Published in final edited form as:

Cardiol Young. 2019 August ; 29(8): 1051–1056. doi:10.1017/S1047951119001471.

Biomarkers Improve Prediction of 30-day Unplanned Readmission or Mortality after Pediatric Congenital Heart Surgery

Jeremiah Brown^{1,2,3}, Meagan E. Stabler², Devin M. Parker¹, Luca Vricella⁴, Sara Pasquali⁵, JoAnna K. Leyenaar^{1,6}, Andrew R. Bohm¹, Todd MacKenzie^{1,3}, Chirag Parikh⁷, Marshall L. Jacobs^{8,9}, Jeffrey P. Jacobs^{8,9}, Allen D. Everett⁹

¹The Dartmouth Institute for Health Policy and Clinical Practice, Geisel School of Medicine, Lebanon, NH

²Department of Epidemiology, Dartmouth Geisel School of Medicine, Hanover, NH

³Department of Biomedical Data Science, Geisel School of Medicine, Hanover, NH

⁴Division of Cardiac Surgery, Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD

⁵Division of Pediatric Cardiology, Department of Pediatrics, C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, MI

⁶Department of Pediatrics, Dartmouth-Hitchcock Medical Center, Lebanon, NH

⁷Division of Nephrology, Department of Medicine, Johns Hopkins University, Baltimore, MD

⁸Division of Cardiovascular Surgery, Department of Surgery Johns Hopkins All Children's Heart Institute, Johns Hopkins All Children's Hospital and Florida Hospital for Children, Saint Petersburg, Tampa, and Orlando, FL

⁹Division of Pediatric Cardiology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD.

Abstract

Objective: To evaluate the association between novel pre-and post-operative biomarker levels and 30-day unplanned readmission or mortality after pediatric congenital heart surgery.

Methods: Children aged 18 years or younger undergoing congenital heart surgery (n=162) , at Johns Hopkins Hospital from 2010–2014 were enrolled in the prospective cohort. Collected novel pre-and postoperative biomarkers include: soluble suppression of tumorigenicity 2, Galectin-3, N-terminal prohormone of brain natriuretic peptide and glial fibrillary acidic protein. A model based on clinical variables from the Society of Thoracic Surgery database was developed and evaluated against two augmented models.

Corresponding Author: Jeremiah R. Brown, PhD, MS, HB 7505 Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756; Ph: 603 653 3576; Fax: 603 653 3554; jbrown@dartmouth.edu.

Reprint request author: Jeremiah R. Brown

Conflicts of Interest: None.

Results: Unplanned readmission or mortality within 30-days of cardiac surgery occurred among 21 (13%) children. The clinical model augmented with pre-operative biomarkers demonstrated a statistically significant improvement over the clinical model alone with an receiver operating characteristics curve to 0.754 (95% CI:0.65 – 0.86) compared to 0.617 (95% CI: 0.47 – 0.76; p-value 0.012). The clinical model augmented with pre-and postoperative biomarkers demonstrated a significant improvement over the clinical model alone, with an receiver operating characteristics curve of 0.802 (95% CI: 0.72 – 0.89; p-value 0.003).

Conclusions: Novel biomarkers add significant predictive value when assessing the likelihood of unplanned readmission or mortality after pediatric congenital heart surgery. Further exploration of the utility of these novel biomarkers during the peri- or post-operative period to identify early risk of mortality or readmission will aid in determining the clinical utility and application of these biomarkers into routine risk assessment.

