Prognostic value of N-terminal pro-form B-type natriuretic peptide (NT-proBNP) in patients with congenital heart disease undergoing cardiac surgery: a systematic review and meta-analysis of cohort studies

Ziqiang Gong[1#], Dexiu Xing[2#], Rong Wu[1], Senmao Zhang[1], Changxiang Ye[1], Yan Chen[1], Xiaoling Liu[1], Lizhang Chen[1,3], Tingting Wang[1,4]

[1]Department of Epidemiology and Health Statistics, Xiangya School of Public Health, Central South University, Changsha, China; [2]Medical Records Statistics Room of Medical Affair Department, Hunan Provincial People's Hospital (The First Affiliated Hospital of Hunan Normal University), Changsha, China; [3]Hunan Provincial Key Laboratory of Clinical Epidemiology, Changsha, China; [4]National Health Commission Key Laboratory for Birth Defect Research and Prevention, Hunan Provincial Maternal and Child Health Care Hospital, Changsha, China

Contributions: (I) Conception and design: L Chen, T Wang; (II) Administrative support: L Chen; (III) Provision of study materials or patients: D Xing, Z Gong; (IV) Collection and assembly of data: T Wang, D Xing; (V) Data analysis and interpretation: Z Gong, R Wu, S Zhang, C Ye, Y Chen, X Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Lizhang Chen, PhD. Department of Epidemiology and Health Statistics, Xiangya School of Public Health, Central South University, 110 Xiangya Road, Changsha 410078, China. Email: liche4005@126.com; Tingting Wang, PhD. National Health Commission Key Laboratory for Birth Defect Research and Prevention, Hunan Provincial Maternal and Child Health Care Hospital, Changsha 410078, China. Email: wangting91123@126.com.

Background: To perform an updated and comprehensive meta-analysis on the prognostic value of N-terminal pro-form B-type natriuretic peptide (NT-proBNP) in patients with congenital heart disease (CHD) undergoing cardiac surgery.

Methods: A systematic search was conducted until September 2021 for relevant studies published in PubMed, Web of Science Database and Embase. Based on the average values, NT-proBNP concentrations were classified as high and low levels. The outcomes of interest were mortality, cardiovascular events, and other postoperative outcomes. A random-effects model was used to calculate composite risk estimates and corresponding 95% confidence intervals (CIs). Possible sources of heterogeneity and stability of results were analyzed using subgroup and sensitivity analyses.

Results: A total of 32 studies published between 2008 and 2021 involving 7,571 participants were included. Results showed CHD patients at high NT-proBNP levels yielded an increased risk of mortality [risk ratio (RR) =1.14; 95% CI: 1.08–1.20] and cardiovascular events (RR =2.02; 95% CI: 1.26–3.24) compared with those at low NT-proBNP levels. No significant association was found between NT-proBNP and risks for other postoperative outcomes in CHD patients undergoing cardiac surgery (RR =1.73; 95% CI: 0.86–3.47). Significant heterogeneity was detected across studies regarding these risk estimates. Subgroup analysis found heterogeneity in the risk estimate of mortality was explained by geographic region, type of CHD, and assay method of NT-proBNP. Sensitivity analysis supported the robustness of results.

Conclusions: Compared with CHD patients at low NT-proBNP levels, CHD patients at high NT-proBNP levels had elevated risks of mortality and cardiovascular events. Further large-scale and well-controlled studies are needed to confirm our findings.

Keywords: Congenital heart disease (CHD); N-terminal pro-form B-type natriuretic peptide (NT-proBNP); cardiac surgery; systematic review; meta-analysis

Introduction

Congenital heart disease (CHD) is defined as clinically significant structural malformations of the heart and/or intrathoracic great vessels appearing in embryonic stage (1). Currently, CHD is the most common birth defects worldwide and the primary cause of perinatal mortality (2,3), with birth prevalence about 8.9‰ in China (4) and 10‰ worldwide (5) Owing to remarkable success in pediatric cardiology and open-heart surgery, the number of adult patients with CHD is gradually increasing over the past few decades and will increase further over time. However, most cardiac surgical repairs are palliative rather than curative (6-8). Lots of CHD survivors undergoing heart surgery still have an elevated risk of cardiovascular events, such as arrhythmias and heart failure. In this case, to develop a prognostic tool for the risk of adverse events in patients with CHD undergoing cardiac surgery over the long term is necessary; it will be helpful for early identification and prevention and timely intervention of adverse events in patients with CHD undergoing cardiac surgery, and will help to prolong survival and enhance the quality of life of CHD patients.

As a well-recognized marker of heart failure in the general population, N-terminal pro-form B-type natriuretic peptide (NT-proBNP) has gained lots of interest over the last few years (6). NT-proBNP is an inactive by-product of B-type natriuretic peptide (BNP), which is synthesized by the ventricular myocytes and released into the circulation. It is a marker of volume expansion, increased myocardial wall stress, and cardiac pressure overload (9). NT-proBNP can be facilely measured with commercial kits (10). The reference levels of NT-proBNP's vary with age and to the type of assay method (11).

With the application of NT-proBNP in the diagnosis and management of pediatric patients with various CHD phenotypes (6,12-15), quite a few studies have focused on the prognostic value of NT-proBNP in CHD patients undergoing cardiac surgery. However, the findings were inconsistent and sometimes conflict (16-20). At present, only one meta-analysis on this topic has been performed (21). The meta-analysis merely focused on patients with aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI) and evaluated the correlation of NT-proBNP with mortality. A comprehensive and timely meta-analysis of the prognostic value of NT-proBNP in congenital heart surgery is still lacking.

Therefore, we aimed to perform a comprehensive and updated meta-analysis about the prognostic value of NT-proBNP in CHD patients undergoing cardiac surgery. The results of our study could be helpful to facilitate heart team's decision. Besides, our findings will help clinicians make more informed decisions in the management of patients undergoing cardiac surgery for correction/palliation of CHD. We present the following article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting checklist and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-155/rc) (22,23).

Methods

Search strategy

Two authors (D Xing and Z Gong) independently identified studies published in English in PubMed, Web of Science Database, and Embase by September 2021. Relevant studies assessing the prognostic value of NT-proBNP in patients with CHDs undergoing cardiac surgery were identified. The following search terms were used: (I) congenital heart disease, congenital heart anomalies, congenital heart defect, congenital cardiac malformation, congenital heart malformation, congenital cardiac disease, congenital cardiac defect, congenital cardiac anomalies, congenital cardiovascular disease, cardiovascular defect, cardiovascular malformation, and cardiovascular anomalies; (II) NT-proBNP, N-terminal pro-BNP, N-terminal pro-brain natriuretic peptide, N-terminal pro-B-type natriuretic peptide, proBNP, amino-terminal pro-brain natriuretic peptide, aminoterminal pro-B-type natriuretic peptide, N-terminal prohormone B-type natriuretic peptide, BNP, B-type natriuretic peptide, brain natriuretic peptide, N-terminal proBNP, and natriuretic peptide. Afterwards, the authors manually searched and reviewed reference lists

of relevant reviews and identified studies.

