Blood biomarkers in patients with repaired Tetralogy of Fallot (rTOF); A systematic review and meta-analysis

Alborikan S, MSc,[a,b,c] Von Klemperer K, MD,[d] Bhan A, MD [d], Walker F, MD,[d] Pandya B, MD,[d] Badiani S, MD,[a,b] Bhattacharyya S, MD,[a,b,e] E Petersen S, [a,b,f] Lloyd G, MD[a,b,e]

a) Barts Heart Centre, St Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom

b) William Harvey Research Institute, Queen Mary University of London, London, United Kingdom

c) King Fahad Specialist Hospital, Cardiac department, Dammam, Saudi Arabia

d) Grown-up Congenital Heart Disease Services, Barts Heart Centre, St. Bartholomew's Hospital, London, UK

e) Institute of Cardiovascular science, UCL, London, UK

f) NIHR Barts Biomedical Research Centre.

Corresponding author

Sahar Alborikan: Sahar.borikan@nhs.net

Telephone number: +447482474733

Address: Echocardiography Laboratory, Barts Heart Centre, St Bartholomew's Hospital, West Smithfield, London, Greater London EC1A 7BE, United Kingdom.

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Abstract

Background: The clinical use and prognostic value of plasma brain natriuretic peptide (NT-proBNP) and soluble suppression of tumourigenicity-2 (sST2) levels are not known in patients with repaired Tetralogy of Fallot (rTOF).

Objectives: We evaluated blood biomarkers in rTOF patients by combining the available evidence, focussing on prognosis, adverse echocardiographic findings and exercise intolerance.

Methods: This systematic review and meta-analysis were carried out in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. For the primary prognostic outcomes, a meta-analysis was performed. For hemodynamic outcomes, a pooled meta-analysis of correlation coefficients (r) was performed. The study protocol was registered with PROSPERO(CRD42020211897).

Results: We analysed 1479 patients with repaired TOF in 23 studies. Mean age was 22.7±8.3 years. The mean value of NT-proBNP was 174.4.1±56.4 pg/ml while ST2 drawn from two investigations was 26.95 ng/ml. There was no difference in mean NT-proBNP between older and younger subjects (160.4 ±37.7 vs190.6 ±72.9, pg/ml, respectively; p>.05). NT-proBNP levels were higher in TAP studies than others with other RVOT intervention (191.6± 57 vs 151±46, pg/ml, p<.05). Elevated NT-proBNP levels were associated with an increased risk of adverse cardiovascular outcomes including death, arrhythmias and acute heart failure with a hazard ratio (HR) of 1.18(95% CI 1.07-1.31, p.001). We noted a moderate correlation between NT-proBNP levels and exercise intolerance, RV structural and volumetric changes (r= -.52, r=.41, P<.001).

Conclusions: NT-proBNP levels are elevated in patients with surgically repaired TOF and are associated with an increased risk of cardiovascular adverse outcomes and exercise intolerance.

Key words: Repaired Tetralogy of Fallot; Natriuretic peptide; NT-proBNP; Transannular patch; Right ventricle.

Abbreviation and Acronyms

rTOF: repaired Tetralogy of Fallot

NT-proBNP: Plasma brain natriuretic peptide

sST2: soluble suppression of tumourigenicity-2

RV: Right ventricle

LV: Left ventricle

PR: Pulmonary regurgitation

TAP: Transannular patch

RVD: Right ventricular dimension

RVEDV: Right ventricular end diastolic volume

PVR: Pulmonary valve replacement

Introduction

Despite 90% long term survival in patients with repaired TOF (rTOF), an increasing number of late complications are present such as right and left ventricular dysfunction, arrhythmia and exercise intolerance related to residua which dictate the need for reintervention (1-4). The degree of pulmonary regurgitation and its relationship to right ventricle (RV) remodelling and symptoms is variable but, in some cases, leads to the development of life-threatening atrial and, ventricular arrhythmias and sudden cardiac death (2,5).

Clinical management is aimed at identifying patients at risk who need intervention. Symptoms are a poor guide to selection as the majority of adult survivors of TOF are asymptomatic (3,6). Using blood biomarkers such as plasma brain natriuretic peptide (NT-proBNP) and soluble suppression of tumourigenicity-2 (sST2) is an emerging adjunct to the existing tools to predict disease progression and potentially could help identify appropriate patients for intervention. NT-proBNP is known to be elevated in asymptomatic patients with repaired TOF compared to other types of congenital heart disease (CHD) (7-11), however, clear data about the usefulness in diagnostics and prognostication in this population is not yet available.

In order to better understand the relationship between NT-proBNP and sST2 in patients with repaired TOF, we undertook this systematic review and meta-analysis to combine the available evidence, focussing on their prognostic value and their association with adverse hemodynamic echocardiographic findings.

Material and Methods

Systematic review and meta-analysis

The systematic review and meta-analysis were carried out in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. The protocol of this study was previously published and registered in the international Prospective Register of Systematic reviews (PROSPERO) (CRD42020211897). The flow diagram in figure 1 demonstrates the literature search based on the PRISMA guidelines.

Inclusion and exclusion criteria

This review was limited to studies published in English. Inclusion criteria were (a) prospectively or retrospectively conducted cohort, cross sectional, single and multicenter studies; (b) Blood biomarkers included in methodology and; (c) adult and adolescent patients with repaired TOF. Studies excluded from the review were those (a) without blood biomarkers data; (b) not published in English and; (c) non rTOF.

Information sources and search strategy

A comprehensive retrospective search of the literature was conducted using databases including MEDLINE, Pubmed, EBM review- Cochrane Database of systematic review, Wiley Online library and EBM reviews, utilising a combination of the following search keywords: "blood biomarkers in Tetralogy of Fallot'", "NT-proBNP in TOF", "sST2 in adult survivors of TOF ",'' Pro-brain natriuretic peptide in CHD'', "Severe pulmonary regurgitation and blood biomarkers". There was no limitation on age. The search included all studies between 1988 and 2020.