Keywords

pediatric congenital heart disease; biomarkers; prediction; readmission

Introduction

Among children undergoing pediatric congenital heart surgery, 10%–20% experience 30-day unplanned hospital readmission and 4% of surgeries result in death.^{1–4} Repeat hospitalizations among children place an emotional and financial burden on the patient's family, as well a strain on the health care system.⁵ To reduce unplanned readmission and mortality, prediction models have been developed to aid clinicians in identifying those at greatest risk of adverse events.⁶ However there has been little emphasis on prediction of readmission or mortality following congenital heart surgery in children, particularly with assessment of biomarkers compare to clinical models alone.^{7,8}

Two well-established biomarkers in the adult heart failure literature are soluble suppression of tumorigenicity 2 and n-terminal prohormone of brain natriuretic peptide.⁹ Emerging data has supported the use of these biomarkers for diagnostic and monitoring for pediatric heart disease.¹⁰ A pediatric heart transplant study found elevated soluble suppression of tumorigenicity 2 levels predicted episodes of acute rejection.¹¹ Others have reported elevated soluble suppression of tumorigenicity 2 and n-terminal prohormone of brain natriuretic peptide levels predicted poor functional characteristics and clinical outcomes among pediatric patients with idiopathic or heritable pulmonary arterial hypertension.¹²

Other biomarkers that may have additive predictive value include proteins galectin-3 and glial fibrillary acidic protein.^{13,14} In adults, elevated galectin-3 was associated with an increased risk of cardiovascular-related hospitalization or death.¹⁵ Recent studies have identified glial fibrillary acidic protein as an early marker of brain injury among children undergoing surgery for congenital heart defects.^{16–18}

Although these biomarkers are established in the adult population, research highlighting the ability of these biomarkers to predict readmission or mortality among children undergoing congenital heart surgery is limited. Therefore, the purpose of this study was to evaluate

added predictive ability novel biomarkers against clinical risk factors alone and 30-day unplanned readmission or mortality after pediatric congenital heart surgery.

Methods

The current study analyses a prospective cohort of pediatric patients who underwent congenital heart surgery at Johns Hopkins Hospital between 2010 to 2014 (n=244). Children were excluded if they were >18 years of age (n=9), weighted 2.5 kg or less at the time of birth (n=1), had an unknown prematurity status (n=2), or did not have preoperative biomarkers collected (n=70). The final cohort consisted of 162 pediatric congenital heart surgery patients (Figure 1).

Patient, clinical, and outcome data were collected using a software platform that is approved by The Society of Thoracic Surgeons as being suitable for submission of data to the Society of Thoracic Surgeons Congenital Heart Surgery Database. Blood samples were collected immediately prior to surgery and at the end of bypass. Biomarkers were measured using Meso Scale Discovery as previously described.^{16,19–25} Institutional Review Board approved this study for the prospective cohort with child/parental consent.

Outcome

The composite study endpoint was unplanned readmission or mortality within 30 days following discharge from the index surgical admission and verified via data linkage between state all-payers claims data, chart review, and the National Death Index using Social Security numbers and date of birth. Mortality included in-hospital mortality during the index surgical admission or mortality within 30 days after discharge from the surgical admission. Readmissions were defined as the first unplanned admission within 30 days of an index hospitalization where the congenital heart surgery occurred.

Predictive models

We developed three predictive models. The first was a clinical risk model adapted from the Society of Thoracic Surgeons Congenital Heart Surgery Database mortality risk model.²⁶ A backwards stepwise regression model included cardiopulmonary bypass time, any preoperative risk factor, STAT mortality category, prior cardiothoracic operation and any major complication. The second model was an augmented clinical risk model with the addition of preoperative Galectin-3, soluble suppression of tumorigenicity 2, N-terminal prohormone of brain natriuretic peptide, and glial fibrillary acidic protein. The third model was an augmented clinical risk model with the addition of a pre-and postoperative galectin-3, soluble suppression of tumorigenicity 2, N-terminal prohormone of brain natriuretic peptide and glial fibrillary acidic protein. Biomarker ranges are outlined in Table 1.

Statistical Analysis

Descriptive statistics and univariate analyses were used to describe the sample and compare patient and clinical characteristics by 30-day readmission or mortality. Multivariate logistic regression and the area under the receiver operating characteristics curve,^{27,28} were utilized

to explore variables to be included in the models. The two models were evaluated via area under the receiver operating characteristics curve, net reclassification improvement and integrated discrimination improvement analyses.^{29,30} The discriminating ability of the regression model was determined by the area under the receiver operating characteristics curve and bootstrap to calculate 95% confidence interval's around the receiver operating characteristics curves.^{31,32} See online supplement for detailed methods.