Exposures and outcomes of interest

In our study, the exposure of interest was NT-proBNP level. It was collected within ±3 months of the echocardiogram (17). The concentration of NT-proBNP above the average concentration was identified as high NT-proBNP level, otherwise, was low NT-proBNP level. The outcomes of interest were mortality, cardiovascular events, and other postoperative outcomes. Outcome of mortality was defined as all-cause mortality after congenital heart surgery. Defined as a combined endpoint, cardiovascular events included heart failure, arrhythmia (requiring treatment), thromboembolic events (pulmonary embolism, myocardial infarction, or ischemic cerebrovascular accident), and cardiac reinterventions (percutaneous or surgical) (24). Other postoperative outcomes included prolonged intensive care unit (ICU) stay (ICU stay >24 h), prolonged mechanical ventilation (mechanical ventilation time >48 h), hospitalization (for cardiac reasons), and acute kidney injury (AKI).

Study selection

We have expanded our inclusion criteria specifically to avoid omitting any studies when screening titles and abstracts. First, studies published in English reporting the prognostic value of NT-proBNP in CHD patients undergoing cardiac surgery were included. Afterwards, a full-text review of all selected studies was performed. Studies that met the following criteria were included: they were (I) cohort studies, (II) regarded individuals with CHD undergoing cardiac surgery as the study subjects, (III) had sufficient data to extract and estimate relative risk and their 95% confidence intervals (CIs), including the risk ratio (RR), odds ratio (OR), hazard ratio (HR), and data to calculate them, and (IV) were published in English. Conversely, studies were excluded if they (I) were case reports, conference abstracts, review papers, qualitative studies, experimental studies, case-control studies, or cross-sectional studies; (II) were duplicate publications. When there was more than one study concerning the same population of CHD, we only included the most comprehensive or recent published one.

Study quality assessment

All included studies were assessed for study quality using the Newcastle-Ottawa Scale (NOS) of cohort studies, and the quality of the included studies was independently assessed by two authors (D Xing and Z Gong). NOS assesses the quality of each study through three modules comprising a total of 8 items, each rated 1–9 stars. The NOS for cohort studies consists of the following three modules: (I) the selection of cohorts, (II) the comparability of cohorts, and (III) the evaluation of outcomes. The first and third modules have a total of seven items with a total score of seven stars; the second module has one item with a total score of two stars. Studies with a score of ≥6 (median) stars were considered to have high-quality methodological studies.

Data extraction

Two of our authors (D Xing and T Wang) independently completed the extraction of data from each included study using standardized forms, with a third reviewer involved in mediating disagreements when consensus could not be reached. The data we extracted includes: the first author and year of publication, study period, geographic region, study design, participants, sample size, age composition, type of CHD, type of surgery, assay method of NT-proBNP, assay time of NT-proBNP, controlled confounders, reported outcomes, and follow-up time. If both unadjusted and adjusted values were present in the study, we extracted the adjusted values preferentially.

Statistical analysis

RR was used as the measurement of prognostic value of NT-proBNP in CHD patients undergoing cardiac surgery. Separate meta-analyses were performed for three outcomes including mortality, cardiovascular events, and other postoperative outcomes. Random effects models were used to calculate the pooled RRs and their corresponding 95% CIs. Cochran's Q statistic (P<0.10 was considered to have significant heterogeneity) and I^2 statistic (I^2>50% was considered to have significant heterogeneity) were used to quantitatively detect heterogeneity between studies.

Subgroup analysis was used to explore possible mediators of heterogeneity, and we analyzed the following variables: geographic region (e.g., European countries, non-European countries), type of CHD [e.g., AS, tetralogy of Fallot, systemic right ventricle, transposition of the great arteries (TGA), multiple types of CHD], type of surgery (e.g., TAVI, Fallot repair, Mustard or Senning,
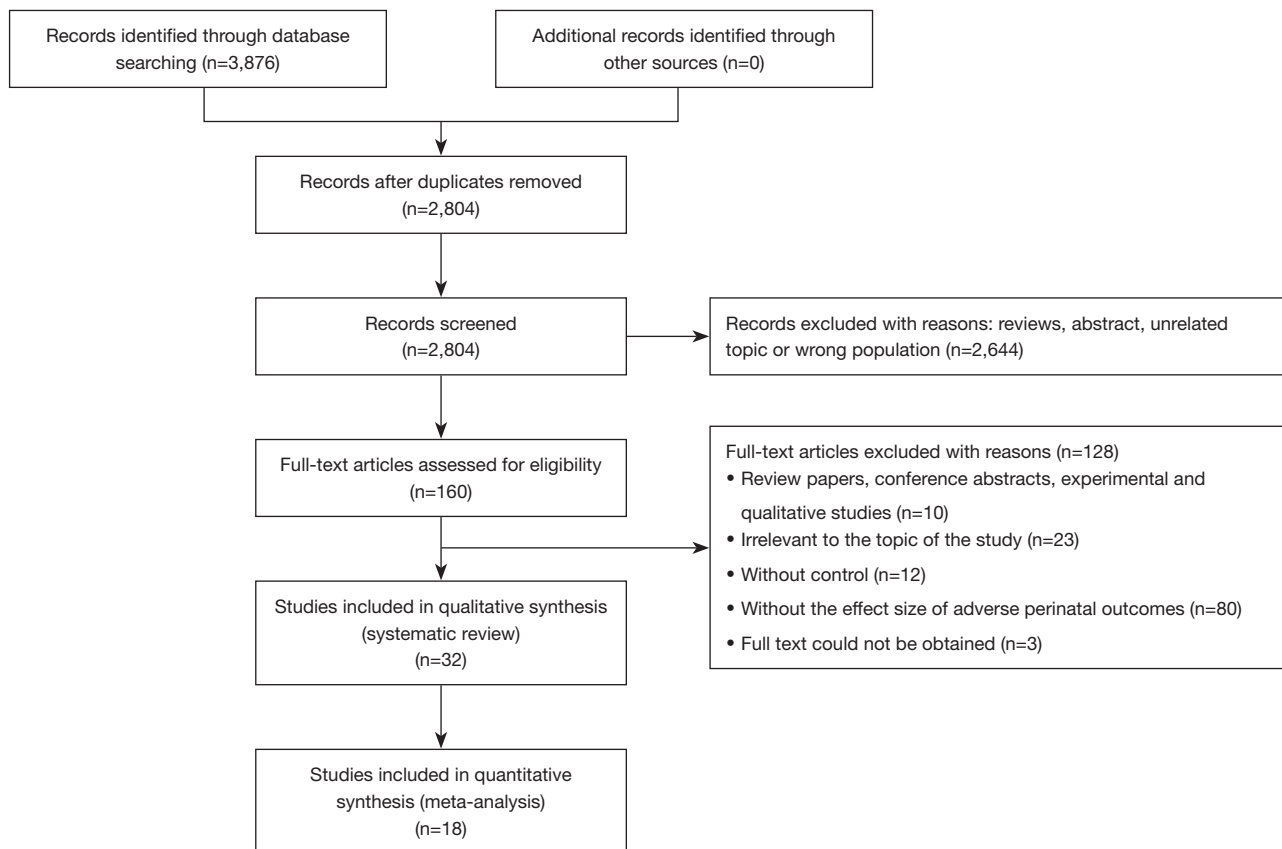
```
┌─────────────────────────────┐   ┌─────────────────────────────┐
│ Records identified through  │   │ Additional records identified│
│ database searching (n=3,876)│   │ through other sources (n=0) │
└──────────────┬──────────────┘   └──────────────┬──────────────┘
               └───────────────┬─────────────────┘
                               ▼
              ┌─────────────────────────────┐
              │ Records after duplicates    │
              │ removed (n=2,804)           │
              └──────────────┬──────────────┘
                             ▼
```

