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# Prognostic Value of NT-proBNP and 3 Months Readmission or Mortality after Congenital Heart Surgery

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## ABSTRACT

**Background:** The use of NT-proBNP in predicting outcomes after juvenile congenital heart surgery is uncertain. **Objective:** We wanted to determine whether the novel biomarker NT-proBNP might be used to identify babies at increased risk of readmission or death after congenital heart surgery. **Patients and Methods:** This was a cross-sectional study done from April 2021 to January 2022, at Pediatric Intensive Care Units at Alhusien and Bab Alsharia University Hospitals. Our study included 100 patients in the pediatric and adolescent age group. Biomarkers were assessed using an enzyme-linked immunosorbent assay with patterned arrays and electrochemiluminescence detection. The manufacturer's specifications were respected while repurposing pre-owned kits and equipment. **Results:** Soluble suppression of tumorigenicity 2 pre and postoperative values were significantly associated with readmission. Postoperative NT-ProBNP values were significantly associated with readmission. Only preoperative soluble suppression of tumorigenicity 2 with cut-off value of 1.46 showed significant association with readmission with sensitivity and specificity of 84.6 and 79.3% respectively. Postoperative NT-ProBNP and soluble suppression of tumorigenicity 2 with cut-off values of 904.12 and 1.46 respectively showed significant association with readmission with sensitivity and specificity of 95.5% and 97.7% respectively for NT-ProBNP and sensitivity and specificity 84.6% and 74.7% respectively for soluble suppression of tumorigenicity 2. No laboratory parameter change showed significant association with readmission. **Conclusion:** Postoperative NT-proBNP levels were strongly related with readmission after juvenile congenital heart surgery, with good sensitivity and specificity.

**Key words:** Congenital Heart Surgery, Mortality, NT-proBNP, Pediatrics, Readmission.

## INTRODUCTION

Prior to discharge, newborns with substantial congenital heart disease (CHD) may display signs of cyanosis, congestive heart failure (CHF), weak pedal pulses, or a failed neonatal CHD pulse oximetry test [(1)]. Shock or cyanosis will ensue if a CHD lesion depends on a patent ductus arteriosus (PDA) to transmit flow to either the systemic or pulmonary circulation. As pulmonary vascular resistance lowers, CHD lesions that enable blood shunting to the pulmonary circulation develop symptoms of pulmonary excess circulation [(2)].

Only a few studies have been done on children with congenital heart disease and their likelihood of readmission after cardiac surgery, compared to children with asthma and other chronic conditions. Unfortunately, payers are increasingly viewing many of these readmissions as unintended consequences of the initial treatment or hospitalisation, and both the government and commercial insurance companies have advocated for withholding payment for the additional expenses incurred as a result of the readmission [(3)].

As a means of reducing the number of avoidable readmissions and deaths, predictive models have been created to assist doctors in quickly identifying patients with a high risk of bad outcomes. Biomarkers have been used to predict readmission and death following congenital heart surgery, however this has been compared to clinical models alone [(4)]. Many risk models for adult cardiac surgery patients have been created, but no such models have been produced for children requiring CHD surgery [(5)]. When it comes to pediatric cardiac surgery, it's unclear if the cardiac biomarker, N-terminal Pro-Brain Natriuretic Peptide (NT-proBNP), can be used effectively [(6)]. Myocytes produce N-terminal proBNP in response to cardiac chamber dilation and wall stress. In the preoperative and early postoperative period, this hemodynamic load may suggest readmission or death. Prognostic variables are becoming more important as the emphasis shifts to improving long-term outcomes and quality of life for children with CHD [(7)].

If NT-proBNP may predict outcomes after pediatric congenital heart surgery, it is still debatable. As part of our effort to identify neonates at high risk of readmission or mortality after congenital heart surgery, we tested the novel biomarker NT-proBNP.

