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# Change in N-terminal pro B-type natriuretic peptide levels and clinical outcomes in children undergoing congenital heart surgery☆

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ABSTRACT

*Objective:* To examine the association between change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and prognosis after congenital heart disease (CHD) surgery.
*Methods:* NT-proBNP level was measured in 873 children before and at 1, 12, 36 and 72 h after cardiac surgery. Patients were followed up at 30, 90 and 180 days after surgery. The clinical outcomes of interest included prolonged intensive care unit (ICU) stay (>3 days), prolonged mechanical ventilation (>48 h), and occurrence of adverse events (i.e. death, readmission, and infection).
*Results:* NT-proBNP increased after surgery, peaking at 12 h, and decreased progressively thereafter. Median NT-proBNP change (i.e. preoperative minus postoperative level at 72 h after surgery) was −1212.68 pg/mL (interquartile range: −3099.87 to −66.81). Adverse events occurred in 29.4% of patients. Multivariate logistic regression showed that lower body surface area (BSA), higher, the Risk Adjustment for Congenital Heart Surgery-1 score and smaller age were significantly associated with an increased risk of prolonged ICU-stay and mechanical ventilation. A decrease or a slight increase in NT-proBNP was associated with a lower risk. In multivariate cox regression, a decrease or a slight increase in NT-proBNP was associated with a lower risk of death. In addition to quartile of the NT-proBNP change, BSA was a significant predictor for adverse events. The associations for prolonged ICU-stay and mechanical ventilation were U-shaped, according to the restricted cubic spline models. The association between NT-proBNP change and death was inconclusive.
*Conclusions:* Increase in NT-proBNP may be a useful marker for adverse outcomes in children with CHD after cardiac surgery.



## 1. Introduction

Congenital heart disease (CHD) is one of the most common congenital malformations with an incidence of approximately 9 per 1000 live births [1]. Despite the great progress achieved in the last few years, CHD remains an important cause of death in children [2] and the resulting mortality is increasing in China [3]. Compared with older children, neonates and infants are affected more by the adverse events following CHD surgery [4,5]. Therefore, an accurate indicator is needed to predict children's postoperative prognosis and as a result to improve their clinical outcomes.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is synthesized and released into the circulation by ventricular myocytes in response to pressure overload, volume expansion, and increase in myocardial wall stress [6]. Recently, measurement of NT-proBNP as a prognostic indicator of early postoperative outcomes for pediatric and congenital heart surgery has been investigated [7–9]. However, findings are inconsistent. For example, Qu et al. found that 1-hour postoperative NT-proBNP level might be a strong prognostic predictor of prolonged mechanical ventilation, intensive care unit (ICU) stay, and inotropic therapy [7]. Other studies demonstrated that preoperative NT-proBNP was a significant predictor of duration of ICU stay and that the 12 hour

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postoperative NT-proBNP peak correlated with the therapeutic intervention scoring system and prolonged mechanical ventilation [10,11]. In contrast, a study of 115 neonates and infants with CHD showed no relationship between absolute BNP levels and postoperative outcomes [4].

There is a great variability in NT-proBNP values within CHD characterized by different hemodynamic and clinical conditions [12], the measurement at an isolated time point seems to provide limited predictive value. Research monitoring postoperative NT-proBNP level of cardiac transplant patients has demonstrated that changes of NT-proBNP level over time is a better prognostic tool than the absolute value [13,14]. In patients with heart failure, NT-proBNP change level was the strongest predictor of an adverse outcome [15–17]. Literature shows that NT-proBNP change offered prognostic value in adults diagnosed with heart failure, however further research is needed to confirm the prognostic value of NT-proBNP change among children undergoing congenital heart surgery.

The objective of the present study was therefore to examine the association between change in level of NT-proBNP and prognosis in patients after repair of congenital heart disease with cardiopulmonary bypass (CPB).

## 2. Methods

### 2.1. Participants

This retrospective cohort study was conducted at Guangzhou Women and Children's Medical Center. Between June 2015 and January 2017, 1037 children (<18 years) who underwent CHD surgery and had NT-proBNP assays before and at 1, 12, 36 and 72 h after surgery were eligible to participate in the study. Exclusion criteria included preoperative arrhythmia ($n = 8$), infective endocarditis ($n = 2$), myocarditis ($n = 5$), pericardial disease ($n = 4$), and renal dysfunction ($n = 6$). Those who were diagnosed of single ventricular ($n = 16$), patent ductus arteriosus ($n = 83$) or were unable to be separated from CPB ($n = 40$) were also excluded. The study was approved by the Medical Ethics Committee of Guangzhou Women and Children's Medical Center and was implemented in accordance with Good Clinical Practice and the Declaration of Helsinki.