Results

There were 162 pediatric patients included in this study (Table 2), 8.6% (n= 14) were neonates, 42.0% (n=68) were infants and 49.4% (n=80) were children aged 1–18 years old. Unplanned readmission or mortality at 30-days occurred in 21 children and had a significantly higher likelihood of having a prior cardio-thoracic operation, any pre-operative factor, and higher STAT category (Table 2).

The association of biomarkers and readmission or mortality are described in Table 3. The odds of experiencing 30-day hospital readmission or mortality increased by 66% with each additional unit increase in preoperative log-transformed soluble suppression of tumorigenicity 2 (unadjusted odds ratio 1.66, 95% confidence interval 1.16 – 2.37). After adjusting for covariates based on the Society of Thoracic Surgeons mortality risk model, the odds of readmission or mortality increased by 85% with each additional unit increase in preoperative log-transformed soluble suppression of tumorigenicity 2 (adjusted odds ratio 1.85, 95% confidence interval 1.02 – 3.36).

Figure 2 illustrates the added statistically significant predictive value of preoperative log-transformed biomarker model (receiver operating characteristics curve of 0.754; 95% confidence interval: 0.65 – 0.86) compared to the clinical model alone (receiver operating characteristics curve: 0.617; 95% confidence interval 0.47 – 0.76; $p = 0.012$). This finding suggests the biomarkers significantly improve the ability to discriminate between children with and without readmission or mortality at 30-days. The added predictive value of preoperative biomarkers was supported by a net reclassification improvement 0.056 (p -value: 0.648), and integrated discrimination improvement 0.0571 (p -value: 0.007) results.

Figure 3 illustrates the added predictive value of pre- and post-operative log-transformed biomarkers with an area under the receiver operating characteristics curve of 0.802 (95%CI: 0.72 – 0.89) compared to the clinical model alone ($p=0.003$), demonstrating inclusion of both pre- and post-operative biomarker further improve discrimination between children with and without 30-day readmission or mortality. The added predictive value of pre- and postoperative biomarkers resulted in a net reclassification improvement 0.097 (p -value: 0.467), and integrated discrimination improvement 0.082 (p -value: <0.001).

Discussion

We are the first to report that biomarkers have the potential to improve risk prediction for 30-day readmission or mortality following pediatric congenital heart surgery. The addition of novel and clinically available biomarkers resulted in a statistically significant

improvement in the performance of predictive models from receiver operating characteristics curve value of 0.617 to 0.802 ($p=0.003$).

Pre-and postoperative log-transformed soluble suppression of tumorigenicity 2 and Galectin-3 were associated with 30-day unplanned readmission or mortality after pediatric congenital heart surgery. After adjusting for clinical characteristics and the novel preoperative biomarker panel, preoperative soluble suppression of tumorigenicity 2 remained significantly associated with 30-day readmission or mortality. Therefore, preoperative soluble suppression of tumorigenicity 2 values may be used to improve preemptive identification of children at greatest risk of 30-day hospital readmission or mortality following congenital heart surgery. An improved understanding of a child's statistically estimated risk of readmission or mortality can be helpful when determining the appropriate timing of surgery, surgical alternatives, tailored operative care or hospital discharge approaches.

Soluble suppression of tumorigenicity 2 and Galectin-3 are cardiac biomarkers indicative of myocardial fibrosis and remodeling.³³ These are well-established biomarkers in the adult heart failure literature that have shown to be predictive of hospitalization and mortality.^{34–36} However, research to support the pediatric application of soluble suppression of tumorigenicity 2 and galectin-3 is limited. Soluble suppression of tumorigenicity 2 has been linked with acute rejection after pediatric heart transplantation patients, as well as functional class among pediatric patients with idiopathic or primary pulmonary hypertension.^{11,12} Determination of normative soluble suppression of tumorigenicity 2 levels for children with congenital heart disease, as well as patient and clinical care factors responsible for soluble suppression of tumorigenicity 2 elevations are needed. Mohammed and colleagues found elevated galectin-3 levels to be associated with the presence of heart failure in children with congenital heart disease.³⁷ Galectin-3 levels have also been shown to differ between Ross heart failure classes as well as ventricular size and function.³⁷ A greater understanding of the role of galectin-3 among children who underwent pediatric congenital heart surgery is needed.