## PATIENTS AND METHODS

This was a cross-sectional study done from April 2021 to January 2022, at Pediatric Intensive Care Units (ICU) at Alhusien and Bab Alsharia University Hospitals. Our study included 100 patients in the pediatric and adolescent age group.

All ICU patients' ages one month to 18 years who underwent at least one congenital heart surgery were included in the study. For our assessment, we examined all relevant reports from the previous five years. Data on patients, surgeries, and outcomes were gathered. Patients with an uncertain preterm status, those weighing less than



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2.5 kg, and those beyond the age of 18 were barred from participating.

Samples of pre and postoperative blood were taken (heparinized plasma) before and after the skin incision was made. It was necessary to freeze and preserve the materials before conducting the analysis. Biomarkers ***(NT-ProBNP, Soluble suppression of tumorigenicity 2, Galectin-3, Glial fibrillary acidic protein (ng/ml))*** were assessed using an enzyme-linked immunosorbent assay with patterned arrays and electrochemiluminescence detection. In the case of pre-owned kits and equipment, we adhered to the guidelines provided by the manufacturer.

***Blood samples were taken after 30 min at supine rest. Biomarkers were measured with a chemiluminescent immunoassay kit (Roche Diagnostics, Indianapolis, Indiana, USA) on an Elecsys 2010 analyzer.***

**Outcome**

Unplanned readmission or death within three months of release from the index surgical hospitalization was the composite study outcome, which was confirmed by integrating state all-payers' claims data, chart review, and the National Death Index utilizing Social Security numbers and dates of birth. In-hospital mortality during the index surgical hospitalization was defined as well as death within three months after release from the surgical stay. The first unexpected admission within three months of an initial hospitalization when the congenital heart surgery happened was described as a readmission.

**Ethical Approval:** The study was approved by the Ethics Board of the Al-Azhar University and an informed written consent was taken from each participant's parent in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

***Statistical Analysis***

IBM SPSS version 22.0 was used to analyses computer-generated data. To express quantitative data, mean+standard deviation (SD) were used and were compared by independent t-test for normally distributed data or MWU test for not normally distributed data. Qualitative data were presented by percentages and numbers and were compared by Chi-Square test. Correlation with Pearson correlation. P less than 0.05 was considered significant.

**RESULTS**

There was no significant difference between subjects reported readmission or mortality and those who did not except in prior cardiothoracic operation, but, ***the difference in weight is significant*** (Table 1).

Table (1): Readmission and no readmission patient's characteristics

| | **No readmission or Mortality (n=87) (%)** | **Readmission or Mortality (n=13) (%)** | **P value** |
|---|---|---|---|
| **Age group** | | | |
| **Neonates** | 7 (8.05%) | 2 (15.38%) | 0.997 |
| **Infants** | 37 (42.53%) | 5 (38.46%) | |
| **Children** | 43 (49.43%) | 6 (46.15%) | |
| **Age (Days) mean+ SD** | 874.33 ± 1486.53 | 1398.33 ± 2874.18 | 0.31 |
| **Gender** | | | |
| **Male** | 34 (39.08%) | 6 (46.15%) | 0.63 |
| **Female** | 53 (60.92%) | 7 (53.85%) | |
| **Weight** | | | |
| **> 10$^{th}$ percentile** | 80 (91.95%) | 11 (84.62%) | 0.388 |
| **< 10$^{th}$ percentile** | 7 (8.05%) | 2 (15.38%) | |
| **Weight (kg) mean+ SD** | 16.63 ± 1.5 | 26.45 ± 6.6 | <0.001* |
| **Prematurity among infants and children** | 13 (14.9%) | 1 (7.69%) | 0.48 |
| **STAT level** | | | |
| **1** | 40 (45.98%) | 3 (23.08%) | 0.26 |
| **2** | 20 (22.99%) | 5 (38.46%) | |
| **> 3 or missing** | 27 (31.03%) | 5 (38.46%) | |
| | | | |
| **Prior cardiothoracic operation** | 14 (16.09%) | 6 (46.15%) | 0.011* |
| **Non-Cardiac congenital anomaly** | 11 (12.64%) | 2 (15.38%) | 0.78 |
| **Chromosomal abnormality** | 22 (25.29%) | 5 (38.46%) | 0.32 |

*: Significant, SD: Standard deviation

Only NT-ProBNP and Soluble suppression of tumorigenicity 2 (ng/ml) showed significant difference between the two sub-groups (Table 2).