Study selection and eligibility criteria

The following steps were performed (figure 1). (1) Identification of titles through database searching. (2) Removal of duplicates. (3) Titles and abstracts screening. (4) Full text sources for further screening. (5) studies which gave outcomes were selected for quantitative analysis. The primary end points of the study were (a) levels of NT-proBNP in patients with repaired TOF; (b) prognostic value of NT-proBNP to composed major cardiovascular outcomes (MACE), defined as the occurrence of acute heart failure, arrhythmias or death from any cause. The secondary end points were (a) association of elevated NT-proBNP levels with hemodynamic echocardiographic changes and to exercise capacity into pooled meta-analysis.

Data extraction

Data collected by one reviewer (S.A) who determined the eligibility of the studies, according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines, and verified by a second expert reviewer (G.L). To prevent bias, the screening was performed independently. The following data were extracted: first author's name, country, year of publication, number of patients included, study design, age, plasma NT-proBNP levels, sST2 when available, correlation coefficients (r) and the conclusion together with main findings of the study. For prognostic analysis, hazard ratios, outcomes measure (mortality or major adverse cardiovascular outcomes), and follow up duration were collected.

Statistical analysis

Studies were divided into (i) those that reported in an adult population and (ii) those reported in a population younger than 18 years old. For the continuous outcome variables, data were presented as mean differences (MD) ± standard deviation. Statistical analyses for the primary results were conducted using SPSS statistics version 26 (IBM corp, London, United Kingdom). For the prognostic studies, a comprehensive meta-analysis was performed using Review Manager (version 5.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). The generic inverse variance method was used to combine log hazard ratios (log HR) and standard errors of the log HR (SElogHR). A fixed-effects model was used to pool the log hazard ratios and 95% confidence interval for all-cause mortality in each study.

For the secondary outcomes, a pooled meta-analysis of correlation coefficients (r) (random effects) using MedCalc (MedCalc software, Belgium, Version 19.6.4) was performed. We pooled the values of correlation coefficients and number recruited in each study. The appraisal of the heterogeneity among studies was conducted via the Q statistics and I^2 statistics, with a value of 0%–24.9% considered insignificant, 25%–49.9% mild, 50%–74.9% moderate, and ≥75% considered severe (12). Publication bias was evaluated by the Begg's test and Egger's test, and a P value <.05 indicated potential publication bias. All p values were two tailed, and the statistical significance was set at <.05.

Quality assessment

The methodological quality of the individual studies was evaluated using the Newcastle-Ottawa Scale (NOS) (13). Each study was judged on eight items, categorised into three groups: cohort selection, the comparability of the groups and the outcome. Stars were awarded for each item, with a maximum score of 9. It assigns a maximum of 4 stars for selection, 2 stars for comparability, and 3 stars for exposure/outcome assessment. Studies with <5 stars were considered low quality, 5–7 stars moderate quality, and >7 stars high quality (table 1). The quality assessment showed an acceptable overall quality, risk of bias and applicability concerns.

Publication bias

We assessed publication bias by visual inspection of the funnel plot of all included studies. The absence of any asymmetric distribution suggested there was no publication bias. In the subgroup analysis of the comprehensive correlation meta- analysis, Begg's test and Egger's test were used to assess the possibility of publication bias in our analysis and any p value <0.05 was considered a significant publication bias.

Results

Literature search outcomes

The literature search identified a total of 300 potentially eligible studies. After the exclusion of irrelevant studies, 224 were screened thoroughly through abstract and/or full text. 99 articles were excluded due to duplication. Of the remaining 125 articles, 50 articles were excluded, as they did not meet the inclusion criteria. Full text article assessment was performed for the remaining 75 articles and 52 articles were further excluded due to unavailability of the full text, leading to a total of 23 articles included in this review. Figure 1 shows the PRISMA flow chart for the systematic selection of studies during the literature search.

Characteristics of selected studies

Of the 23 articles, 13 (57%) reported adult survivors of rTOF (14-26), while 10 studies (43%) were reported on a younger group (27-36). 4 studies (17%) were cross-sectional studies (16,20,22,24), and 19 studies (83%) were cohort studies (14,15,17-19,21,23,25-36). Of those, 18 studies (95%) were conducted prospectively (14,15,17-19,21,23,25-28,30-36) and one study retrospectively (29). All of the included studies reported NT-proBNP and only 2 studies included sST2 in their methodology (14,15). 10 articles (43%) reported the association of NT-proBNP with echocardiographic hemodynamic and structural changes (20,24-26,28-31,33,35). 4 articles (17%) reported the association of NT-proBNP and exercise capacity (24-26,35). 3 articles (13%) reported the prognostic value of NT-proBNP for adverse outcomes (15,17,18) and 2 articles investigated the levels of NT-proBNP following pulmonary valve replacement (PVR) (27,34). Sample size ranged from 16 to 177, and the publication year ranged from 2005 to 2019. Mean age of included participants ranged from 12 to 35 years. All included studies

were single centre with different designs. Baseline characteristics of the included studies are shown in table 1.

Plasma brain natriuretic peptide level (NT-proBNP) in asymptomatic adult and adolescent patients with repaired TOF

Data was collected on 1479 patients with repaired TOF in 23 studies. Mean age in the total population was 22.7±8.3 years. Mean age of the older group was 29±4.5 years and the mean age of the younger group was 14±1.1 years. The mean value of NT-proBNP was 174.4.1±56.4 pg/ml, but ranged from 71.4 to 295 pg/ml. There was no significant difference in mean NT-proBNP between older and younger subjects (160.4 ±37.7 vs 190.6 ±72.9, pg/ml, respectively; p>.05). Mean value of sST2 drawn from two investigations was 26.95 ng/ml (table2).