### 2.2. Clinical procedure

The pre-operative anesthesia management, surgical procedure (including sternotomy, establishment of CPB, correction of cardiac defects, closure of thoracic cavity and suture of skin), and post-operative cardiac intensive care unit (CICU) management were performed following the standard institutional practice. All patients were admitted to the CICU intubated and mechanically ventilated after operation. Post-operative follow-up was performed at 30, 90 and 180 days after surgery in an outpatient clinic setting.

### 2.3. Data collection

Therapy was recorded during the course of hospitalization and the course of outpatient visits. Blood samples for NT-proBNP assay were collected from patients before and at 1, 12, 36, 72 h after surgery. The NT-proBNP levels were measured using a commercially available fluorescence immunoassay (competitive Enzyme Immuno Assay; ReLIAII, ReLIA Diagnostic Systems, Shenzhen, China) and Multi-Detection Microplate Reader (VICTOR X5; PerkinElmer, Waltham, Mass). The measurable range of NT-proBNP on this device is 5 to approximately 35,000 pg/mL. Any level >35,000 pg/mL was recorded as 35,000 for statistical evaluation.

Clinical data were collected retrospectively from the medical records, including age, gender, weight, body surface area (BSA) and main diagnosis, surgical time, the Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1) score, CPB duration, and aortic cross clamp (ACC) duration. The patients were divided into 3 subgroups of age according to clinically relevant data (neonates, i.e., <1 month, infants, i.e. 1–12 months, and children, i.e., >12 months–16 years).

### 2.4. Outcome measures

The short-term adverse outcomes were prolonged ICU-stay (>3 days) and prolonged mechanical ventilation (>48 h). The medium-term clinical outcomes were adverse events during study period, including death and any of the following events: a) hospital readmission, b) infections (respiratory tract, surgical site, and urinary tract infections), c) postoperative reintubation, d) post-operative cardiac arrest, and e) unplanned re-operation. Adverse events were confirmed by consulting clinical records and phone calls.

### 2.5. Statistical analyses

NT-proBNP change was calculated as preoperative NT-proBNP level minus NT-proBNP level at 72 h. Clinical data were compared by the quartiles of NT-proBNP change. Continuous variables are summarized as median (interquartile range, IQR) and compared using Kruskal-Wallis test. Categorical variables are expressed as number (percentage, %) and compared by chi-square test. Probabilities of adverse events by the quartiles of NT-proBNP change were estimated by Kaplan-Meier method. Multivariate logistic regression and cox proportional hazard models were used to identify variables affecting the short-term adverse outcomes and the medium-term clinical outcomes, respectively. Discrimination of the models was assessed with area under the ROC curve (AUC) and Harrell's C index. The non-linear associations between NT-proBNP change as a continuous variable and the risks of the short-term adverse outcomes and the medium-term clinical outcomes were determined using restricted cubic spline (RCS). Statistical analysis was performed using R 3.4.1 software, SPSS version 19.0 (SPSS, Chicago, IL, USA) and GraphPad Prism Version 5.0 (La Jolla, CA, USA).

## 3. Results

A total of 873 children (84 neonates, 630 infants and 159 children) were enrolled in the study. We described perioperative NT-proBNP changes in the study population as a whole and in each age group. For the entire study population, NT-proBNP increased after surgery, peaking at 12 h, and decreased progressively thereafter. The patterns were similar in neonates, infants and children (Supplementary Fig. 1). Therefore, we combined results from the three age groups and analyzed them as a single group.

### 3.1. Characteristics of children by the quartile of NT-proBNP change

The distribution of NT-proBNP change is given in Supplementary Fig. 2. More than half of them were negative numbers, denoting an increased NT-proBNP level after cardiac surgery. The characteristics of study participants by the quartiles of NT-proBNP change are shown in Table 1. Sixty-five percent of the children were male and 45.7% had ventricular septal defect. Children in the first and the fourth quartile of NT-proBNP change were younger and lower BSA and their CBP and ACC time were also longer than in the remaining quartiles. And those with the greatest increase or decrease in NT-proBNP had the highest level of NT-proBNP before and at 1 h, 12 h, 36 h and 72 h after surgery.