Although N-terminal prohormone of brain natriuretic peptide is a well-established adult cardiac biomarker, it was not associated with 30-day unplanned readmission or death in this study. This is an important finding as the use of biomarkers for the assessment and management of morbidity in adults might not translate directly to children. This could be due to heart structural differences, growth and development influence on biomarker assessment, and differences in the pathogenesis of diseases.³⁸ Although N-terminal prohormone of brain natriuretic peptide has been shown to be associated with pediatric diagnosis of congenital heart disease and more complex cardiac defects, less is known about N-terminal prohormone of brain natriuretic peptide with unplanned repeat hospitalizations.^{39,40} In contrast, glial fibrillary acidic protein has been shown to be beneficial in identifying and monitoring brain injury during cardiac surgery.¹⁶ Although related to many important poor outcomes^{15,18}, it might not be, as indicated from the current study, associated with pediatric unplanned readmission or mortality.

There are increasing efforts to identify children at increased risk of readmission following congenital heart surgery.^{41–45} Kogon and colleagues identified ethnicity, preoperative failure to thrive and postoperative length of stay as significant predictors of readmission². Others reported arrhythmia, post-pericardiotomy syndrome, and infectious complications were the most common readmission diagnoses,⁴⁶ or found infectious complications to be a common readmission diagnosis in children who had previously undergone Norwood palliation for hypoplastic left heart syndrome⁴⁷. 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 Society of Thoracic Surgeons Congenital Heart Surgery Database mortality risk model. In addition to clinical data, our study demonstrates adding biomarkers to pediatric congenital heart disease risk models significantly improve predict of readmission and mortality.

There are several limitations to consider. We initially applied covariates from the contemporary version of the Society of Thoracic Surgeons Congenital Heart Surgery Database mortality risk model in our risk adjustment.^{26,48} Due to the limited number of events in our cohort, we were unable to adjust for all covariates and elected to perform a backwards stepwise regression model informed by the Society of Thoracic Surgeons Congenital Heart Surgery Database mortality risk model. Second, the occurrence of our composite endpoint was dominated by readmission, which occurred more frequently than mortality. The relatively small proportion of patients with our combined endpoint after congenital heart surgery may have obscured some of the statistical associations between the biomarkers and our model covariates. In addition, a larger sample size would have improved our power to assess the performance of the biomarkers in the preoperative setting. 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. Finally, this is single center prospective study where the study population could be more homogeneous than a multi-center study.

Our findings indicate that these biomarkers can be used for early identification of children at increased risk of readmission or death after pediatric congenital heart surgery. The addition of biomarkers significantly improve discrimination of a clinical model to predict readmission or mortality following pediatric congenital heart surgery. Clinical application of novel biomarkers may be helpful when determining the appropriate timing of surgery, surgical alternatives, operative care approaches, and/or readiness for hospital discharge. In addition to these clinical applications, our findings can inform future research determining patient and clinical care factors responsible for elevated levels of cardiac biomarkers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Financial Support: This research is supported by the National Heart Lung and Blood Institute R01HL119664 (PI: Brown). All authors are research staff or investigators on the grant.