14 studies (61%) reported NT-proBNP in a population where a trans-annular patch (TAP) was used as a surgical approach (15,16,18-21,23,24,26,28,31,33-35). 9 studies (39%) were reported in a population with other RVOT intervention, such as pulmonary valvotomy or infundibulectomy and/or no reports (14,17,22,25,27,29,30,32,36). Mean NT-proBNP levels were higher in TAP studies than others (191.6± 57 vs 151±46, pg/ml, p<.05) (figure 2).

Meta-analysis on the effect of NT-proBNP on cardiovascular outcomes

The prognostic primary outcomes of all-cause mortality, heart failure and sustained ventricular arrhythmias occurred in 113 patients, as reported in table 3. Three studies (13%) in asymptomatic adult populations investigated the relationship between NT-proBNP and cardiovascular outcomes. The mean NT-proBNP drawn from these investigations was 243± 113 pg/ml. Heng et al demonstrated that NT-proBNP levels were significantly related to all-cause mortality with the longest mean observation time of 10 years among the studies (HR 1.15, 95% CI 1.03-1.28, p<.01). In univariate Cox analysis, the best cut off value of NT-proBNP level to predict all-cause mortality was 147 pg/ml (AUC .68, P.04) (17).

In the second study elevated NT-proBNP levels were the strongest predictor of other adverse outcomes such as sustained ventricular arrhythmias and heart failure, with a mean observation time of 6.9 years (HR 2.83, 95% CI 1.1-7.28, P <.029). In multivariate Cox analysis, the best cut off value of NT-proBNP level to predict adverse clinical events was 232 pg/ml (AUC .873, P.004) (sensitivity of 76.9%, specificity of 85.3%) (18).

In the last study, Laqqan et al reported that elevated NT-proBNP levels were significant predictor of all-cause mortality with a mean observation time of two years (HR 1.3, 95% CI 1.0-1.69, p<.001) (table 3). The authors constructed ROC curves demonstrating the best cut off value of NT-proBNP level to predict heart failure, which was 349.5 pg/ml (AUC .875, P.001) (sensitivity of 71.4%, specificity of 88.9%) (table3) (15).

After an average 6.3 years of follow up, high NT-proBNP levels were associated with an increased risk of cardiovascular outcomes including death, arrhythmias and acute heart failure with a hazard ratio (HR) of 1.18 (95% CI 1.07-1.31, p.001) (figure 3).

Meta-analysis of the association between NT-proBNP and hemodynamic echocardiographic changes

The relationship between NT-proBNP and RV structural, functional and volumetric changes was investigated in 10 (43%) articles. Of these 10 articles, 4 (40%) were reported in the older group, while 6 (60%) were reported in the paediatric group. Most of these articles demonstrated that elevated NT-proBNP levels were associated with either RV dilatation, higher RV end diastolic volumes, RV systolic dysfunction and with severity of pulmonary regurgitation or diastolic dysfunction (20,24-26,28-31,33,35). Only three studies (13%) evaluated the association between raised levels of NT-proBNP and left ventricular parameters. Higher NT-proBNP levels were associated with LV dysfunction (18,20), with LV indexed volume (18), and with LV indexed dimensions (35). Two studies proposed a cut-off NT-proBNP values of 145 pg/ml that could predict the presence of RV dilatation (ROC .95, sensitivity 71%, specificity 100%) (30), and a value of 115 pg/ml (ROC .87, sensitivity 71%-, specificity 78%) that could predict the presence of RV dilatation and/or dysfunction (33).

The meta- analysis showed a statistically significant association of elevated NT-proBNP levels to RV size and right ventricular end diastolic volume (RVEDV). The weighted average (random effects) correlation coefficient among 10 studies was .41 (95% CI .32-.48, P<.001) (table4). The study with the highest correlation was by Cheung et al., 2007 (r=.69, 95% CI .44-.83, P<.001), however, this study was one of the lowest weighted studies included in the analysis, with 31 participants (35). Figure 4a shows the forest plot of pooled correlation coefficients. Visual evaluation of the forest plot suggests that there is a mild degree of heterogeneity which confirmed by I^2 (values of 31.7%, p.15). We observed publication bias by Begg's test (p = <.05) or Egger's test (p = <.05) (figure 4b).

There was a strong association between NT-proBNP and the severity of pulmonary regurgitation. The pooled analysis showed statistically significant association of elevated NT-proBNP levels to severity of pulmonary regurgitation in 5 studies (50%) (20,29,30,31,35). The weighted average (random effects) correlation coefficient was .34 (95% CI .16-.50, P<.001). Figure 4c shows the forest plot of pooled correlation coefficients. Visual assessment of the forest plot suggests a modest degree of heterogeneity, which confirmed by I^2 (values of 69.2 %, p<.05). We observed no publication bias by Begg's test (p= >.05) or Egger's test (p = >.05) (figure 4d).

Meta-analysis of the association between NT-proBNP and reduced exercise capacity in patients with repaired TOF

The relationship between NT-proBNP and exercise intolerance was investigated in 4 articles (17%) (24-26,35**)**. Of these 4 articles, 3 (75%) were reported in adults (24-26), while 1 article was reported in paediatrics (35). All 4 studies supported the relationship between increased NT-proBNP levels and exercise intolerance in asymptomatic patients with repaired TOF (table4).

The pooled analysis showed a statistically significant association of elevated NT-proBNP levels and reduced exercise capacity in this population. The weighted average (random effects) correlation coefficient among 4 studies was -.54 (95% CI -.60- -.36, P<.001) (Table4). Figure 4e shows the forest plot of pooled correlation coefficients. Visual evaluation of the forest plot suggests that there is insignificant degree of heterogeneity which confirmed by I^2 (values of 18.9 %, p>.05). We observed no publication bias by Begg's test (p= >.05) or Egger's test (P = >.05) (figure 4f).

