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REVIEW

Blood biomarkers predicting adverse clinical outcomes in congenital heart disease patients, with consideration for pulmonary valve replacement

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Objective: This review aims to make a brief overview of blood biomarkers' clinical decision limits, possibly aiding in outcome prediction in all-aged Tetralogy of Fallot patients. Potentially, these biomarkers could also assist in necessity and timing of pulmonary valve replacement. **Methods**: Studies with all-aged patients with Tetralogy or Pentalogy of Fallot and blood biomarkers, BNP, NT-proBNP and hs-cTn, usage in clinical outcome prediction were included. Additionally, pulmonary valve replacement indications were considered. Other congenital heart diseases, biomarkers irrelevant to clinical outcome and associated pathologies or physiological status were the exclusion criteria. Keywords, Tetralogy and Pentalogy of Fallot, pulmonary valve replacement, blood biomarkers, yielded 69 suitable studies from Google Scholar, PubMed and Web-of-Science. 30 studies were selected. **Results**: Blood biomarkers were increased in TOF patients in comparison to controls; the higher the values, the worse adverse outcomes. Blood biomarkers combined with other biomarkers, imagistic methods or parameters showed promising results in outcome prediction. **Conclusions**: Blood biomarkers are validated as follow-up predictors in congenital heart disease paediatric patients. Further research is required to establish age-appropriate clinical decision limits. Pulmonary valve replacement timing remains controversial.

Keywords: congenital heart disease, tetralogy of Fallot, pentalogy of Fallot, blood biomarkers, pulmonary valve replacement

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Introduction

Tetralogy of Fallot (TOF) and Pentalogy of Fallot (POF)

Congenital heart disease (CHD) is the most common congenital malformation and the leading cause of infant mortality [1]. TOF is the most common cyanotic CHD [2] [3]. It affects up to 10% of CHD patients [4]. TOF occurs due to anterior-superior deviation of ventricular septum into the right ventricular (RV) outflow tract. This results in four anatomical lesions: ventricular septal defect, pulmonary stenosis, right ventricle hypertrophy and dextropositioned aorta [1][5]. Deoxygenated blood from the RV partially bypasses the pulmonary circulation and is mixed with oxygenated blood from the left ventricle (LV). Thus, inadequate oxygen delivery to the systemic circulation results. If aforementioned pathological anomalies are associated with atrial septal defect, the nomination changes from TOF to POF [6].

Outcomes and pulmonary valve replacement (PVR)

Unrepaired TOF has a poor prognosis: only 50% survive until 3 years of age. Earlier and improved diagnosis has enabled appropriate full repair already in infancy [4]. Successes in surgical procedures have enhanced patient survival. Thus, adults with rTOF (repaired Tetralogy of Fallot) outnumber paediatric patients, 30-year survival rate being around 90% [5]. Nonetheless, most patients remain with some degree of pulmonary valve incompetence requiring reintervention in adulthood [4].

Increasing risk of non-cardiac and cardiac complications, such as severe arrhythmias, ventricular dysfunction and sudden death, is due to longstanding pulmonary regurgitation (PR). PR in turn causes RV overload and increasing RV filling pressures [5]. Symptomatic heart failure (HF) is progressively recognised complication in adults with CHD [4]. With pulmonary valve replacement (PVR) the end-diastolic and end-systolic volumes can be reduced by 30-50%, reducing the adverse long-term outcomes [7]. Despite the observed benefit, optimal timing of PVR is challenging [8]. Too early intervention can result in conduit dysfunction, but PVR should occur prior to RV dysfunction development, significant RV dilation indicating irreversible myocardial changes [3].

Blood biomarkers

Biomarkers reflect the presence or severity of a disease. Ideally, the markers are easily measurable and are sensitive and specific to the disease stage they are intended for. This makes them especially useful in paediatric cardiology since many children cannot express their symptoms accurately [9].

Cardiac myocytes synthesise and release natriuretic peptides (NPs) in response to abnormal ventricular wall stress, such as increased volume and pressure of the heart [10] [11]. The concentrations are confounded by several factors: age, sex, renal function and body mass index [12].

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Brain natriuretic peptide (BNP) is released primarily from ventricular myocytes in response to myocardial stretch or stress in pressure or volume overloaded stages [12]. It improves myocardial relaxation through natriuresis, diuresis and vasodilation [12]. It can be used as a prognostic marker in paediatric cardiac surgery [13]. BNP values peak in infancy, decreasing to adult levels by 6 years of age [7]. In healthy adults, the BNP concentration is about 10 pg/mL [12].

In adults, BNP and N-terminal segment of its pro-hormone (NT-proBNP), are considered the first-line biomarkers in diagnosis of acute and chronic HF [14]. They can also provide information in evaluation of cardiac functions in paediatric patients with a suspected CHD [13]. NT-proBNP range of 8-13 pmol/L is normal for adults [15].