Table (2): Comparison between readmission and no readmission patients

| | | No readmission or Mortality (n=87) (%) | Readmission or Mortality (n=13) (%) | P Value |
|---|---|---|---|---|
| **Pre** | NT-ProBNP (pg/ml) | 5084.12 ± 3200.12 | 7894.39 ± 4561.82 | 0.035* |
| | Soluble suppression of tumorigenicity 2 (ng/ml) | 1.91 ± 0.27 | 1.69 ± 0.26 | 0.0059* |
| | Galectin-3 (ng/ml) | 15.59 ± 6.94 | 17.44 ± 5.81 | 0.23 |
| | Glial fibrillary acidic protein (ng/ml) | 0.00542 ± 0.004003 | 0.00636 ± 0.003426 | 0.267 |
| **Post** | NT-ProBNP (pg/ml) | 8427.94 ± 6463.3 | 14142.29 ± 8540.79 | 0.6241 |
| | Soluble suppression of tumorigenicity 2 (ng/ml) | 2.34 ± 0.3 | 2.67 ± 0.44 | 0.0023 |
| | Galectin-3 (ng/ml) | 26.86 ± 12.98 | 31.4 ± 10.16 | 0.204 |
| | Glial fibrillary acidic protein (ng/ml) | 0.11 ± 0.08 | 0.14 ± 0.09 | 0.234 |
| **Change percentage** | NT-ProBNP (pg/ml) | 0.88 ± 1.33 | 8.23 ± 19.01 | 0.596 |
| | Soluble suppression of tumorigenicity 2 (ng/ml) | 0.43 ± 0.28 | 0.45 ± 0.25 | 0.61 |
| | Galectin-3 (ng/ml) | 1.34 ± 1.76 | 1.06 ± 0.94 | 0.787 |
| | Glial fibrillary acidic protein (ng/ml) | 565.49 ± 4656.39 | 28.18 ± 20.47 | 0.826 |

*: Significant, Data are presented as mean±standard deviation

There was significant difference between pre and postoperative NT-ProBNP, Soluble suppression of tumorigenicity 2, Galectin-3, Glial fibrillary acidic protein (Table 3).

**Table (3):** Comparison between pre and postoperative laboratory results in all cases

| | Total Pre-operative (N=100) | Total Post-operative (N=100) | P Value |
|---|---|---|---|
| **NT-ProBNP (pg/ml)** | 5449.45 ± 3510.09 | 13399.42 ± 8494.73 | <0.0001* |
| **Soluble suppression of tumorigenicity 2 (ng/ml)** | 1.72 ± 0.27 | 2.38 ± 0.34 | <0.0001* |
| **Galectin-3 (ng/ml)** | 15.83 ± 6.81 | 27.45 ± 12.7 | <0.0001* |
| **Glial fibrillary acidic protein (ng/ml)** | 0.005542 ± 0.00393 | 0.1128 ± 0.0785 | <0.0001* |

*: Significant, Data are presented as mean±standard deviation

Soluble suppression of tumorigenicity 2 pre and postoperative values were significantly associated with readmission. Postoperative NT-ProBNP values were significantly associated with readmission (Table 4).