Discussion

This systematic review and meta-analysis demonstrate that NT-proBNP levels are generally elevated in asymptomatic patients with repaired TOF irrespective of age. It showed that NT-proBNP is associated with a range of echocardiographic changes including structural RV changes, RV volume, severity of pulmonary regurgitation and most importantly the deterioration in exercise capacity, clinical condition and mortality. We found that patients with a TAP surgical approach had higher values of NT-proBNP compared to other approaches, suggesting an adverse hemodynamic response.

Plasma brain natriuretic peptide concentration is known to be high in patients with repaired TOF with reference values previously reported as age and gender related (7-11,29,37,38). In contrast in this meta-analysis, we found no difference in NT-proBNP levels between adults and adolescents (160.4 ±37.7 vs 190.6 ±72.9 pg/ml, $p>.05$), suggesting that other anatomical and functional factors, are more important in these patients. Unlike other pathologies such as LV systolic dysfunction, NT-proBNP levels appear to be linked more to RV volumes and surgical selection techniques than underlying patient characteristics. This mirrors the finding that reduced exercise tolerance has no relation to age, but to the surgical selection (39).

NT-proBNP concentrations correlated with RV structural and volumetric changes in the majority of included investigations in this review (20,24-26,28-31,33,35). Our pooled meta-analysis results revealed a moderate association between NT-proBNP levels and RV structural and volumetric changes (r=.41, 95% CI .32-.48, P<.001) (table 4). High concentrations of plasma natriuretic peptide are associated with reduced exercise capacity in adult congenital heart disease (ACHD), but this has not to date been specifically demonstrated in patients with repaired TOF (40). In the studies included in this analysis that evaluated exercise capacity using cardiopulmonary exercise testing (CPET), the majority of patients with high levels of NT-proBNP were asymptomatic, but with reduced exercise capacity (24-26). There were two studies that showed contrary findings (19,20). Looking at these study populations, they were heavily drawn from populations with low NT-proBNP levels and nearly normal functional reserve (124 and 151, pg/ml), and (max VO_2 of 80 and 77, %), suggesting that they were biased towards the most clinically stable patients. In our pooled meta-analysis, despite relatively fewer studies investigating the link between NT-proBNP and exercise capacity, we found a higher modest correlation with exercise if it was compared with the structural and volumetric RV changes (r= -.54 vs r=.41, p<.001).

In terms of intervention studies and NT-proBNP, only two investigations in the included analysis observed a notable reduction in NT-proBNP levels after 6 months following PVR (27,34). These findings may have an important clinical implication that could contribute to the complex debate about the decision-making of timing PVR by having an additive value in detecting any deterioration in cardiac function and functional capacity (22,41,42). Rare documentation of sST2 data which drawn from only two investigations in this review was evident and this limits our sST2 assessment in patients with repaired TOF (14,15). A raised NT-proBNP could potentially detect early RV dysfunction and identify patients who are in need of surgical intervention. This would require identifying specific cut off value of NT-proBNP which predict adverse outcomes.

The prognostic value of NT-proBNP in adult congenital heart disease has not been widely described, and particularly in patients with repaired TOF. Our meta-analysis evaluating the prognostic data from three investigations in adults showed that elevated NT-proBNP levels (mean of 243± 113 pg/ml) in asymptomatic patients were significantly associated with the increased risk of all-cause mortality and major cardiac events, such as acute heart failure, sustained ventricular arrhythmias and death (HR of 1.18 (95% CI 1.07-1.31, p.001). NT-proBNP levels were reported by Laqqan et al as an excellent predictor of adverse outcomes in a low-risk population, with an AUC of .875 corresponding to NT-proBNP>349 pg/ml (15). This was much greater than the other two studies included with observed prognostic relevance (147 and 232 pg/ml) (17,18). This suggests that the magnitude of the mortality deficit is closely linked to the BNP value, with higher values indicating significant risk.

This meta-analysis in 1479 patients with repaired TOF is the first meta-analysis in this group with the proposed end points. Currently, evaluation of NT-proBNP levels is not routinely assessed for systematic categorisation used in risk assessment in these patients. Although all included studies were observational investigations with different methodology, definitive conclusions could be drawn. Firstly, our results demonstrate that despite wide variability, elevated NT-proBNP levels seems to be more related to surgical selection than advancing age. This mirrors our recent publication that showed subsequent exercise intolerance in this population is more a function of surgical technique than a function of age (39). Secondly, these studies suggests that NT-proBNP is a reliable non-invasive tool as which could improve risk stratification in these patients if it is integrated into routine clinical care. Finally, our sub-group analysis results of a wide range of NT-proBNP values in relation to hemodynamic changes and exercise capacity suggests that the use of blood biomarkers could be more sensitive to other existing pathology, which could help in risk assessment in a low-risk population. Future prospective studies will need to investigate the use of index and sequential NT-proBNP measurements to predict adverse outcomes and to facilitate clinical decision making in this population.

Study limitations

This systematic review and meta-analysis were limited by inconsistent characteristics of the study population, the variability of NT-proBNP with some degree of heterogeneity and the rare documentation of sST2. All studies were observational cohorts with limited follow up data but with an overall good quality. Larger prospective and longitudinal studies are warranted to draw an accurate prognostic value of NT-proBNP in relation to subsequent hemodynamic changes in these patients.

Conclusions

Our findings form the first summary and meta-analysis on the prognostic effect of NT-proBNP in patients with repaired TOF. We have demonstrated that elevated levels NT-proBNP were associated with an increased risk of cardiovascular adverse outcomes that were not age or gender related, but seems to be more dependent on surgical selection, the stress on the right ventricle and on the subsequent exercise intolerance. NT-proBNP shows promise in improving risk assessment and guiding timing for intervention in patients with repaired TOF.