Figure 1 Flow chart of study selection.

multiple types of cardiac surgery), assay method of NT-proBNP (e.g., electrochemiluminescence, Immulite 2500, information not available), whether adjusted for confounding factors (e.g., adjusted versus unadjusted), and follow-up time (e.g., <1 year, 1–8 years). Then, a Q test for heterogeneity was applied to compare the subgroup differences under the random effects model (P<0.05 implied statistically significant differences). Sensitivity analyses were also conducted by comparing the pooled risk estimates from random-effects model (REM) and fixed-effects model (FEM). Given the limited number of included studies for other postoperative outcomes, subgroup and sensitivity analyses were conducted only for mortality and cardiovascular events. Begg's rank correlation test was used to evaluate publication bias (P<0.05 indicated statistically significant differences). R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria), Comprehensive Meta Analysis Version 2.2 and Review Manager Version 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) were used for all analyses.

In addition, for studies showed levels of NT-proBNP in the form of $\log_n$ (n=2, e, 10), only qualitative descriptions were performed rather than quantitatively combined analysis.

Results

Study characteristics

Two authors (D Xing and Z Gong) independently searched through a search strategy, supplemented by manual searches, and obtained a total of 3,876 studies. Among them, after screening titles and abstracts, 3,716 were deleted because of duplication, irrelevance to this study, or because it was a review. Then, after a full-text review of 160 studies, 128 were excluded. Finally, a total of 32 studies were included in the systematic review, of which 18 studies were included in the meta-analysis (17-20,24-37) and 14 were not (38-51) (*Figure 1*).

The characteristics of the 32 included studies were summarized in *Table 1*, with 14 published after 2016

Table 1 Selected characteristics of 32 included studies of NT-proBNP and CHD

First author, Year	Study period	Geographic region	Study design	Participants	Sample size	Age composition	Type of CHD	Type of surgery	Assay method of NT-proBNP	Assay time of NT-proBNP	Controlled confounders	Outcomes	Follow-up time	Quality scores
Ito 2020	2012	Minnesota, America	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	EG: 130; NEG: 131	Adults only	AS	TAVI	NA	Pre-operation	Echocardiography parameters	Mortality	2.7 years	8
Parker 2019	2010–2014	United States and Canada, Americas	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	Total: 522	Children only	Multiple	Multiple	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation, post-operation	STS score, RACHS-1 category	Mortality	30 days	8
Lin 2019	2004	China, Asia	Retrospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	EG: 148; NEG: 181	Children only	Multiple	Multiple	Competitive enzyme immunoassay; ReLIA II, Shenzhen, China	Pre-operation	Age, gender, weight, cardiopulmonary bypass time, aorta cross clamp time, and RACHS-1 category	Prolonged ICU stay	NA	8
Seoudy 2020	2010–2018	Germany, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	EG: 126; NEG: 378	Adults only	AS	TAVI	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	Age and gender	Mortality	1.8 years	7
Burke 2018	2015–2016	United States, Americas	Retrospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	EG: 46; NEG: 96	Adults only	AS	TAVI	NA	Pre-operation	None	Mortality, cardiovascular events, prolonged ICU stay	30 days	7
Vale 2018	2008–2014	Portugal, Europe	Retrospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	Total: 151	Adults only	AS	TAVI	ECLIA; Roche Diagnostics, Mannheim, Germany	Post-operation	STS score, ejection fraction, major bleeding, and comorbidities	Mortality	1 year	7
Qu 2017	2014	China, Asia	Retrospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	Total: 363	Children only	Multiple	Multiple	Competitive enzyme immunoassay; ReLIA II, Shenzhen, China	Pre-operation	RACHS-1 category	Prolonged ICU stay, prolonged mechanical ventilation	3 days	7
Popelová 2017	2005–2015	Czech Republic, Europe	Retrospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	Total: 87	Adults only	TGA	Mustard or Senning	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	None	Mortality	6.4 years	6
Baldenhofer 2017	2009–2011	Germany, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	Total: 100	Adults only	AS	TAVI	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	None	Cardiovascular events	1 year	6
Stundl 2017	2009–2014	Germany, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	EG: 113; NEG: 348	Adults only	AS	TAVI	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	None	Mortality, cardiovascular events	1 year	7
Baggen 2017	2011–2013	the Netherlands, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	EG: 297; NEG: 298	Adults only	Multiple	Multiple	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	Age and sex	Cardiovascular events	3.5 years	7
Westhoff-Bleck 2016	2003–2013	Germany, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	Total: 81	Adults only	TOF	Fallot repair	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	None	Cardiovascular events	6.9 years	7
Stähli 2015	2008–2012	Switzerland, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	EG: 122; NEG: 122	Adults only	AS	TAVI	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	Age and gender	Mortality	9 months	7
Lindman 2015	2000–2014	United States, Americas	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	Total: 345	Adults only	AS	TAVI	NA	Pre-operation	Sex, glomerular filtration rate, diabetes mellitus, obstructive lung disease, NYHA class, and aortic mean gradient	Mortality	1.9 years	7
Krau 2015	2011–2013	Germany, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	EG: 154; NEG: 163	Adults only	AS	TAVI	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	None	Mortality	2 years	7
Bucholz 2015	NA	United States, Americas	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	EG: 51; NEG: 51	Children only	Multiple	Multiple	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation, post-operation	Age, preoperative estimated GFR percentile, hospital site, RACHS-1 category, and CPB time	AKI, prolonged ICU stay	NA	6

Table 1 (*continued*)

Table 1 (continued)