**Table (4):** Correlation between readmission and laboratory parameters

| | Readmission | | |
|---|---|---|---|
| | | r | P Value |
| **Pre** | NT-ProBNP pg/ml | 0.141 | 0.161 |
| | Soluble suppression of tumorigenicity 2 | 0.274 | 0.005852* |
| | Galectin-3 | 0.091717 | 0.364115 |
| | Glial fibrillary acidic protein | 0.08083 | 0.424032 |
| **Post** | NT-ProBNP pg/ml | 0.218 | 0.029* |
| | Soluble suppression of tumorigenicity 2 | 0.333 | 0.000704* |
| | Galectin-3 | 0.121042 | 0.230286 |
| | Glial fibrillary acidic protein | 0.142647 | 0.156838 |
| **Change** | NT-ProBNP pg/ml | -0.14 | 0.888 |
| | Soluble suppression of tumorigenicity 2 | 0.032647 | 0.747114 |
| | Galectin-3 | -0.05638 | 0.577431 |
| | Glial fibrillary acidic protein | -0.04202 | 0.68 |

*: Significant

Only preoperative soluble suppression of tumorigenicity 2 with cut-off value of 1.46 showed significant association with readmission with sensitivity and specificity of 84.6 and 79.3% respectively (Table 5).

**Table (5): Association between pre-operation parameters and readmission**

| | Cut off | Area | Sensitivity (%) | Specificity (%) | P Value |
|---|---|---|---|---|---|
| **NT-ProBNP pg/ml** | 212.04 | 0.586207 | 92.3 | 95.4 | 0.317641 |
| **Soluble suppression of tumorigenicity 2** | 1.46 | 0.726348 | 84.6 | 79.3 | 0.008694* |
| **Galectin-3** | 12.64 | 0.604332 | 84.6 | 60.9 | 0.226498 |
| **Glial fibrillary acidic protein** | 0.0023 | 0.595933 | 84.6 | 71.3 | 0.266112 |

*: Significant

Postoperative NT-ProBNP and soluble suppression of tumorigenicity 2 with cut-off values of 904.12 and 1.46 respectively showed significant association with readmission with sensitivity and specificity of 95.5% and 97.7% respectively for NT-ProBNP and sensitivity and specificity 84.6% and 74.7% respectively for soluble suppression of tumorigenicity 2 (Table 6).

**Table (6): Association between post-operation parameters and readmission**

| | Cut off | Area | Sensitivity (%) | Specificity (%) | P. Value |
|---|---|---|---|---|---|
| **NT-ProBNP pg/ml** | 904.12 | 0.693634 | 95.5 | 97.7 | 0.024793* |
| **Soluble suppression of tumorigenicity 2** | 2.09 | 0.763484 | 84.6 | 74.7 | 0.002256* |
| **Galectin-3** | 18.29 | 0.609637 | 84.6 | 70.1 | 0.203755 |
| **Glial fibrillary acidic protein** | 0.023 | 0.603448 | 84.6 | 87.4 | 0.230458 |

*: Significant

No laboratory parameter change showed significant association with readmission (Table 7).

**Table (7): Association between change between pre and post-operation parameters and readmission**

| | Cut off | Area | Sensitivity (%) | Specificity (%) | P Value |
|---|---|---|---|---|---|
| **NT-ProBNP pg/ml** | 0.0955 | 0.502683 | 92.3 | 94.2 | 0.975205 |
| **Soluble suppression of tumorigenicity 2** | 0.149 | 0.547406 | 84.6 | 80.2 | 0.582942 |
| **Galectin-3** | 0.241 | 0.523256 | 84.6 | 75.6 | 0.787648 |
| **Glial fibrillary acidic protein** | 3.32 | 0.519678 | 84.6 | 88.4 | 0.819704 |

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## DISCUSSION

Many patients are being readmitted to the hospital within a short period of time after they have been discharged. This group of patients is being targeted more intensely by insurance companies looking to cut down on payments to cover the rising costs of readmission [(3)].