Cardiac troponin is released as a consequence of cardiac myocyte necrosis as in HF or myocardial ischemia [16]. High-sensitivity cardiac troponin (hs-cTn) elevations correlate with cardiovascular morbidity, mortality, and cardiovascular events in adults with CHD [17].

This systematic review aims to make a brief overview of potential blood biomarker clinical decision limits. These limits could be then applied to predict adverse clinical outcomes in all-aged TOF patients. Also, the necessity and correct timing of PVR is evaluated.

Methods

Studies with all-aged TOF patients and the usage of blood biomarkers, BNP, NT-proBNP and hs-cTn, in the clinical outcome prediction were included. Thus, in the review it was possible to divide the material into separated tables and subsections, concerning separately paediatric and adult patients. In addition, indications for PVR were considered. Exclusion criteria consisted of other CHDs, usage of other biomarkers showing no importance in clinical outcome or other associated pathological or physiological conditions.

Material was retrieved from Google Scholar, Web-of-Science and PubMed. Publication dates were focused on the past 10 years. For TOF, the studies were searched by using advanced search methods with keywords TOF, PVR and blood biomarker. The search yielded approximately 3,860 studies in total. Regarding POF, the keywords, Pentalogy of Fallot, blood biomarker and pulmonary valve replacement, yielded approximately 64 studies. In total, a number of 69 applicable studies were retrieved.

Each study title and abstract were screened to identify relevant articles. Language of the publications was restricted to English. The three blood biomarkers included to the study, BNP, NT-proBNP and hs-cTn, were the focus when selecting the articles. The studies had to include research about Tetralogy and/or Pentalogy of Fallot and minimum one of the aforementioned blood biomarkers. PVR was additional accepted criterion. Out of retrieved studies, 30 studies were selected for the final review.

Results

The literature search yielded in total of 30 potential studies. Sensitivity indicates the ability of disease detection of a test; with high sensitivity tests many individuals who are sick, receive a positive result. Specificity describes the ability of identification of people without the disease; high sensitivity tests give only a few false positives.

BNP in paediatric patients

Table I summarises the BNP cut-off values and clinical indications in paediatric patients.

A review by Nawaytou and Bernstein showed that BNP ≥40 pg/mL, with an accuracy of 84%, differentiated cardiac from pulmonary disease. BNP levels also correlated with exercise capacity, degree of pulmonary insufficiency and RV dimensions [9].

Hirono et al. stated cut-off of ln BNP 4.1412, with 66.7% sensitivity and 100.0% specificity, predicting reoperation in patients with rTOF. BNP could be utilised in assessing RV load, which in turn could be a potential prognostic indicator of RV condition [18].

Cantinotti et al. focused on distinguishing hemodynamically significant cardiovascular disease from other disease processes, specifically in paediatric outpatients with chronic LV dysfunction due to cardiomyopathies. BNP levels <300 pg/mL, with 93% sensitivity and 95% specificity, had a 0.88 predictive value and a negative predictive value of 0.97 for adverse cardiovascular events [13].

BNP in adults

Table II summarises the BNP cut-off values and clinical indications in adults.

Nir et al. predicted death during follow-up at cut-off of >78 pg/mL with 100% sensitivity and 76% specificity [19].

Villafáne et al., stated a greater increase in BNP was reported in TOF patients compared to controls when evaluating ventricular function and HF [3].

Heng concluded BNP level being a predictor of adverse outcomes of sustained arrhythmia and mortality. It was also associated with functional capacity, LV dysfunction and mortality in HF patients. In rTOF patients, elevated BNP correlated with RV end-diastolic dimensions and the PR severity [6].

Heng et al. noted abnormal BNP concentrations in 79% of rTOF patients, at ≥5.3 pmol/L, and in 70% of asymptomatic patients [20].

NT-proBNP in paediatric patients

Table III summarises the NT-proBNP cut-off values and clinical indications in paediatric patients.

Paolino et al., presented a cut-off value of >133.2 pg/mL indicating dilated RV end-diastolic and end-systolic volumes over centile 95. It also predicted PVR, based on RV end diastolic volume, with 75% sensitivity and 55%

Table I. brain natriuretic peptide cut-off values and their indications in paediatric patients

Studies	Patient number and age	Cut-off values	Clinical outcomes
Kapoor et al. [28]	250, <1-year-old to >18-year-old	>290 pg/mL	Increased probability of adverse outcomes in the intensive care unit
Nawaytou and Bernstein [9]	49 infants and children 42, age 0-7 days 58 of 7 days to 19-year-old 29, 1 month to 7-year-old	≥40 pg/mL 40 pg/mL and ≥170 pg/mL ≥30 pg/mL	Differentiation of cardiac from pulmonary disease Differentiation of paediatric patients and neonates, respectively, with a heart disease from those without Sensitivity and specificity for diagnosing HF
Hirono et al. [18]	58 patients, 1-18 years	4.1412 (ln BNP)	Reoperation in rTOF patients
Cantinotti et al. [13]	53, from 2 months to 21-year-old	<300 pg/mL	Adverse cardiovascular outcomes in paediatric outpatients with chronic LV dysfunction with 0.97 negative prediction