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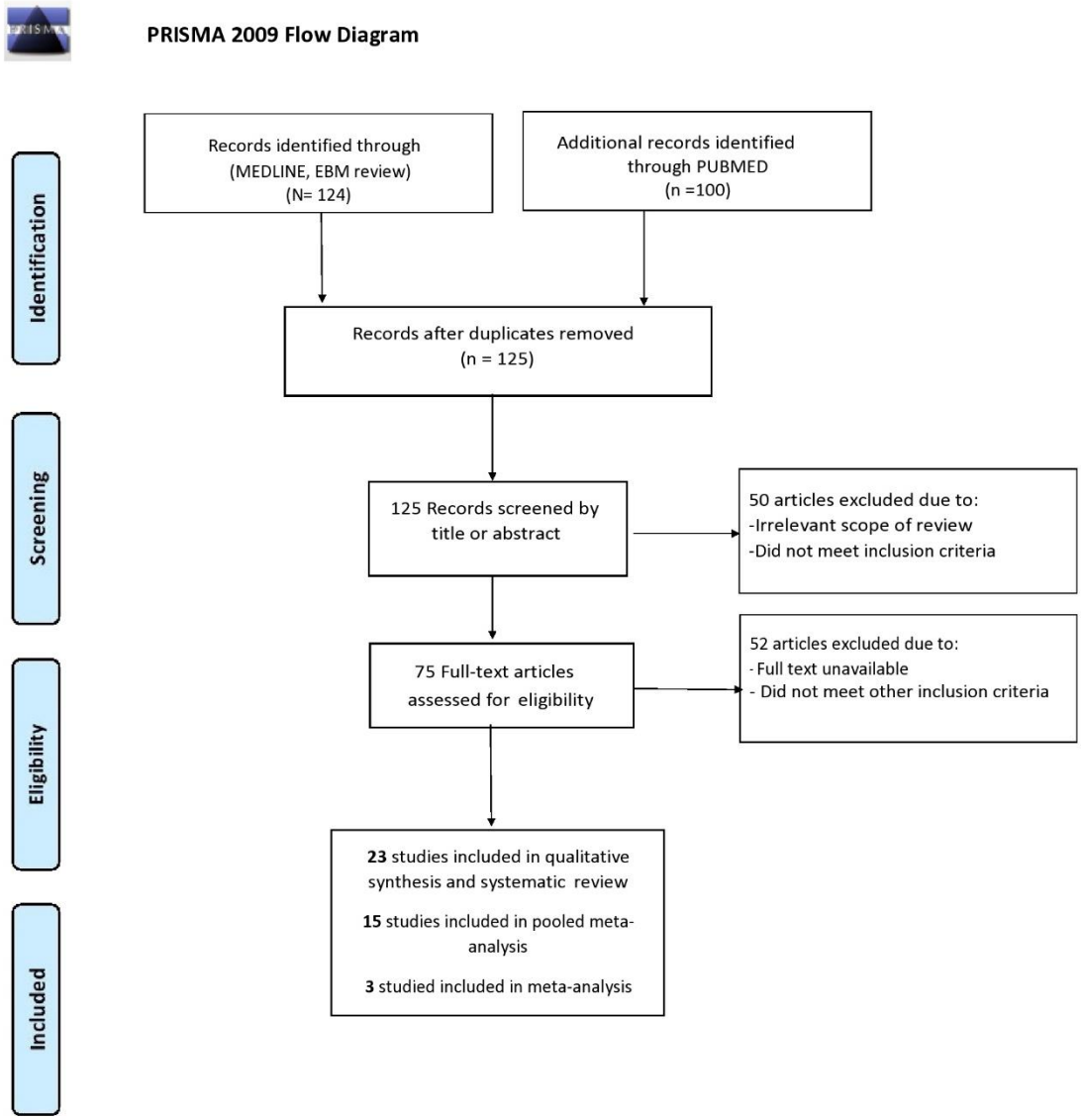
Figure Legends

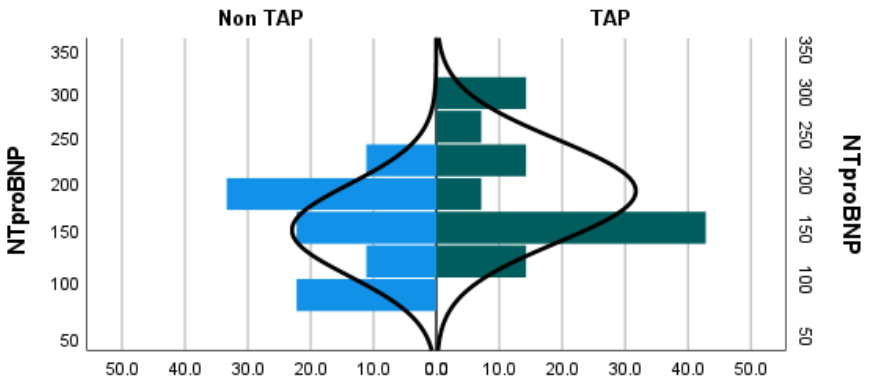
Figure1. The PRISMA flow chart displaying the selection of studies and reasons for exclusion

Figure 2. Difference in mean NT-proBNP between TAP and non-TAP studies

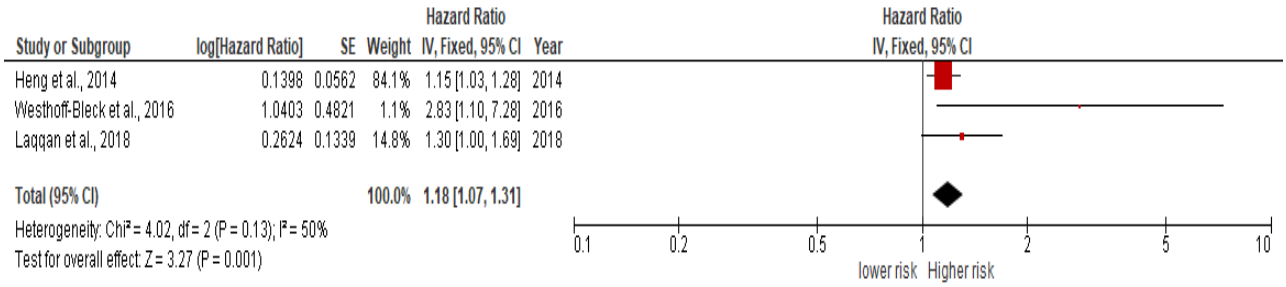
Figure 3. Forest plot of the hazard ratios of high NT-proBNP values with cardiovascular outcomes in patients with repaired TOF