### 3.2. Incidence of adverse events by the quartiles of NT-proBNP change

During the follow-up period, 257 (29.4%) children developed at least one of the adverse events (including 14 deaths). The numbers of the adverse outcomes by the quartiles of the NT-proBNP change are given in Table 2. Those with either the greatest increase or the greatest decrease in the NT-proBNP change had higher rates of prolonged ICU-stay, prolonged mechanical ventilation, death, and overall adverse events. Kaplan-Meier survival analysis showed that those in the first quartile had the highest risk of death (log rank test, $P = 0.006$) and the highest risk of overall adverse events combined ($P < 0.001$) (Supplementary Fig. 3).

### 3.3. Multivariate analysis of the risk factors of adverse events

Multivariate logistic regression showed that lower BSA, higher RACHS-1 score and younger age were significantly associated with an increased risk of prolonged ICU-stay. A decrease or a slight increase in NT-proBNP was associated with a lower risk. The AUC for this model was 0.78 (95% CI 0.75–0.81). For prolonged mechanical ventilation, female, lower BSA, higher RACHS-1 score and smaller age were risk factors. A decrease or a slight increase in NT-proBNP was associated with a lower risk. The model had good discrimination (AUC 0.80, 95%CI 0.77–0.83). In multivariate cox regression, compared to Quartile 1, Quartile 2 and Quartile 3 of the NT-proBNP change were associated with a lower risk of death. Harrell's c-index was 0.73 (95%CI 0.59–0.88) for this model. In addition to quartile of the NT-proBNP change, BSA was a significant predictor for the overall incidence of adverse events, but the Harrell's c-index was 0.61 (95%CI 0.57–0.65) (Table 3).