First author, Year	Study period	Geographic region	Study design	Participants	Sample size	Age composition	Type of CHD	Type of surgery	Assay method of NT-proBNP	Assay time of NT-proBNP	Controlled confounders	Outcomes	Follow-up time	Quality scores
Sinning 2015	2010–2013	Germany, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	Total: 310	Adults only	Multiple	TAVI	Immulite 2500; Siemens Medical Solutions Diagnostics, La Garenne Colombes, France	Pre-operation	None	Mortality	1 year	7
Frogoudaki 2014	NA	Greece, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	Total: 76	Adults only	Multiple	Multiple	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	Neutrophil gelatinase-associated lipocalin	Mortality, cardiovascular events	1.7 years	6
Borz 2014	2006–2012	France, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	EG: 118; NEG: 118	Adults only	Multiple	TAVI	Immulite 2500; Siemens Medical Solutions Diagnostics, La Garenne Colombes, France	Pre-operation	None	Mortality, cardiovascular events, AKI	1 year	7
Seiffert 2014	NA	Germany, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	Total: 347	Adults only	AS	TAVI	NA	Pre-operation	Age and sex	Mortality	1 year	7
Ribeiro 2014	NA	Canada, Americas	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	EG: 148; NEG: 185	Adults only	AS	TAVI	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	Sex, chronic atrial fibrillation, chronic obstructive pulmonary disease, estimated glomerular filtration, and stroke volume index	Mortality	4 years	7
Westhoff-Bleck 2013	2003–2013	Germany, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	Total: 116	Adults only	Systemic right ventricle	Mustard or Senning	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	NYHA class, tricuspid regurgitation, systemic ventricular function, and history of tachyarrhythmia	Mortality, cardiovascular events, hospitalisation	7.3 years	7
Elhmidi 2013	2007–2010	Germany, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	EG: 123; NEG: 250	Adults only	AS	TAVI	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	None	Mortality	1 year	7
Lange 2012	2007–2010	Germany, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	Total: 420	Adults only	AS	TAVI	NA	Pre-operation	Stroke, STS score, and ejection fraction	Mortality	6 months	7
Rérez-Piaya 2011	2007–2008	Spain, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	Total: 68	Children only	Multiple	Open-heart surgery	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	Age and RACHS-1 category	Prolonged ICU stay	2 days	7
Spargias 2011	2007–2010	Greece, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	EG: 27; NEG: 54	Adults only	AS	TAVI	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	None	Mortality	1.4 years	6
Pfister 2010	2008–2009	Germany, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	EG: 15; NEG: 16	Adults only	Multiple	TAVI	NA	Pre-operation	None	Mortality	2 months	6
Carmona 2008	2004–2005	Brazil, Americas	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	Total: 46	Children only	Multiple	NA	ELISA; Biomedica, Vienna, Austria	Pre-operation	Age and gender	Mortality	NA	6
Røsjø 2014	2009–2012	Norway, Europe	Prospective cohort study	EG: patients with AS needed to surgery; NEG: Age, body mass index and gender-matched healthy control subjects	EG: 57; NEG: 13	Adults only	AS	TAVI	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	Age, body mass index, and gender	Mortality	3.5 years	8
Hirono 2014	2008–2012	Japan, Asia	Prospective cohort study	EG: patients with TOF after surgical repair; NEG: Age-matched healthy control patients	EG: 58; NEG: 53	Children only	TOF	NA	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	Age	Reoperation	NA	7
Seoudy 2021	2010–2019	the Netherlands, Europe	Prospective cohort study	EG: patients from hospital with high NT-proBNP level; NEG: patients from hospital with low NT-proBNP level	Total: 349	Adults only	AS	TAVI	ECLIA; Roche Diagnostics, Mannheim, Germany	Pre-operation	Age, gender, congenital diagnosis, NYHA class, cardiac medication and systemic ventricular function	Mortality	1 year	8
Green 2021	2010–2014	United States, Americas	Retrospective cohort study	EG: patients with AS needed to surgery; NEG: Age, body mass index and gender-matched healthy control subjects	Total: 162	Children only	Multiple	Multiple	ELISA	Pre-operation, post-operation	STS score	Hospitalisation	NA	7

NT-proBNP, N-terminal pro-form B-type natriuretic peptide; CHD, congenital heart diseases; EG, exposed group; NEG: non-exposed group; AS, aortic stenosis; TAVI, transcatheter aortic valve implantation; NA, not available; ECLIA, electrochemiluminescence; STS score, Society of Thoracic Surgeons score; RACHS-1 category, Risk Adjustment for Congenital Heart Surgery-1 category; ICU, intensive care unit; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; NYHA class, New York Heart Association functional class; GFR, glomerular filtration rate; CPB, cardiopulmonary bypass; AKI, acute kidney injury; ELISA, enzyme-linked immunosorbent assay.

(17,18,24-28,37-42,51) and 18 published before 2016 (19,20,29-36,43-50). The studies were published between 2008 and 2021 involving a total of 7,571 participants. Twenty-one (65.6%) studies (18-20,24,26-31,33-37,40,41,45-47,49) were conducted in the European countries and 11 (34.4%) studies (17,25,32,38,39,42-44,48,50,51) in non-European countries. All studies sampled CHD patients from clinic-based population. Eight (25.0%) studies were targeted on children, while the others were targeted on adults. Sixteen (50.0%) studies included patients with AS, one study included patients with systemic right ventricle, one study included patients with TGA, two studies included patients with tetralogy of Fallot (TOF), while the remaining studies included multiple types of CHD patients. Regarding type of surgery, TAVI was reported in 19 (59.4%) studies, Mustard or Senning in two studies, Fallot repair in one study, open-heart surgery in one study, multiple types of surgery in seven studies, while the information was not available in two studies. For the assay method of NT-proBNP, electrochemiluminescence immunoassay (ECLIA) was used in 20 (62.5%) studies, competitive enzyme immunoassay in two studies, chemiluminescence immunoassay (Immulite 2500) in two studies, enzyme-linked immunosorbent assay (ELISA) in two studies, while the method used in the remaining studies was unclear. Twenty-eight (87.5%) studies measured NT-proBNP levels at pre-operation, one study measured NT-proBNP levels at post-operation, and three studies measured NT-proBNP levels both at pre-operation and post-operation. All but 11 studies (34.4%) adjusted or matched for age, sex, and other possible confounders. For the follow-up time, 16 studies (50.0%) were <1 year, 11 studies (34.4%) were 1–8 years, while the others were unclear.

Out of the 32 included studies, 24 studies reported on mortality (17 of them were able to extract the information needed for the meta-analysis); nine studies reported on cardiovascular events (eight of them provided sufficient information for meta-analysis); 11 studies reported on other postoperative outcomes (three of them provided sufficient information for meta-analysis), specifically, two reported on AKI, five studies reported on prolonged ICU stay, one study reported on prolonged mechanical ventilation, two studies reported on hospitalisation, and one study reported on reoperation.

All included studies were cohort studies, so the NOS of cohort studies was used to assess study quality. Each study had a score of ≥6, as shown in *Table 1*.

NT-proBNP levels and risk of mortality

Risk estimate between NT-proBNP levels and mortality in patients with CHDs undergoing cardiac surgery are summarized in *Figure 2*. Overall, CHD patients at high NT-proBNP levels yielded a significantly increased risk of mortality compared with those at low NT-proBNP levels (RR =1.14; 95% CI: 1.08–1.20; n=17). However, significant heterogeneity was detected (I^2=90%; P<0.1). The Begg's rank correlation test did not find potential evidence of publication bias (z=1.36, P=0.20). Sensitivity analysis was performed by comparing the pooled risk estimates of mortality from REM and FEM; result showed that the risk estimate of mortality associated with the high level of NT-proBNP based on the two methods were not significantly different (REM: RR =1.14, 95% CI: 1.08–1.20; FEM: RR =1.02, 95% CI: 1.01–1.03).

Subgroup analyses for risk estimates between NT-proBNP levels and mortality in patients with CHD undergoing cardiac surgery were summarized in *Table 2*. Overall, the variables "geographic region" (χ^2=6.29, P=0.01), "type of CHD" (χ^2=15.20, P<0.01), and "assay method of NT-proBNP" (χ^2=6.90, P=0.03) could serve as moderators of heterogeneity, however, neither of the variables "type of surgery" nor "whether adjusted for confounding factors" could explain the source of heterogeneity (all P>0.05). Specifically, the risk of mortality associated with a higher level of NT-proBNP increased further when data focused on European countries (RR =1.10; 95% CI: 1.05–1.16), studies included patients with AS (RR =1.81; 95% CI: 1.38–2.39), studies measured NT-proBNP by ECLIA (RR =1.11; 95% CI: 1.05–1.16), studies followed up less than or equal to 1 year (RR =1.59; 95% CI: 1.19–2.12), and studies followed up 1 to 8 years (RR =2.66; 95% CI: 1.54–4.57).