Figure 4. A pooled meta-analysis in 10 studies

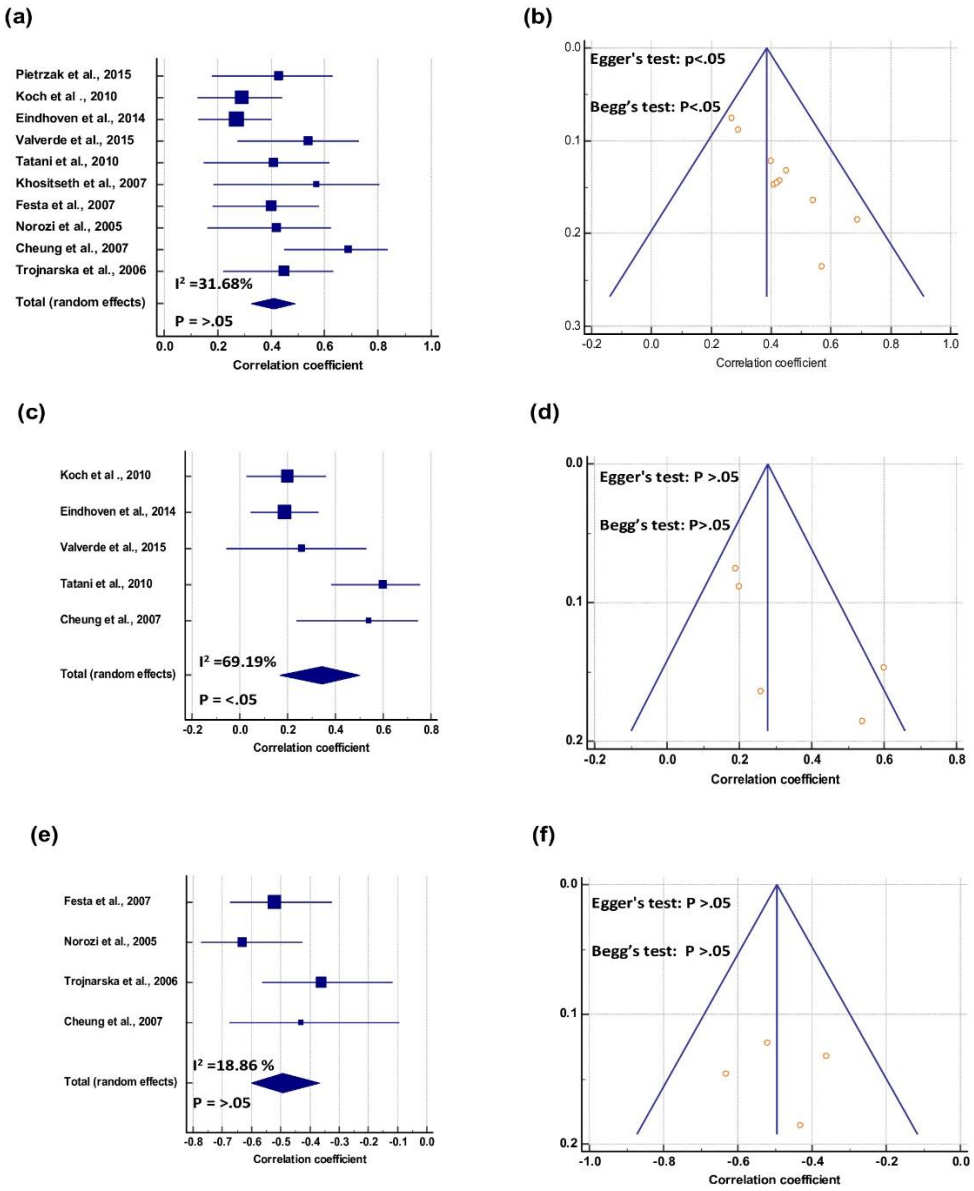

PRISMA 2009 Flow Diagram
Identification
Screening
Eligibility
Included
Records identified through (MEDLINE, EBM review) (N= 124)
Additional records identified through PUBMED (n =100)
Records after duplicates removed (n = 125)
125 Records screened by title or abstract
50 articles excluded due to:
-Irrelevant scope of review
-Did not meet inclusion criteria
75 Full-text articles assessed for eligibility
52 articles excluded due to:
- Full text unavailable
- Did not meet other inclusion criteria
23 studies included in qualitative synthesis and systematic review
15 studies included in pooled meta-analysis
3 studied included in meta-analysis



TAP = studies with transannular patch; non-TAP = studies with other type of RVOT intervention such as pulmonary valvotomy or infundibulectomy and/or no reports.



Data are displayed as HR (95% CI). Heterogeneity as reported by I^2 (I^2= 50%, P.13).


(a)
Pietrzak et al., 2015
Koch et al ., 2010
Eindhoven et al., 2014
Valverde et al., 2015
Tatani et al., 2010
Khositseth et al., 2007
Festa et al., 2007
Norozi et al., 2005
Cheung et al., 2007
Trojnarska et al., 2006
Total (random effects)
I² =31.68%
P = >.05
0.0 0.2 0.4 0.6 0.8 1.0
Correlation coefficient
(b)
Egger's test: p<.05
Begg's test: P<.05
0.0 0.1 0.2 0.3
-0.2 0.0 0.2 0.4 0.6 0.8 1.0
Correlation coefficient
(c)
Koch et al ., 2010
Eindhoven et al., 2014
Valverde et al., 2015
Tatani et al., 2010
Cheung et al., 2007
Total (random effects)
I² =69.19%
P = <.05
-0.2 0.0 0.2 0.4 0.6 0.8
Correlation coefficient
(d)
Egger's test: P >.05
Begg's test: P>.05
0.0 0.1 0.2
-0.2 0.0 0.2 0.4 0.6 0.8
Correlation coefficient
(e)
Festa et al., 2007
Norozi et al., 2005
Trojnarska et al., 2006
Cheung et al., 2007
Total (random effects)
I² =18.86 %
P = >.05
-0.8 -0.7 -0.6 -0.5 -0.4 -0.3 -0.2 -0.1 0.0
Correlation coefficient
(f)
Egger's test: P >.05
Begg's test: P >.05
0.0 0.1 0.2
-1.0 -0.8 -0.6 -0.4 -0.2 0.0
Correlation coefficient