References

1. Yang Q, Chen H, Correa A, Devine O, Mathews TJ, Honein MA. Racial differences in infant mortality attributable to birth defects in the United States, 1989–2002. Birth defects research Part A, Clinical and molecular teratology. 2006;76(10):706–713. [PubMed: 17022030]
2. Kogon B, Jain A, Oster M, Woodall K, Kanter K, Kirshbom P. Risk factors associated with readmission after pediatric cardiothoracic surgery. Ann Thorac Surg. 2012;94(3):865–873. [PubMed: 22682942]
3. Dabal RJ, Kirklin JK, Kukreja M, et al. The modern Fontan operation shows no increase in mortality out to 20 years: a new paradigm. The Journal of thoracic and cardiovascular surgery. 2014;148(6):2517–2523.e2511. [PubMed: 25277471]
4. Knowles RL, Bull C, Wren C, Dezateux C. Mortality with congenital heart defects in England and Wales, 1959–2009: exploring technological change through period and birth cohort analysis. Archives of disease in childhood. 2012;97(10):861–865. [PubMed: 22753769]
5. Mackie AS, Gauvreau K, Newburger JW, Mayer JE, Erickson LC. Risk factors for readmission after neonatal cardiac surgery. Ann Thorac Surg. 2004;78(6):1972–1978; discussion 1978. [PubMed: 15561011]
6. Kansagara D, Englander H, Salanitro A, et al. Risk prediction models for hospital readmission: a systematic review. JAMA. 2011;306(15):1688–1698. [PubMed: 22009101]
7. Tregay J, Wray J, Bull C, et al. Unexpected deaths and unplanned re-admissions in infants discharged home after cardiac surgery: a systematic review of potential risk factors. Cardiology in the young. 2015;25(5):839–852. [PubMed: 25547262]
8. Polineni S, Parker DM, Alam SS, et al. Predictive Ability of Novel Cardiac Biomarkers ST2, Galectin-3, and N-terminal prohormone of brain natriuretic peptide Before Cardiac Surgery. Journal of the American Heart Association. 2018;7(14).
9. Gaggin HK, Januzzi JL. Biomarkers and diagnostics in heart failure. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2013;1832(12):2442–2450. [PubMed: 23313577]
10. Fernandes BA, Maher KO, Deshpande SR. Cardiac biomarkers in pediatric heart disease: A state of art review. World journal of cardiology. 2016;8(12):719–727. [PubMed: 28070239]
11. Mathews LR, Lott JM, Isse K, et al. Elevated ST2 Distinguishes Incidences of Pediatric Heart and Small Bowel Transplant Rejection. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2016;16(3):938–950.
12. Chida A, Sato H, Shintani M, et al. Soluble ST2 and N-terminal pro-brain natriuretic peptide combination. Useful biomarker for predicting outcome of childhood pulmonary arterial hypertension. Circulation journal : official journal of the Japanese Circulation Society. 2014;78(2):436–442. [PubMed: 24304538]
13. Yang Z, Wang KKW. Glial Fibrillary acidic protein: From intermediate filament assembly and gliosis to neurobiomarker. Trends in neurosciences. 2015;38(6):364–374. [PubMed: 25975510]
14. Dumic J, Dabelic S, Fogel M. Galectin-3: an open-ended story. Biochimica et biophysica acta. 2006;1760(4):616–635. [PubMed: 16478649]
15. Opotowsky AR, Baraona F, Owumi J, et al. Galectin-3 Is Elevated and Associated With Adverse Outcomes in Patients With Single-Ventricle Fontan Circulation. Journal of the American Heart Association. 2016;5(1).
16. Magruder JT, Hibino N, Collica S, et al. Association of nadir oxygen delivery on cardiopulmonary bypass with serum glial fibrillary acid protein levels in paediatric heart surgery patients. Interactive cardiovascular and thoracic surgery. 2016;23(4):531–537. [PubMed: 27316657]
17. Vedovelli L, Padalino M, Simonato M, et al. Cardiopulmonary Bypass Increases Plasma Glial Fibrillary Acidic Protein Only in First Stage Palliation of Hypoplastic Left Heart Syndrome. The Canadian journal of cardiology. 2016;32(3):355–361. [PubMed: 26481085]
18. Vedovelli L, Padalino M, D'Aronco S, et al. Glial fibrillary acidic protein plasma levels are correlated with degree of hypothermia during cardiopulmonary bypass in congenital heart disease surgery. Interactive cardiovascular and thoracic surgery. 2017;24(3):436–442. [PubMed: 28040762]