**Table 1**
Characteristics of the children with CHD ($N = 873$) by the quartiles of the NT-proBNP change.

| | Quartile 1 ($n = 219$) | Quartile 2 ($n = 218$) | Quartile3 (n = 218) | Quartile4 (n = 218) | $\chi^2$/F | P |
|---|---|---|---|---|---|---|
| Type of CHD | | | | | | |
| Ventricular septal defect | 50(12.5%) | 117(29.3%) | 137(34.3%) | 95(23.8%) | 238.57 | <0.001 |
| Atrial septal defect | 4(9.3%) | 12(27.9%) | 18(41.9%) | 9(20.9%) | | |
| Tetralogy of fallot | 44(66.7%) | 17(25.8%) | 1(1.5%) | 4(6.1%) | | |
| Atrioventricular septal defect | 16(44.4%) | 9(25.0%) | 5(13.9%) | 6(16.7%) | | |
| Transposition of the great arteries | 29(58.0%) | 4(8.0%) | 2(4.0%) | 15(30.0%) | | |
| Anomalous pulmonary venous connection | 10(20.8%) | 10(20.8%) | 12(25.0%) | 16(33.3%) | | |
| Coarctation of the aorta | 8(19.5%) | 3(7.3%) | 7(17.1%) | 23(56.1%) | | |
| Pulmonary atresia | 23(59.0%) | 8(20.5%) | 4(10.3%) | 4(10.3%) | | |
| Double outlet right ventricle | 7(38.9%) | 3(16.7%) | 3(16.7%) | 5(27.8%) | | |
| Pulmonary stenosis | 2(12.5%) | 6(37.5%) | 5(31.2%) | 3(18.8%) | | |
| Interrupted aortic arch | 2(16.7%) | 0(0%) | 1(8.3%) | 9(75.0%) | | |
| Other types of CHD | 24(22.9%) | 29(27.6%) | 23(21.9%) | 29(27.6%) | | |
| Demographics | | | | | | |
| Age | | | | | 77.69 | <0.001 |
| Neonates (<30 d) | 25(29.8%) | 5(6%) | 5(6%) | 49(58.3) | | |
| Infants (<1 y) | 163(25.9%) | 167(26.5%) | 158(25.1%) | 142(22.5%) | | |
| 1–16 y | 31(19.5%) | 46(28.9%) | 55(34.6%) | 27(17.0%) | | |
| Gender | | | | | | |
| Female | 69(22.7%) | 83(27.3%) | 74(24.3%) | 78(25.7%) | 2.23 | 0.524 |
| Male | 150(26.4%) | 135(23.7%) | 144(25.3%) | 140(24.6%) | | |
| [a]BSA ($m^2$) | 0.29(0.25–0.33) | 0.31(0.27–0.36) | 0.32(0.28–0.39) | 0.28(0.24–0.31) | 56.97 | <0.001 |
| RACHS-1 | | | | | | |
| Change in NT-proBNP | −5883.39(−8960.04 to −4085.28) | −1919.26(−2291.58 to −1579.24) | −696.52(−948.69 to −433.55) | 1761.22(454.83 to 7307.06) | | |
| [a]NT-proBNP level | | | | | | |
| Preoperative level | 1032.30(350.34 to 2720.61) | 610.03(250.57 to 1231.01) | 826.78(237.98 to 1959.56) | 5870(2713.42 to 15,000.00) | 328.93 | <0.001 |
| 1-h postoperative level | 2202.04(611.07 to 5346.18) | 874.59(350.88 to 2146.82) | 894.97(314.05 to 2172.28) | 5934.08(2334.59 to 14,543.39) | 212.25 | <0.001 |
| 12-h postoperative level | 10,533.52(5889.56 to 18,867.54) | 5028.69(3387.10 to 8688.56) | 3744.08(2277.89 to 7145.61) | 8858.38(4660.64 to 17,095.99) | 168.53 | <0.001 |
| 36-h postoperative level | 8598.36(5703.54 to 14,434.87) | 3542.65(2479.89 to 5424.82) | 2656.05(1662.97 to 3852.91) | 5452.31(3072.71to 10,706.47) | 261.04 | <0.001 |
| 72-h postoperative level | 7732.56(5367.20 to 12,777.89) | 2651.50(2110.52 to 3358.00) | 1530.23(1001.87 to 2271.50) | 2917.12(1805.39 to 6409.37) | 411.44 | <0.001 |
| [a]CBP time | 101.5(75.0 to 153.25) | 70.0(60.0 to 97.0) | 66.0(57.0 to 85.5) | 86.0(60.0 to 129.0) | 84.65 | <0.001 |
| [a]ACC time | 54.0(38.0 to 77.3) | 36.5(27.8 to 53.0) | 36.0(27.0 to 48.8) | 40.5(30.0 to 52.0) | 58.46 | <0.001 |

Data are expressed as n (%) or median (interquartile range); CHD, congenital heart disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; RACHS-1, Risk Adjustment for Congenital Heart Surgery-1; CPB, cardiopulmonary bypass; ACC, aorta cross clamp.
[a] P-value of Kruskal-Wallis test.

### *3.4. Restricted cubic spline model for the associations of NT-proBNP change and risks of adverse events*

Fig. 1 shows the non-linear associations of the NT-proBNP change as a continuous variable with prolonged ICU-stay (A), prolonged mechanical ventilation (B) and overall adverse events (C), after adjusting for the confounding variables. Approximately U-shaped relationships were observed for prolonged ICU-stay and mechanical ventilation but not for the overall adverse events.

## 4. Discussion

In this study, we found that among children with CHD, NT-proBNP increased after surgery, peaking at 12 h and decreased progressively thereafter, the change patterns were similar in neonates, infants and children, which were consistent with the results of previous study [11]. The increase in NT-proBNP may be mainly due to transient postsurgical ventricular dysfunction [18]. Contrary to our finding, Cantinotti, M et al. found that BNP values dropped after surgery (where preoperative values were very high) in neonates while significantly increased in older children [19]. This inconsistency might partly be explained by the differences in study populations and the combinations of CHD subtypes, because circulating BNP levels are more related to the type of CHD rather than to disease severity [20]. For example, BNP is higher in patients with transposition of the great arteries than those in atrial septal defect [9].

**Table 2**
Numbers of events by the quartiles of the change in NT-proBNP.

| Outcome | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | P |
|---|---|---|---|---|---|
| Prolonged ICU-stay | 168(35.6%) | 95(20.1%) | 67(14.2%) | 142(30.1%) | <0.001 |
| Prolonged MV | 141(38.6%) | 59(16.2%) | 41(11.2%) | 124(34.0%) | <0.001 |
| Death | 9(64.3%) | 1(7.1%) | 1(7.1%) | 3(21.4%) | 0.006 |
| Adverse outcome | 89(34.6%) | 51(19.8%) | 47(18.3%) | 70(27.2%) | <0.001 |

NT-proBNP, N-terminal pro-brain natriuretic peptide; ICU, intensive care unit; MV, mechanical ventilation.