(a) Forest plot of the 10 studies evaluated in meta-analysis for the assessment of the association between NT-proBNP levels and RV size and RVEDV. **(b)** Funnel plot of all the 10 studies, where there is publication bias. **(c)** Forest plot of the 5 studies evaluated in meta-analysis for the assessment of the association between NT-proBNP levels and PR. **(d)** Funnel plot of all the 5 studies, where there is no publication bias. **(e)** Forest plot of the 4 studies evaluated in meta-analysis for the assessment of the association between NT-proBNP levels and VO_2 max. **(f)** Funnel plot of all the 4 studies, where there is no publication bias.

Table1. Study characteristics of the included studies, results and the quality assessment.

Author	Country	Study type	N*	Age, years	NT-proBNP pg/ml	ST2, ng/ml	Clinical Outcomes	Quality assessment
Geenen et al., 2019	Netherlands	Prospective cohort	176	33(25-41)	141.45	24	-ST2 was associated with adverse cardiovascular events. -No association between ST2 and NT-proBNP levels	Moderate quality
Laqqan et al., 2018	Germany	Prospective cohort	61	28.2±12	164	29.9	-ST2 levels is significantly elevated in patient with CHD -Elevated NT-proBNP and ST2 levels are strong predictors of all-cause mortality in complex CHD	Moderate quality
Westhoff-bleck et al., 2016	Germany	Prospective cohort	81	26.3±7.4	168±148	n/a	-NT-proBNP levels and pulmonary regurgitation were strong predictors of adverse outcomes in asymptomatic patients -NT-proBNP levels were associated with LV parameters and not with RV	Moderate quality
Kitagawa et al., 2015	USA	Prospective cohort	33	14.5±2.8	71.4±46.1	n/a	-Elevated NT-proBNP levels were reduced after PVR	Poor quality
Pieniak et al., 2015	Poland	Prospective cohort	52	13.7±3.42	286±269.2	n/a	-Elevated NT-proBNP levels were associated with right ventricular function and exercise intolerance. -Elevated NT-proBNP levels were associated with exercise intolerance	Moderate quality
Valverde et al., 2015	Spain	Prospective Cohort	40	14.3±6.7	175±109	n/a	-NT-proBNP levels were associated with RV dilatation and PR -NT-proBNP >145 pg/ml could predict the presence of RV volume overload and dilatation	Poor quality
Menting et al., 2015	Netherlands	Prospective cohort	94	32.8±9.5	124±221	n/a	-Elevated NT-proBNP level, -No relationship between NT-proBNP and exercise capacity	High quality
Hong et al., 2014	United Kingdom	Prospective cohort	90	32.7±11.3	147 ±254	n/a	-Elevated levels of NT-proBNP in asymptomatic TOF patients. - NT-proBNP >132 pg/ml was a predictive value of mortality	Moderate quality
Eindhoven et al., 2014	Netherlands	Cross sectional	177	34.6±11.8	151±317	n/a	-Elevated NT-proBNP levels were associated with LV dysfunction, RVD and significant PR -NT-proBNP levels were not associated with exercise capacity	Moderate quality
Luijnenburg et al., 2013	Netherlands	Cross sectional	51	21±8	132±94	n/a	-Elevated NT-proBNP levels were associated with RV dysfunction and diastolic dysfunction	Poor quality
Koch et al., 2010	Germany	Retrospective cohort	130	16.1±7.1	200 ±110	n/a	-Elevated NT-proBNP levels. -Elevated NT-proBNP levels were correlated with right ventricular volume, severe PR and exercise capacity	High quality
Tacci et al., 2010	Brazil	Prospective cohort	49	14.7	211±219	n/a	-Elevated NT-proBNP levels were associated with RVD, diastolic dysfunction and severity of PR	Moderate quality
Apitz et al., 2009	Germany	Prospective cohort	16	14.2	179±396	n/a	-Elevated NT-proBNP levels	Poor quality
Zaroff et al., 2007	Czechs	Prospective Cohort	21	35	168±92	n/a	-Elevated NT-proBNP levels in asymptomatic adult survivors of TOF	Moderate quality
Kliengtseth et al., 2007	Thailand	Prospective cohort	21	12.1±2.5	295.75±389.11	n/a	-Elevated NT-proBNP levels were associated with RVD, RVEDV and dysfunction -NT-proBNP>115 pg/ml could be used as a marker in the detection of RV dilatation and dysfunction	Moderate quality
Oesterhof et al., 2006	Netherlands	Cross sectional	42	30 (17-57)	108±133	n/a	-Elevated NT-proBNP levels were associated with RV volume overload and severity of PR	Moderate quality