19. Bembea MM, Savage W, Strouse JJ, et al. Glial fibrillary acidic protein as a brain injury biomarker in children undergoing extracorporeal membrane oxygenation. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*. 2011;12(5):572–579.
20. Stewart A, Tekes A, Huisman TA, et al. Glial fibrillary acidic protein as a biomarker for periventricular white matter injury. *American journal of obstetrics and gynecology*. 2013;209(1): 27.e21–27. [PubMed: 23467054]
21. Brunetti MA, Jennings JM, Easley RB, et al. Glial fibrillary acidic protein in children with congenital heart disease undergoing cardiopulmonary bypass. *Cardiology in the young*. 2014;24(4):623–631. [PubMed: 23845562]
22. Hori D, Ono M, Rappold TE, et al. Hypotension After Cardiac Operations Based on Autoregulation Monitoring Leads to Brain Cellular Injury. *The Annals of thoracic surgery*. 2015;100(2):487–493. [PubMed: 26089226]
23. Hori D, Everett AD, Lee JK, et al. Rewarming Rate During Cardiopulmonary Bypass Is Associated With Release of Glial Fibrillary Acidic Protein. *The Annals of thoracic surgery*. 2015;100(4): 1353–1358. [PubMed: 26163357]
24. Ennen CS, Huisman TA, Savage WJ, et al. Glial fibrillary acidic protein as a biomarker for neonatal hypoxic-ischemic encephalopathy treated with whole-body cooling. *American journal of obstetrics and gynecology*. 2011;205(3):251.e251–257. [PubMed: 21784396]
25. Brown JR, Jacobs JP, Alam SS, et al. Utility of Biomarkers to Improve Prediction of Readmission or Mortality After Cardiac Surgery. *The Annals of thoracic surgery*. 2018;106(5):1294–1301. [PubMed: 30086283]
26. O'Brien SM, Jacobs JP, Pasquali SK, et al. The Society of Thoracic Surgeons Congenital Heart Surgery Database Mortality Risk Model: Part 1-Statistical Methodology. *The Annals of thoracic surgery*. 2015;100(3):1054–1062. [PubMed: 26245502]
27. Hajian-Tilaki K Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. *Caspian Journal of Internal Medicine*. 2013;4(2):627–635. [PubMed: 24009950]
28. Cook NR, Ridker PM. The Use and Magnitude of Reclassification Measures for Individual Predictors of Global Cardiovascular Risk. *Annals of internal medicine*. 2009;150(11):795–802. [PubMed: 19487714]
29. Pencina MJ, D'Agostino RB, Pencina KM, Janssens ACJW, Greenland P Interpreting Incremental Value of Markers Added to Risk Prediction Models. *American Journal of Epidemiology*. 2012;176(6):473–481. [PubMed: 22875755]
30. Cook NR, Paynter NP. Performance of Reclassification Statistics in Comparing Risk Prediction Models. *Biometrical Journal Biometrische Zeitschrift*. 2011;53(2):237–258. [PubMed: 21294152]
31. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143(1):29–36. [PubMed: 7063747]
32. Efron B, Tibshirani R. Bootstrap Methods for Standard Errors, Confidence Intervals, and Other Measures of Statistical Accuracy. *Statistical Science*. 1986;1(1):54–75.
33. Meeusen JW, Johnson JN, Gray A, et al. Soluble ST2 and galectin-3 in pediatric patients without heart failure. *Clinical biochemistry*. 2015;48(18):1337–1340. [PubMed: 26277636]
34. Tang WH, Shrestha K, Shao Z, et al. Usefulness of plasma galectin-3 levels in systolic heart failure to predict renal insufficiency and survival. *The American journal of cardiology*. 2011;108(3):385–390. [PubMed: 21600537]
35. Rehman SU, Mueller T, Januzzi JL Jr. Characteristics of the novel interleukin family biomarker ST2 in patients with acute heart failure. *Journal of the American College of Cardiology*. 2008;52(18):1458–1465. [PubMed: 19017513]
36. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128(16):1810–1852. [PubMed: 23741057]
37. Mohammed LA, Gafar HS, Hussien NR Galectin-3 as Early Detector of Heart Failure in Children with Congenital Acyanotic Heart Disease. *Clinical Medicine and Diagnostics*. 2014;4(5):90–98.