There were five (43,45,46,48,49) studies dealing with NT-proBNP levels as log-transformed data. Carmona *et al.* (48) assessed children younger than 18 months with CHD undergoing cardiac surgery and suggested that preoperative NT-proBNP level was associated with higher overall mortality. Lindman *et al.* (43), Seiffert *et al.* (45), and Røsjø *et al.* (49) assessed adults older than 70 years with AS undergoing TAVI and showed that preoperative NT-proBNP levels were associated with a significantly higher risk of mortality, while Lange *et al.* (46). did not find a significant association between preoperative NT-proBNP levels and risk of mortality in AS patients over 70 years old and undergoing TAVI.
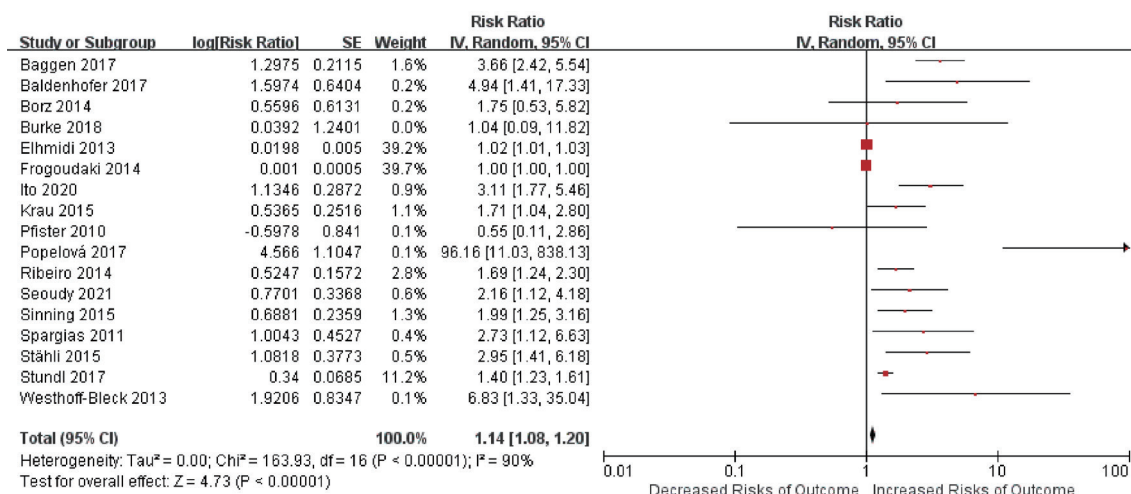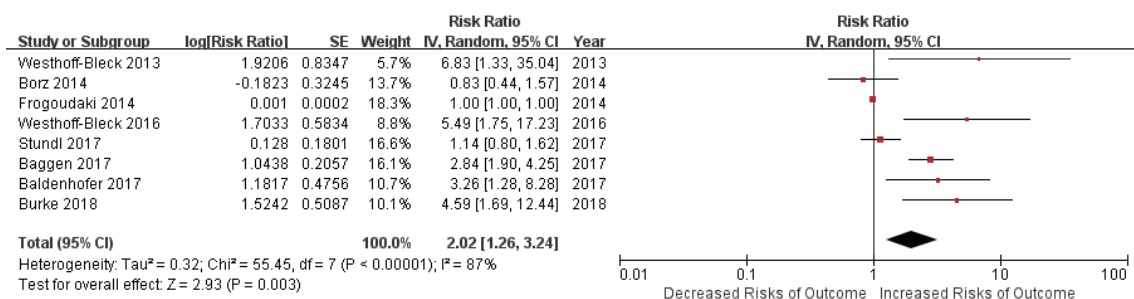
Figure 2 Forest plot of NT-proBNP and risk of mortality. CI, confidence interval; IV, inverse variance; SE, standard error; NT-proBNP, N-terminal pro-form B-type natriuretic peptide.

NT-proBNP levels and risk of cardiovascular events

Risk estimate between NT-proBNP levels and cardiovascular events in patients with CHDs undergoing cardiac surgery are summarized in *Figure 3*. Overall, CHD patients at high NT-proBNP levels had a significantly higher risk of cardiovascular events compared with those at low NT-proBNP levels (RR =2.02; 95% CI: 1.26–3.24; n=8). However, significant heterogeneity was detected (I^2=87%; P<0.1). The Begg's rank correlation test did not find potential evidence of publication bias (z=0.99, P=0.32). Sensitivity analysis was performed by comparing the pooled risk estimates of mortality from REM and FEM. The results showed that the risk estimate of cardiovascular events associated with the high level of NT-proBNP based on the two methods was not significantly different (REM: RR =2.02; 95% CI: 1.26–3.24; FEM: RR =1.01, 95% CI: 1.01–1.02).

Subgroup analyses for risk estimates between NT-proBNP levels and cardiovascular events in patients with CHD undergoing cardiac surgery were summarized in *Table 3*. Overall, none of the variables "geographic region", "type of CHD", "type of cardiac surgery", and "whether adjusted for confounding factors" could explain the source of heterogeneity (all P>0.05). Specifically, when data focused on European countries (RR =1.82; 95% CI: 1.13–2.92), studies adjusted for confounding factors (RR =2.17; 95% CI: 1.83–5.69), the risk of cardiovascular events associated

with NT-proBNP levels increased further, and studies were followed-up 1 year to 8 years (RR =2.67; 95% CI: 1.09–6.59).

NT-proBNP levels and risk of other postoperative outcomes

Risk estimate between NT-proBNP levels and other postoperative outcomes in patients with CHD undergoing cardiac surgery are summarized in *Figure 4*. Overall, CHD patients at high NT-proBNP levels did not yield a significantly increased risk of other postoperative outcomes compared with those at low NT-proBNP levels (RR =1.73; 95% CI: 0.86–3.47; n=3). However, significant heterogeneity was detected (I^2=71%; P<0.1), and no publication bias was detected by Begg's rank correlation test (z=0.52, P=0.60). Subgroup and sensitivity analysis were not performed due to the limited number of included studies.