Khatami et al., 2006	Switzerland	Prospective cohort	23	13.2	231±228	n/a	-Elevated NT-proBNP levels in asymptomatic patients with chronic PR. -NT-proBNP levels were significantly reduced after 6 months post PVR	Poor quality
Norozi et al., 2006	Germany	Prospective cohort	59	30±8	150±141	n/a	-NT-proBNP levels could be replaced (Vo_2, %) max to re-stratify CHD patients with impaired cardiac function	Moderate quality
Exercise investigations								
Berg et al., 2009	Netherlands	Prospective Cohort	51	15(7-26)	94.3	n/a	-Normal NT-pro BP levels with preserved exercise capacity	Poor quality
Fesa et al., 2007	Italy	Cross-sectional study	70	21±1	218±283	n/a	-Elevated NT-proBNP levels were associated with RVD, function and RVEDV and with exercise intolerance	Moderate quality
Cheung et al., 2007	China	Prospective cohort	32	14.7±3.1	154	n/a	-Elevated NT-proBNP levels were associated with RVD, RVEDV, PR and with exercise intolerance	Moderate quality
Trojnarska et al., 2006	Poland	Prospective cohort	60	27.6±8.2	250±200	n/a	-Elevated NT-proBNP levels were associated with exercise intolerance	Moderate quality
Norozi et al., 2005	Germany	Prospective cohort	50	27.8±1.7	164±23	n/a	-Elevated NT-proBNP levels were associated with RVD, RVS' and with exercise intolerance	Poor quality

Vo_2 = maximum predicted oxygen uptake; PVR= pulmonary valve replacement; PR= Pulmonary regurgitation; RVD= Right ventricular dimensions; RVEDV= right ventricular end diastolic volume; RVS'= right ventricular peak systolic velocity; N/A= not available.

Table2. Baseline characteristic of population included.

Baseline characteristics	**N=1479 patients**	**Older (13 studies)**	**Younger (10studies)**	**P value**
Age±SD, years	22.7±8.3	29±4.5	14±1.1	**<.05**
NT-proBNP, pg/ml	174.4.1±56.4	160.4±37.7	190.6 ±72.9	>.05
sST2, ng/ml	26.95*	n/a	n/a	n/a
Surgical type	**TAP (14)**	**Non-TAP (9)**	**-**	**P value**
NT-proBNP, pg/ml	191.6± 57	151±46		**<.05**

TAP= Transannular patch; N/A = Not available.

*A value of sST2 drawn from two investigations.

Table3. Studies included in meta-analysis.

Author	Cohort size	Age (years)	NT-proBNP pg/ml	Follow up (years)	Cardiovascular events
Heng et al., 2014	90	32+5	147±254	10 (.7-12.4)	**83** **7 deaths:** **2** sudden cardiac death **2** perioperative right ventricular failure **1** severe Aortic stenosis **1** respiratory sepsis **1** unknown
Weshoff-Bleck et al., 2016	81	26.3+7.4	232±175	6.9+2.6	**13** sustained supraventricular arrhythmias or heart failure
Laqqan et al., 2018	61	28.2+12	349.5	2.11+2	**17** **Major adverse cardiac events**, defined as the occurrence of acute heart failure or death from any cause

Table 4. Studies included into pooled meta-analysis of the correlation coefficients.

Study	N number	Correlation coefficients, r (95% CI)	P.value	Association conclusions
Pietrzak et al., 2015	52	r= -.43 (0.178-0.629)*	p<.001	-With RVD and RVS'
Koch et al., 2010	130	r= 0.29 (0.124-0.440)* r= 0.20 (0.0288-0.360)**	p<.001	-With RVD and severity of PR
Valverde et al., 2015	40	r= 0.54 (0.275-0.729)* r= 0.26 (-0.0561-0.529)**	p<.001	-With RVD and severity of PR
Westhoff-bleck et al., 2016	81	r= -.412**** r= 0.019 *****	p<.05	-With LV dysfunction and not with RV structural changes -With LVEDVI
Eindhoven et al., 2014	177	r = 0.27 (0.128-0.402)* r = 0.19 (0.0437-0.328)** r = - 0.367****	p<.001	-With RVD and severity of PR -With LV dysfunction
Tatani et al., 2010	49	r = 0.41 (0.146-0.620)* r = 0.60 (0.384-0.754)**	p<.001	-With RVD, diastolic dysfunction and severity of PR
Khositseth et al., 2007	21	r = 0.57 (0.183-0.804)*	p<.001	-With RVD, RVEDV and dysfunction
Festa et al., 2007	70	r = 0.40 (0.182-0.580)* r = - 0.52 (-0.673- -0.325)***	p<.001	-With RVD, systolic function and RVEDV -With exercise capacity
Norozi et al., 2005	50	r = .42 (0.160-0.625)* r = -.63 (-0.773- -0.426)***	p<.001	-With RVD, RVS'. -With exercise capacity
Cheung et al., 2007	32	r = 0.69 (0.449-0.837)* r = 0.54 (0.236-0.748)** r = -0.43 (-0.677- -0.0956)*** r = .47, p.006******	p<.001	-With RVD, RVEDV and severity of PR -With exercise capacity -With LV Indexed dimensions
Trojnarska et al., 2006	60	r = .45 (0.221-0.632)* r = - 0.36(-0.563- -0.117)***	p<.001	-With RVD -With exercise capacity
Pooled correlation coefficients	**-**	**-NT-proBNP & RV structural changes=.41 (95% CI .32-.48)*** **-NT-proBNP & severity of PR =.34 (95% CI .16-.50)**** **-NT-proBNP & Vo_2 max= -.54 (95% CI -.60- -.36)*****	**p<.001**	**-Moderate correlation between NT-proBNP and RV structural and hemodynamic changes** **-Higher moderate correlation with reduced exercise capacity**

RVD=Right ventricular dimensions; RVS'=right ventricular peak systolic velocity PR= pulmonary regurgitation; LVEDVI= Left ventricular end diastolic volume index; RVEDV=right ventricular end diastolic volume; N/A= not available.

*****Correlation coefficient between NT-proBNP and RVD and RVEDV.

****** Correlation coefficient between NT-proBNP and severity of pulmonary regurgitation.

******* Correlation coefficient between NT-proBNP and Vo_2 max.

******** Correlation coefficient between NT-proBNP and LV dysfunction.

***** Correlation coefficient between NT-proBNP and LV end diastolic volume index.

****** Correlation coefficient between NT-proBNP and LV indexed dimensions.