Anticipating postoperative prognosis is essential to optimize the care for patients with CHD [21]. While many studies have shown that single (preoperative or 1 h) measurement of NT-proBNP or BNP were predictive of adverse postoperative outcomes in CHD [7,10], few studies have examined the prognostic value of the NT-proBNP change during perioperative period and clinical outcomes in pediatric CHD children. Change in NT-proBNP reflects aberrant myocardial dynamics in a manner not captured by other physiologic markers. The present study showed that the combination of change in NT-proBNP, BSA, RACHS-1, age provided moderate prognostic information for short-term and medium-term clinical outcomes in children with CHD undergoing cardiac surgery. The findings is similar to previous studies that BSA and Aristotle score were strong predictors of clinical outcomes in

**Table 3**
Multivariate regression for short-term and medium-term adverse clinical outcomes.

| Multivariate logistic regression | Prolonged ICU-stay | | | Prolonged MV | | |
|---|---|---|---|---|---|---|
| | OR (95%CI) | P | AUC (95%CI) | OR (95%CI) | P | AUC (95%CI) |
| BSA | 0.16(0.03–1.00) | 0.050 | | 0.11(0.01–1.01) | 0.050 | |
| RACHS-1 score | 2.55(1.89–3.42) | <0.001 | | 2.58(1.94–3.43) | <0.001 | |
| Female vs. male | – | – | | 1.48(1.05–2.09) | 0.025 | |
| Age (vs. neonates) | | | | | | |
| Infants | 0.27(0.11–0.66) | 0.009 | 0.78(0.75–0.81) | 0.45(0.22–0.89) | 0.022 | 0.80(0.77–0.83) |
| Children | 0.19(0.07–0.57) | 0.004 | | 0.33(0.13–0.84) | 0.020 | |
| Quartiles of the NT-proBNP change (vs. Quartile 1) | | | | | | |
| Quartile 2 | 0.28(0.17–0.45) | <0.001 | | 0.26(0.16–0.41) | <0.001 | |
| Quartile 3 | 0.18(0.11–0.29) | <0.001 | | 0.18(0.11–0.29) | <0.001 | |
| Quartile 4 | 0.43(0.26–0.69) | 0.001 | | 0.60(0.39–0.94) | 0.024 | |

| Multivariate cox regression | Death | | | Adverse events | | |
|---|---|---|---|---|---|---|
| | HR (95%CI) | P | Harrell'C index (95%CI) | HR (95%CI) | P | Harrell'C index (95%CI) |
| BSA | | | 0.73(0.59–0.88) | 0.18(0.04–0.71) | 0.015 | 0.61(0.57–0.65) |
| Quartiles of the NT-proBNP change (vs. Quartile 1) | | | | | | |
| Quartile 2 | 0.12(0.02–0.94) | 0.044 | | 0.49(0.34–0.71) | <0.001 | |
| Quartile 3 | 0.12(0.02–0.94) | 0.043 | | 0.48(0.33–0.70) | <0.001 | |
| Quartile 4 | 0.34(0.09–1.27) | 0.109 | | 0.69(0.49–0.95) | 0.022 | |

ICU, intensive care unit; MV, mechanical ventilation; BSA, body surface area; OR, odds ratio; CI, confidence interval; AUC, area under the curve; NT-proBNP, N-terminal pro-brain natriuretic peptide. HR, hazard ratio.

children with CHD [19,22]. Furthermore, prior study has reported that an increased concentration of BNP at the first 24 h has been associated with low cardiac output syndrome and prolonged mechanical ventilation [23]. One study of 182 patients with heart failure found that the variation in NT-proBNP was the strongest predictor of an adverse outcome, with a ≥30% increase in NT-proBNP was associated with a higher risk of death within 6 months after discharge [15]. In HF patients, compared with a model without NT-proBNP, adding change in NT-proBNP significantly improved the discrimination of the multivariable model [24]. The consistent message from these analyses, along with our findings, is that there might be an association between increased NT-proBNP and the occurrence of adverse outcomes. However, the previous studies had either relatively small sample size or focused mainly on adult patients.