There were four (42,44,47,50) studies dealing with NT-proBNP levels as log-transformed data. These studies all assessed children younger than 7 years with CHD undergoing cardiac surgery. Qu *et al.* (42), Bucholz *et al.* (44), and Rérez-Piaya *et al.* (47) all reported that NT-proBNP levels associated with a significantly higher risk of prolonged ICU stay in pediatric CHD patients, and Bucholz *et al.* (44), showed a significant relationship between NT-proBNP levels and AKI. Hirono *et al.* (50) demonstrated a significant increased risk estimate between preoperative NT-proBNP

Table 2 Subgroup analysis for NT-proBNP levels and risk of mortality

Subgroup variables	No. of studies	Pooled RR (95% CI)	I^2 (%)	P for heterogeneity	Test for subgroup differences	
					χ^2	P
Geographic region	17				6.29	0.01
Europe	14	1.10 (1.05, 1.16)	91.0	<0.01		
Non-Europe	3	2.09 (1.27, 3.45)	46.0	0.16		
Type of CHD					15.20	<0.01
AS	10	1.81 (1.38, 2.39)	88.0	<0.01		
TGA	1	96.16 (11.03, 838.13)	–	–		
Systemic right ventricle	1	6.83 (1.33, 35.04)	–	–		
Multiple	5	1.64 (0.81, 3.32)	92.0	<0.01		
Type of surgery					3.74	0.15
TAVI	13	1.79 (1.39, 2.30)	86.0	<0.01		
Mustard or Senning	2	23.20 (1.75, 307.82)	73.0	0.06		
Multiple	2	1.88 (0.53, 6.70)	97.0	<0.01		
Assay method of NT-proBNP					6.90	0.03
ECLIA	12	1.11 (1.05, 1.16)	92.0	<0.01		
Immulite 2500	2	1.96 (1.27, 3.01)	0.0	0.84		
NA	3	1.56 (0.46, 5.26)	54.0	0.12		
Whether adjusted for confounding factors					1.12	0.29
Adjusted	7	2.34 (1.37, 3.99)	93.0	<0.01		
Unadjusted	10	1.68 (1.23, 2.28)	86.0	<0.01		
Follow-up time					2.67	0.10
<1 year	9	1.59 (1.19, 2.12)	84.0	<0.01		
1–8 years	8	2.66 (1.54, 4.57)	93.0	<0.01		

NT-proBNP, N-terminal pro-form B-type natriuretic peptide; RR, risk ratio; CI, confidence interval; CHD, congenital heart disease; AS, aortic stenosis; TGA, transposition of the great arteries; TAVI, transcatheter aortic valve implantation; ECLIA, electrochemiluminescence immunoassay; NA, not available.

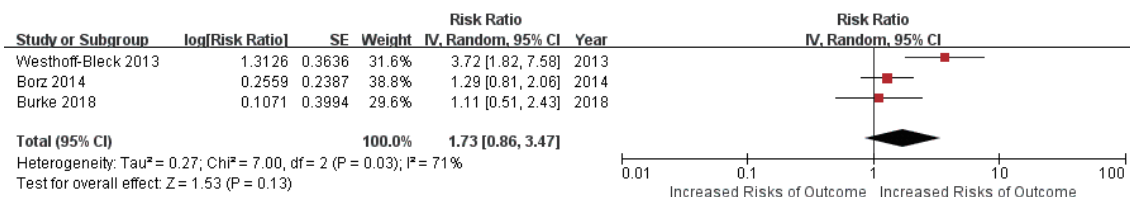**Figure 3** Forest plot of NT-proBNP and risk of cardiovascular events. CI, confidence interval; IV, inverse variance; SE, standard error; NT-proBNP, N-terminal pro-form B-type natriuretic peptide.

Table 3 Subgroup analysis for NT-proBNP levels and risk of cardiovascular events

Subgroup variables	No. of studies	Pooled RR (95% CI)	I^2 (%)	P for heterogeneity	Test for subgroup differences	
					χ^2	P
Geographic region					2.71	0.10
Europe	7	1.82 (1.13, 2.92)	87.0	<0.01		
Non-Europe	1	4.59 (1.69, 12.44)	–	–		
Type of CHD					6.03	0.11
AS	3	2.36 (0.90, 6.16)	80.0	<0.01		
TOF	1	5.49 (1.75, 17.23)	–	–		
Systemic right ventricle	1	6.83 (1.33, 35.04)	–	–		
Multiple	3	1.35 (0.65, 2.77)	92.0	<0.01		
Type of surgery					4.97	0.17
TAVI	4	1.73 (0.87, 3.44)	76.0	<0.01		
Fallot repair	1	5.49 (1.75, 17.23)	–	–		
Mustard or Senning	1	6.83 (1.33, 35.04)	–	–		
Multiple	2	1.65 (0.60, 4.59)	96.0	<0.01		
Whether adjusted for confounding factors					0.00	0.97
Adjusted	3	2.17 (1.83, 5.69)	94.0	<0.01		
Unadjusted	5	2.11 (1.05, 4.24)	78.0	<0.01		
Follow-up time					0.57	0.45
<1 year	4	1.73 (0.87, 3.44)	76.0	<0.01		
1–8 years	4	2.67 (1.09, 6.59)	92.0	<0.01		

NT-proBNP, N-terminal pro-form B-type natriuretic peptide; RR, risk ratio; CI, confidence interval; CHD, congenital heart disease; AS, aortic stenos; TOF, Tetralogy of Fallot; TAVI, transcatheter aortic valve implantation.

Figure 4 Forest plot of NT-proBNP and risk of other postoperative outcomes. CI, confidence interval; IV, inverse variance; SE, standard error; NT-proBNP, N-terminal pro-form B-type natriuretic peptide.

level and reoperation in children corrected TOF.

Discussion

In our study, by utilizing data from 32 published studies involving 7,571 CHD individuals, we provided evidence

on the prognostic value of NT-proBNP in CHD patients undergoing cardiac surgery. Compared with those at low NT-proBNP levels, CHD patients at high NT-proBNP levels had significantly increased risks of mortality and cardiovascular events, whereas the risk of other postoperative outcomes was comparable between

the two groups. As far as we know, our study is the most comprehensive and up-to-date meta-analysis assessing the prognostic value of NT-proBNP in congenital heart surgery.

To date, only one meta-analysis has been performed on the prognostic value of NT-proBNP in CHD patients undergoing cardiac surgery. Based on 16 eligible studies involving a total of 3,679 patients who underwent TAVA for AS, Takagi et al. indicated that high levels of baseline NT-proBNP predict increased mortality after TAVI for AS (OR =1.88) (21). Our study provides supportive evidence for this. Compared with those at low levels of NT-proBNP, patients with CHD undergoing cardiac surgery at high levels of NT-proBNP yielded a significantly increased risk of mortality (RR =1.14); risk estimates were further increased when the data focused only on studies performed in AS patients (RR =1.81) and studies using TAVI as a surgical method (RR =1.79). On the one hand, the sample size of our study is large than that of the previous meta-analysis, which can help to increase the power of our results. On the other hand, in the previous meta-analysis, only the relative risk for mortality associated with high levels of baseline NT-proBNP was estimated. The non-fatal outcomes such as cardiovascular events, which are common and important in CHD patients, are not reported. Unique to our study, the impact of prognostic value of baseline NT-proBNP for risk of cardiovascular events and other postoperative outcomes in CHD patients undergoing cardiac surgery were evaluated. Results showed that high levels of preoperative NT-proBNP were linked with a statistically significant increment in cardiovascular events; this suggests that regular postoperative follow-up of patients with CHD undergoing cardiac surgery to assess their long-term cardiovascular risk might be necessary, which can be helpful for early identification and timely intervention for cardiovascular events and, therefore, decrease in incidence of cardiovascular-related mortality.