38. Goldman J, Becker ML, Jones B, Clements M, Leeder JS. Development of biomarkers to optimize pediatric patient management: what makes children different? *Biomarkers in medicine*. 2011;5(6): 781–794. [PubMed: 22103612]
39. Cantinotti M, Passino C, Storti S, Ripoli A, Zyw L, Clerico A. Clinical relevance of time course of BNP levels in neonates with congenital heart diseases. *Clinica chimica acta; international journal of clinical chemistry*. 2011;412(23–24):2300–2304. [PubMed: 21910979]
40. Holmgren D, Westerlind A, Lundberg PA, Wahlander H. Increased plasma levels of natriuretic peptide type B and A in children with congenital heart defects with left compared with right ventricular volume overload or pressure overload. *Clinical physiology and functional imaging*. 2005;25(5):263–269. [PubMed: 16117728]
41. Chave M, Marques-Vidal P. Factors Associated with Readmission of Patients with Congenital Heart Disease in a Swiss University Hospital. *Pediatric cardiology*. 2017;38(4):650–655. [PubMed: 28154912]
42. Crowe S, Ridout DA, Knowles R, et al. Death and Emergency Readmission of Infants Discharged After Interventions for Congenital Heart Disease: A National Study of 7643 Infants to Inform Service Improvement. *J Am Heart Assoc*. 2016;5(5).
43. Kogon B, Woodall K, Kanter K, Alsoufi B, Oster M. Reducing readmissions following paediatric cardiothoracic surgery: a quality improvement initiative. *Cardiol Young*. 2015;25(5):935–940. [PubMed: 25115729]
44. Vo D, Zurakowski D, Faraoni D. Incidence and predictors of 30-day postoperative readmission in children. *Paediatric anaesthesia*. 2018;28(1):63–70. [PubMed: 29159844]
45. Lawley CM, Lain SJ, Figtree GA, Sholler GF, Winlaw DS, Roberts CL. Mortality, rehospitalizations and costs in children undergoing a cardiac procedure in their first year of life in New South Wales, Australia. *International journal of cardiology*. 2017;241:156–162. [PubMed: 28385359]
46. Turley K, Tyndall M, Roge C, et al. Critical pathway methodology: effectiveness in congenital heart surgery. *The Annals of thoracic surgery*. 1994;58(1):57–63; discussion 63–55. [PubMed: 8037561]
47. Williams DL, Gelijns AC, Moskowitz AJ, et al. Hypoplastic left heart syndrome: valuing the survival. *The Journal of thoracic and cardiovascular surgery*. 2000;119(4 Pt 1):720–731. [PubMed: 10733760]
48. Jacobs JP, Jacobs ML, Maruszewski B, et al. Initial application in the EACTS and STS Congenital Heart Surgery Databases of an empirically derived methodology of complexity adjustment to evaluate surgical case mix and results. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2012;42(5):775–779; discussion 779–780. [PubMed: 22700597]

Figure 1.
Patient flow diagram for the final pediatric cohort (N=162)

Figure 2.

Area under the receiver operating characteristics curve for the clinical risk model with and without preoperative log-transformed biomarkers.

Figure 3.
Area under the receiver operating characteristics curve for the clinical risk model with and without pre- and postoperative log-transformed biomarkers.

Table 1.

