17(23.29)	52(58.43)	
2	43	22(30.14)	21(23.60)	
3	18	11(15.07)	7(7.87)	
4	15	11(15.07)	4(4.49)	
5	10	10(13.70)	0(0)	<0.001
Any prior cardiovascular operation				
Yes	33	24(32.88)	9(10.11)	
No	129	49(67.12)	80(89.89)	<0.001
Any non-cardiac congenital anatomic abnormality				
Yes	21	13(17.81)	8(8.99)	
No	141	60(82.19)	81(91.01)	0.096
Any chromosomal abnormality				
Yes	44	25(34.25)	19(21.35)	
No	118	48(65.75)	70(78.65)	0.066
Any preoperative risk factor				
Yes	26	16(21.92)	10(11.24)	
No	136	57(78.08)	79(88.76)	0.065

Table 2:

Multivariate logistic regression results for a length of stay above median by preoperative or postoperative biomarker measurement.

Unadjusted				*Adjusted	
Biomarker	**Cutpoint**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
NT-proBNP Preoperative	Log continuous	1.48 (1.22–1.80)	<0.001	1.42 (1.13–1.78)	0.002
	Above median vs below (0.039–0.422 ng/mL)	2.63 (1.39–4.97)	0.003	1.67 (0.78–3.57)	0.183
	Tercile 2 (0.251–0.866 ng/mL)	1.51 (0.68–3.36)	0.312	1.41 (0.56–3.58	0.464
	Tercile 3 (0.891–181.58 ng/mL)	4.75 (2.10–10.71)	<0.001	3.87 (1.48–10.10)	0.006
NT-proBNP Postoperative	Log continuous	1.41 (1.17–1.71)	<0.001	1.3 (1.06–1.61)	0.013
	Above median vs below (0.035–0.448 ng/mL)	2.37 (1.26–4.46)	0.008	1.49 (0.71–3.12)	0.287
	Tercile 2 (0.260–0.889 ng/mL	1.28 (0.58–2.84)	0.543	0.97 (0.39–2.40)	0.946
	Tercile 3 (0.937–89.40 ng/mL)	4.35 (1.94–9.75)	<0.001	2.90 (1.17–7.17)	0.021
ST2 Preoperative	Log continuous	2.67 (1.75–4.07)	<0.001	2.36 (1.44–3.85)	<0.001
	Above median vs below (0.451–2.05 ng/mL)	4.56 (2.34–8.87)	<0.001	3.60 (1.67–7.74)	<0.001
	Tercile 2 (1.46–2.34 ng/mL)	1.40 (0.63–3.12)	0.415	1.40 (0.57–3.41)	0.460
	Tercile 3 (2.64–106.32 ng/mL)	5.17 (2.28–11.73)	<0.001	3.38 (1.32–8.67)	0.011
ST2 Postoperative	Log continuous	3.17 (1.95–5.16)	<0.001	2.65 (1.52–4.63)	<0.001
	Above median vs below (0.421–3.29 ng/mL)	3.64 (1.89–6.98)	<0.001	2.55 (1.21–5.33)	0.013
	Tercile 2 (2.45–4.68 ng/mL)	1.29 (0.57–2.89)	0.538	1.26 (0.52–3.05)	0.605
	Tercile 3 (4.73–85.05 ng/mL)	5.64 (2.47–12.88)	<0.001	3.39 (1.31–8.79)	0.012

OR=Odds Ratio CI=Confidence Interval

*Adjusted using a modified version of STS CHSD Mortality Risk Model