Limitations

There are several limitations in our study. First, current literature did not reach an agreement on reference intervals of NT-proBNP, because the existence of several degraded peptides in the sample affected differently commercial methods (52). Hence, results in individual patients should be viewed dialectically. Second, significant heterogeneity was detected between the included cohort studies. To explore heterogeneity sources, subgroup analyses have been carried out according to geographic region, type of CHD, type of surgery, assay method of NT-proBNP, and whether adjusted for confounding factors. Although we found several heterogeneity moderators, such as geographic region, type of CHD, and assay method of NT-proBNP, there was still some evidence of heterogeneity among subgroups. However, the heterogeneity was inevitable and expected given the numerous differences in socioeconomic situation, study population, follow-up time, methodology, and ethnic background. Nevertheless, we believe the effect of heterogeneity to be small in consideration of the steady summary estimates across the subgroup and sensitivity analyses. Besides, significant unmeasured confounding factors may influence the observed prognostic value of NT-proBNP in CHD patients undergoing cardiac surgery in our meta-analysis. Though none of them have sufficiently controlled all latent confounding factors, such as gender, age, body mass index, complications (e.g., diabetes mellitus, lung disease), more than 60% of the studies have adjusted for more than one potential confounding factors. Furthermore, subgroup analysis indicated that the risk estimates of mortality and cardiovascular events in subjects with a higher level of NT-proBNP were comparable between studies adjusted for confounding factor and studies without any adjustment. Besides, because the ability of cohort studies to verify cause and effect is weaker than that of randomized controlled trials, this study only included cohort studies and not randomized controlled trials, so the results of this meta-analysis may have certain limitations. Lastly, this systematic review and meta-analysis merely included studies published in English, so added research in other languages is needed to confirm the findings.

Strengths

Our study has several strengths. First, we included the latest literature, which means that our findings have good implications for current practice. We evaluated, for the first time, the risks of the comprehensive prognosis associated with NT-proBNP levels in CHD patients undergoing cardiac surgery, such as mortality, cardiovascular events, and other postoperative outcomes. Furthermore, the results of the subgroup analyses can address specific questions about geographic region, type of CHD, and assay method of NT-proBNP, and the results of the sensitivity analysis indicated the robustness of prognostic value of NT-proBNP levels in congenital heart surgery. Finally, due to the larger sample size of this meta-analysis, the statistical power

was improved, making the composite risk estimates more realistic and reliable.

Our finding of significant associations between the high level of NT-proBNP and future risk of mortality and cardiovascular events has important clinical and public health implications. Our findings will help clinicians make more informed decisions in the management of patients undergoing cardiac surgery for correction/palliation of CHD. Until more definitive data are available, the measurement of NT-proBNP cannot replace echocardiography, but may serve as a complementary low-cost, simple, promising, and noninvasive tool in the perioperative management of patients with CHD. Further investigation, especially large-scale well-controlled studies on sequential NT-proBNP measurement, is crucially necessary to address the prognostic value of NT-proBNP in congenital heart surgery. Besides, the issue on risks of effect of NT-proBNP in long-term follow-up of CHD patients after surgery is worthy of systematic induction.

Conclusions

Our study showed that CHD patients undergoing cardiac surgery at high NT-proBNP levels had elevated risks of mortality and cardiovascular events when compared with those at low NT-proBNP levels. Further large-scale and well-controlled studies are needed to confirm our findings.

Acknowledgments

Footnote

Provenance and Peer Review: While submitted as a standard submission to the journal, this article is selected as part of the special series "Current Management Aspects in Adult Congenital Heart Disease (ACHD): Part V" published in *Cardiovascular Diagnosis and Therapy*, with joint decision from the editorial office and Guest Editors (Yskert von Kodolitsch, Harald Kaemmerer, Koichiro Niwa). The article has undergone external peer review.

Reporting Checklist: The authors have completed the PRISMA reporting checklist and MOOSE reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-155/rc

Data Sharing Statement: https://cdt.amegroups.com/article/view/10.21037/cdt-22-155/dss

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Mitchell SC, Korones SB, Berendes HW. Congenital heart disease in 56,109 births. Incidence and natural history. Circulation 1971;43:323-32.
2. Krasuski RA, Bashore TM. Congenital Heart Disease Epidemiology in the United States: Blindly Feeling for the

Charging Elephant. Circulation 2016;134:110-3.

3. Saxena A, Mehta A, Sharma M, et al. Birth prevalence of congenital heart disease: A cross-sectional observational study from North India. Ann Pediatr Cardiol 2016;9:205-9.

4. Zhao QM, Ma XJ, Ge XL, et al. Pulse oximetry with clinical assessment to screen for congenital heart disease in neonates in China: a prospective study. Lancet 2014;384:747-54.

5. Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. Am Heart J 2004;147:425-39.

6. Eindhoven JA, van den Bosch AE, Jansen PR, et al. The usefulness of brain natriuretic peptide in complex congenital heart disease: a systematic review. J Am Coll Cardiol 2012;60:2140-9.

7. Oliver JM, Gallego P, Gonzalez AE, et al. Risk factors for excess mortality in adults with congenital heart diseases. Eur Heart J 2017;38:1233-41.

8. Stout KK, Broberg CS, Book WM, et al. Chronic Heart Failure in Congenital Heart Disease: A Scientific Statement From the American Heart Association. Circulation 2016;133:770-801.

9. Daniels LB, Maisel AS. Natriuretic peptides. J Am Coll Cardiol 2007;50:2357-68.

10. Soldin SJ, Soldin OP, Boyajian AJ, et al. Pediatric brain natriuretic peptide and N-terminal pro-brain natriuretic peptide reference intervals. Clin Chim Acta 2006;366:304-8.

11. Teixeira RP, Neves AL, Guimarães H. Cardiac biomarkers in neonatology: BNP/NTproBNP, troponin I/T, CK-MB and myoglobin – a systematic review. Journal of Pediatric and Neonatal Individualized Medicine (JPNIM) 2017;6:e060219.

12. Afshani N, Schülein S, Biccard BM, et al. Clinical utility of B-type natriuretic peptide (NP) in pediatric cardiac surgery--a systematic review. Paediatr Anaesth 2015;25:115-26.

13. Cantinotti M, Giovannini S, Murzi B, et al. Diagnostic, prognostic and therapeutic relevance of B-type natriuretic hormone and related peptides in children with congenital heart diseases. Clin Chem Lab Med 2011;49:567-80.

14. Knirsch W, Häusermann E, Fasnacht M, et al. Plasma B-type natriuretic peptide levels in children with heart disease. Acta Paediatr 2011;100:1213-6.

15. Koch A, Zink S, Singer H. B-type natriuretic peptide in paediatric patients with congenital heart disease. Eur Heart J 2006;27:861-6.

16. Giordana F, D'Ascenzo F, Nijhoff F, et al. Meta-analysis of

predictors of all-cause mortality after transcatheter aortic valve implantation. Am J Cardiol 2014;114:1447-55.

17. Ito S, Miranda WR, Jaffe AS, Oh JK. Prognostic Value of N-Terminal Pro-form B-Type Natriuretic Peptide in Patients With Moderate Aortic Stenosis. Am J Cardiol 2020;125:1566-70.

18. Stundl A, Lünstedt NS, Courtz F, et al. Soluble ST2 for Risk Stratification and the Prediction of Mortality in Patients Undergoing Transcatheter Aortic Valve Implantation. Am J Cardiol 2017;120:986-93.

19. Krau NC, Lünstedt NS, Freitag-Wolf S, et al. Elevated growth differentiation factor 15 levels predict outcome in patients undergoing transcatheter aortic valve implantation. Eur J Heart Fail 2015;17:945-55.