Our study further explored the possibility of a non-linear dose-response relationship between NT-proBNP change and the adverse events, showing a U-shaped curve. The dose-response relationship would help clinicians to identify patients at high risk of adverse outcomes so that they could initiate timely interventions. Previous studies have examined the associations using percent change or ratio [17,23], which is straightforward but might not be able to model the actual dose-response relationship correctly. While many studies suggested that downtrend of NT-proBNP might lead to improved clinical outcomes [24], our restricted cubic spline model showed no relationship between reduce NT-proBNP and reduced risk of adverse events here. The inconsistencies among studies may result from several reasons, for instance, different sampling time, different time-course changes of NT-proBNP, or different types of cardiac diseases.

### 4.1. Limitations

Some limitations of our study should be noted. First, we excluded patients with a single ventricle, patent ductus arteriosus. The exclusion of these children did not allow us to determine the utility of NT-proBNP in the management among them, and therefore further studies are being planned to include these patients. Second, the short interval between pre- and post-operative measurements of NT-proBNP may weaken the prognostic value and the association between NT-proBNP change and the adverse events due to the potential bias of the NT-proBNP change. It would be interesting to know how the NT-proBNP alteration in an extended time interval would change our results.

## 5. Conclusions

Our data indicated that the combination of change in NT-proBNP, BSA, RACHS-1 score, age were better predicted postoperative outcomes. Change in NT-proBNP levels is potentially useful in monitoring prognosis and treatment efficacy. Larger studies with longitudinal changes in

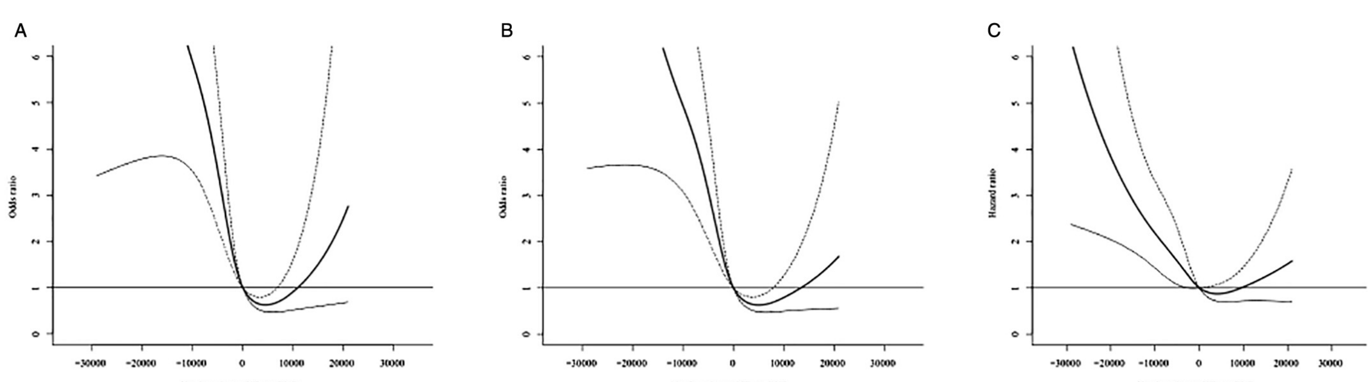


**Fig. 1.** Model for the association of NT-proBNP change from pre-operation to 72 h after surgery and prolonged ICU-stay (A), prolonged mechanical ventilation (B) and adverse events (C). The solid line represents the restricted cubic spline estimate, the tight dotted lines the 95% CI. All analyses are adjusted for age, sex, body surface area, Risk Adjustment for Congenital Heart Surgery-1, cardiopulmonary bypass time; aorta cross clamp time; and log-transformed preoperative NT-proBNP. NT-proBNP, N-terminal pro-brain natriuretic peptide.

NT-proBNP are required to determine whether specific therapeutic interventions can significantly improve clinical outcomes in CHD children after their cardiac surgery.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.02.025.

## Author contributions

Yanqin Cui and Huiying Liang contributed to study data management and analysis; Jiangbo, Qu, Lijuan Li and Kuanrong Li contributed to data collection, manuscript review and revision.

## Conflict of interest

None.

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