Asthma and other chronic medical diseases have been the subject of several investigations [(8,9)]. In children with congenital heart disease, there is a lack of data on readmissions after cardiac surgery.

Within three months after surgery for a congenital heart defect, unexpected readmissions or deaths were connected to pre- and postoperative log-transformed soluble suppressions of NT-proBNP, tumorigenicity 2, and galectin-3. After adjusting for clinical factors and the new preoperative biomarker panel, preoperative soluble suppression of NT-proBNP remained significantly associated with 3 month readmission or mortality. Prior to congenital heart surgery, it may be possible to use preoperative soluble NT-proBNP suppression to identify children at high risk of hospital readmission or mortality three months after surgery. An understanding of a child's statistically anticipated risk of readmission or mortality may aid in determining the appropriate time for surgery, surgical alternatives and individualised operative care, and hospital release guidelines. A similar finding was made by **Brown *et al.*** [(10)].

After three months, **Brown *et al.*** [(10)] observed no association between the adult cardiac biomarker brain natriuretic peptide's N-terminal prohormone and unexpected readmission and death.

Children with CHD and more severe cardiac defects have previously been connected to the N-terminal prohormone, although it is less apparent if this prohormone is associated with unexpectedly frequent hospitalizations [(10)].

BNP and NT-proBNP have been linked to identifying the presence and severity of juvenile heart failure in many investigations in children [(11)]. Patients with systolic dysfunction may need mechanical circulatory assistance, heart transplantation, and inotropic drug therapy after surgery if NT-proBNP and BNP levels are elevated [(12)]. In children with heart failure, NT-proBNP has been utilised to assess treatment success and

the need of medication escalation. Low-risk open heart surgery in children is linked to higher preoperative NT-proBNP levels, which have been linked to postoperative problems such pleural effusion and infection. Additional research has connected elevated levels of NT-proBNP in children with congenital heart disease (CHD) to either left or right ventricular volume overload or dysfunction [(13)]. Studies in a range of adolescent cardiac illnesses demonstrate that natriuretic peptide levels rise in relation to the intensity of symptoms and the extent of remodeling [(14)]. **Bettencourt *et al.*** [(15)] studied 182 patients with decompensated heart failure who were admitted to the hospital on a regular basis. NT-ProBNP levels were classified into three categories by the authors in their studies of how they changed throughout hospitalisation: those whose NT-ProBNP levels dropped by at least 30%, those whose NT-ProBNP levels remained stable, and those whose NT-ProBNP levels rose by at least 30%. More than half of patients with stable NT-ProBNP levels over the six-month study period had a significantly better prognosis than patients whose NT-ProBNP levels increased by more than 30 percent.

It was shown that persons with NT-ProBNP decreases of less than 30 percent were considered to be at risk for events by **Verdiani *et al.*** [(16)]. According to **Parker *et al.*** [(6)] NT-proBNP levels before and after pediatric congenital heart surgery were not associated to readmission or mortality.

As far as we know, this is the first research to correlate changes in laboratory values of study biomarkers with readmission studies at different points in time. It was shown that only preoperative soluble inhibition of tumorigenicity 2 with a cut-off value of 1.46 had an effect on the likelihood of readmission; nevertheless, the sensitivity was 84.6 and specificity was 79%. NT-ProBNP cut-off values of 904.12 and 1.46, respectively, were linked to readmission, with NT-ProBNP sensitivity and specificity of 95.5 percent and 97.7 percent, and soluble suppression of tumorigenicity 2 sensitivity and specificity of 84.6% and 74.7 percent, respectively, with those cut-off values. The NT-ProBNP value was more sensitive and specific, as previously stated.

## CONCLUSION

Postoperative NT-proBNP levels were significantly related with readmission following juvenile congenital heart surgery, with high sensitivity and specificity.

**Declarations:**

**Consent for Publication:** I confirm that all authors accept the manuscript for submission

**Availability of data and material:** Available

**Competing interests:** None

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