20. Borz B, Durand E, Godin M, et al. Does residual aortic regurgitation after transcatheter aortic valve implantation increase mortality in all patients? The importance of baseline natriuretic peptides. Int J Cardiol 2014;173:436-40.

21. Takagi H, Hari Y, Kawai N, et al. Meta-Analysis of Impact of Baseline N-TerminalPro-Brain Natriuretic Peptide Levels on SurvivalAfter Transcatheter Aortic Valve Implantation for Aortic Stenosis. Am J Cardiol 2019;123:820-6.

22. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336-41.

23. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.

24. Baggen VJ, van den Bosch AE, Eindhoven JA, et al. Prognostic Value of N-Terminal Pro-B-Type Natriuretic Peptide, Troponin-T, and Growth-Differentiation Factor 15 in Adult Congenital Heart Disease. Circulation 2017;135:264-79.

25. Burke WT, Trivedi JR, Flaherty MP, et al. Acute Heart Failure at the Time of Transcatheter Aortic Valve Replacement Does Not Increase Mortality. Innovations (Phila) 2018;13:47-50.

26. Popelová JR, Tomková M, Tomek J. NT-proBNP predicts mortality in adults with transposition of the great arteries late after Mustard or Senning correction. Congenit Heart Dis 2017;12:448-57.

27. Baldenhofer G, Laule M, Mockel M, et al. Mid-regional pro-adrenomedullin (MR-proADM) and mid-regional pro-atrial natriuretic peptide (MR-proANP) in severe aortic valve stenosis: association with outcome after

transcatheter aortic valve implantation (TAVI). Clin Chem Lab Med 2017;55:275-83.

28. Westhoff-Bleck M, Kornau F, Haghikia A, et al. NT-proBNP Indicates Left Ventricular Impairment and Adverse Clinical Outcome in Patients With Tetralogy of Fallot and Pulmonary Regurgitation. Can J Cardiol 2016;32:1247.e29-36.

29. Stähli BE, Gebhard C, Saleh L, et al. N-terminal pro-B-type natriuretic peptide-ratio predicts mortality after transcatheter aortic valve replacement. Catheter Cardiovasc Interv 2015;85:1240-7.

30. Sinning JM, Wollert KC, Sedaghat A, et al. Risk scores and biomarkers for the prediction of 1-year outcome after transcatheter aortic valve replacement. Am Heart J 2015;170:821-9.

31. Frogoudaki A, Andreou C, Parissis J, et al. Clinical and prognostic implications of plasma NGAL and NT-proBNP in adult patients with congenital heart disease. Int J Cardiol 2014;177:1026-30.

32. Ribeiro HB, Urena M, Le Ven F, et al. Long-term prognostic value and serial changes of plasma N-terminal prohormone B-type natriuretic peptide in patients undergoing transcatheter aortic valve implantation. Am J Cardiol 2014;113:851-9.

33. Westhoff-Bleck M, Podewski E, Tutarel O, et al. Prognostic value of NT-proBNP in patients with systemic morphological right ventricles: a single-centre experience. Int J Cardiol 2013;169:433-8.

34. Elhmidi Y, Bleiziffer S, Piazza N, et al. The evolution and prognostic value of N-terminal brain natriuretic peptide in predicting 1-year mortality in patients following transcatheter aortic valve implantation. J Invasive Cardiol 2013;25:38-44.

35. Spargias K, Polymeros S, Dimopoulos A, et al. The predictive value and evolution of N-terminal pro-B-type natriuretic peptide levels following transcutaneous aortic valve implantation. J Interv Cardiol 2011;24:462-9.

36. Pfister R, Wahlers T, Baer FM, et al. Utility of NT-pro-BNP in patients undergoing transapical aortic valve replacement. Clin Res Cardiol 2010;99:301-7.

37. Seoudy H, Lambers M, Winkler V, et al. Elevated high-sensitivity troponin T levels at 1-year follow-up are associated with increased long-term mortality after TAVR. Clin Res Cardiol 2021;110:421-8.

38. Parker DM, Everett AD, Stabler ME, et al. The Association Between Cardiac Biomarker NT-proBNP and 30-Day Readmission or Mortality After Pediatric Congenital Heart Surgery. World J Pediatr Congenit

Heart Surg 2019;10:446-53.

39. Lin F, Zheng L, Cui Y, et al. Prognostic value of perioperative NT-proBNP after corrective surgery for pediatric congenital heart defects. BMC Pediatr 2019;19:497.

40. Seoudy H, Kuhn C, Frank J, et al. Prognostic implications of N-terminal pro-B-type natriuretic peptide in patients with normal left ventricular ejection fraction undergoing transcatheter aortic valve implantation. Int J Cardiol 2020;301:195-9.

41. Vale NC, Campante Teles R, Madeira S, et al. Post-procedural N-terminal pro-brain natriuretic peptide predicts one-year mortality after transcatheter aortic valve implantation. Rev Port Cardiol (Engl Ed) 2018;37:67-73.

42. Qu J, Liang H, Zhou N, et al. Perioperative NT-proBNP level: Potential prognostic markers in children undergoing congenital heart disease surgery. J Thorac Cardiovasc Surg 2017;154:631-40.

43. Lindman BR, Breyley JG, Schilling JD, et al. Prognostic utility of novel biomarkers of cardiovascular stress in patients with aortic stenosis undergoing valve replacement. Heart 2015;101:1382-8.

44. Bucholz EM, Whitlock RP, Zappitelli M, et al. Cardiac biomarkers and acute kidney injury after cardiac surgery. Pediatrics 2015;135:e945-56.

45. Seiffert M, Sinning JM, Meyer A, et al. Development of a risk score for outcome after transcatheter aortic valve implantation. Clin Res Cardiol 2014;103:631-40.

46. Lange R, Bleiziffer S, Mazzitelli D, et al. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. J Am Coll Cardiol 2012;59:280-7.

47. Pérez-Piaya M, Abarca E, Soler V, et al. Levels of N-terminal-pro-brain natriuretic peptide in congenital heart disease surgery and its value as a predictive biomarker. Interact Cardiovasc Thorac Surg 2011;12:461-6.

48. Carmona F, Manso PH, Vicente WV, et al. Risk stratification in neonates and infants submitted to cardiac surgery with cardiopulmonary bypass: a multimarker approach combining inflammatory mediators, N-terminal pro-B-type natriuretic peptide and troponin I. Cytokine 2008;42:317-24.

49. Røsjø H, Dahl MB, Bye A, et al. Prognostic value of circulating microRNA-210 levels in patients with moderate to severe aortic stenosis. PLoS One 2014;9:e91812.

50. Hirono K, Sekine M, Shiba N, et al. N-terminal pro-

brain natriuretic peptide as a predictor of reoperation in children with surgically corrected tetralogy of fallot. Circ J 2014;78:693-700.

51. Green MD, Parker DM, Everett AD, et al. Cardiac Biomarkers Associated With Hospital Length of Stay After Pediatric Congenital Heart Surgery. Ann Thorac Surg 2021;112:632-7.

52. Panteghini M, Clerico A. Understanding the clinical biochemistry of N-terminal pro-B-type natriuretic peptide: the prerequisite for its optimal clinical use. Clin Lab 2004;50:325-31.