Pre and postoperative biomarker means and ranges

Preoperative biomarker	Median and IQR (ng/mL)
Soluble suppression of tumorigenicity 2	2.08 (1.25, 3.86)
Galectin-3	15.86 (9.01, 20.79)
N-terminal prohormone of brain natriuretic peptide	0.43 (0.20, 1.73)
Glial fibrillary acidic protein	0.00 (0.00, 0.01)
Postoperative biomarker	
Soluble suppression of tumorigenicity 2	3.33 (2.01, 5.98)
Galectin-3	24.49 (15.38, 37.01)
N-terminal prohormone of brain natriuretic peptide	0.45 (0.17, 1.45)
Glial fibrillary acidic protein	0.07 (0.004, 0.19)

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

Table 2.

Pediatric patient and procedural characteristics by readmission or mortality status (N=162)

Risk Factors	N = (162)	No readmission or mortality N = 141 (%)	Readmission or Mortality N = 21 (%)	p value
Age group				
Neonates	14	11 (81.2)	3 (18.8)	
Infants	68	60 (88.2)	8 (11.8)	
Children	80	70 (87.2)	10 (12.8)	0.755
Age, by days (median, IQR)*		287 (139, 2137)	230 (98, 3726)	0.270
Gender				
Female	65	55 (84.6)	10 (15.4)	
Male	97	86 (88.7)	11 (11.3)	0.453
Weight				
>10 th percentile	148	130 (87.8)	18 (12.2)	
<10 th percentile	14	11 (78.6)	3 (21.4)	0.324
Weight, by kg (median, IQR)*		8.3 (5.8, 19.6)	12.9 (4.2, 44.5)	0.059
Prematurity among neonates and infants				
No	141	121 (85.8)	20 (14.2)	
Yes	21	20 (95.2)	1 (4.8)	0.230
STAT Level				
1	69	65 (94.2)	4 (5.8)	
2	43	33 (76.7)	10 (23.3)	
3	18	17 (94.4)	1 (5.6)	
4	15	12 (80.0)	3 (20.0)	
5	10	7 (70.0)	3 (30.0)	
Missing	7	7 (100.0)	0 (0.0)	0.031
Prior cardiothoracic operation				
No	129	118 (91.5)	11 (8.5)	
Yes	33	23 (69.7)	10 (30.3)	0.001
Any non cardiac congenital anatomic abnormality				
No	141	123 (87.2)	18 (12.8)	
Yes	21	18 (85.7)	3 (14.3)	0.847
Chromosomal abnormality or syndrome				
No	118	105 (89.0)	13 (11.0)	
Yes	44	36 (81.8)	8 (18.2)	0.227
Any preoperative factor ¹				
No	136	123 (90.4)	13 (9.6)	
Yes	26	18 (69.2)	8 (30.8)	0.003

Table 3.

Pre-and postoperative biomarker panel to predict 30-day readmission or mortality after pediatric congenital heart surgery

	Unadjusted OR (95% CI)	Clinical model + biomarker model OR (95% CI)
Preoperative log-transformed biomarkers		
Soluble suppression of tumorigenicity 2	1.66 (1.16 – 2.37) *	1.85 (1.02 – 3.36) *
Galectin-3	1.69 (0.99 – 2.87) *	1.23 (0.63 – 2.41)
Glial fibrillary acidic protein	0.95 (0.90 – 1.01)	0.98 (0.91 – 1.05)
N-terminal prohormone of brain natriuretic peptide	1.07 (0.84 – 1.35)	0.75 (0.49 – 1.14)
Postoperative log-transformed biomarkers		
Soluble suppression of tumorigenicity 2	2.26 (1.36 – 3.75) *	1.74 (1.63 – 4.76) *
Galectin-3	2.12 (1.02 – 4.37) *	1.72 (0.67 – 4.38)
Glial fibrillary acidic protein	0.98 (0.92 – 1.05)	0.97 (0.90 – 1.04)
N-terminal prohormone of brain natriuretic peptide	1.19 (0.94 – 1.51)	1.07 (0.72 – 1.59)

OR: Odds ratio, CI: Confidence Interval,

* P-value < 0.05