CHD – congenital heart disease, HF - heart failure, RV – right ventricle, rTOF – repaired tetralogy of Fallot, PR – pulmonary regurgitation, LV – left ventricle

Table II. brain natriuretic peptide cut-off values and their indications in adult patients and studies combining both patient groups

Studies	Patient number and age	Cut-off values	Clinical outcomes
Nir et al. [19]	2156, all-aged adult patients	>35 pg/mL <35 pg/mL <100 pg/mL >400 pg/mL >35 pg/mL >78 pg/mL	Chronic HF probable Chronic HF improbable Acute HF probable Acute HF improbable Cardiac overload should be considered Predictor of death during follow-up
Villafāne et al. [3]	130 children and adults	37.6 ± 27.5 pg/ml in rTOF patients	11.3 ± 4.5 pg/mL in controls
Heng [6]	90 patients, 32.7 ± 11.3 years	≥15 pmol/L ≤15 pmol/L	19% absolute mortality at 5-year follow-up 3% absolute mortality at 5-year follow-up
Heng et al. [20]	90 patients, 32.7 ± 11.3 years	≥5.3 pmol/L 15.5 pmol/L and 8.9 pmol/L ≥15 pmol/L	In 79% of rTOF patients Increasing trend towards deceased patients compared to survivors 5-fold increased risk of mortality
Eindhoven et al.	770 patients, 4.2 to 30.9 years of age	19-85 pg/mL	Increased values compared to age-matched healthy controls
Khokhar et al. [29]	530 adults, 42 ± 15 years	>100 ng/L	Predicting mortality in CHD adults

CHD – congenital heart disease, rTOF – repaired tetralogy of Fallot

Table III. N-terminal pro BNP cut-off values and their indications in paediatric patients

Studies	Patient number and age	Cut-off values	Clinical outcomes
Paolino et al. [21]	43 patients, 15.1 years in average	>133.2 pg/mL <71.2 pg/mL 187.5 pg/mL	Dilated RV end-diastolic and end-systolic volumes Excluded presence of significant RV end-diastolic and systolic volumes and PR >40% Statistically in correlation with RV dilation and PR fraction
Alborikan et al. [30]	1479 patients, 22.7 ± 8.3 years of age	147 pg/mL 232 pg/mL 349.5 pg/mL 145 pg/mL 115 pg/mL	All-cause mortality Adverse clinical events HF predictor Presence of RV dilatation Presence of RV dilatation and/or dysfunction
Nawaytou and Bernstein [9]	21, 12.06 ± 2.30 years of age	>115 pg/mL	RV dilation and ejection fraction <40%
Hirono et al. [18]	58 patients, 1-18-years	6.2195 (ln NT-proBNP)	Reoperation in rTOF
Nir et al. [19]	2156, all-aged adult patients	<125 pg/mL >125 pg/mL <300 pg/mL >450, >900, >1800 pg/mL <400 pg/mL >200 pg/mL 150-200 pg/mL >125 pg/mL	Chronic HF improbable Chronic HF probable Acute HF improbable at <50, >50 and >75 years Acute HF probable at age groups <50, >50 and >75 years, respectively Acute HF in adults unlikely Acute HF probable Identification of exercise incapacity and dilated RV in systole Cardiac overload

RV – right ventricle, PR – pulmonary regurgitation, HF – heart failure, BNP – brain natriuretic peptide, RV – right ventricle, rTOF – repaired tetralogy of Fallot, PVR – pulmonary valve replacement

specificity, and systolic volume, with 100% sensitivity and 52.5% specificity. 187.5 pg/mL was in correlation with RV dilation for end-diastolic and end-systolic volumes and with PR fraction [21].

Study by Hirono et al., stated ln NT-proBNP cut-off of 6.2195, with 88.9% sensitivity and 91.8% specificity, in predicting reoperation in patients with rTOF. NT-proBNP was found closely in association with right HF in patients, being also a good predictor of PVR necessity, with 88.9% sensitivity and 91.8% specificity [18].

Zegelbone et al. notified significant correlation between NT-proBNP and baseline mean right atrial pressure and RV end-diastolic pressure. NT-proBNP was also found in correlation to age and the ratio between the pulmonary and systemic vascular resistance. However, cardiac magnetic resonance imaging that is often used to evaluate the need for PVR, was not found in correlation with biomarker levels [7].

NT-proBNP in adults

Table IV summarises the NT-proBNP cut-off values and clinical indications in adults.

Eindhoven et al. noted LV ejection fraction to be significantly lower in patients with increased NT-proBNP.

Table IV. N-terminal pro BNP cut-off values and their indications in adult patients and studies combining both patient groups

Studies	Patient number and age	Cut-off values	Clinical outcomes
Eindhoven et al. [22]	177 patients, 34.6 ± 11.8 years of age	15.6 pmol/L	The median value exceeds the normal value in 55% of patients
Jabagi et al. [12]	1586 adults	300 pg/mL	Greater negative predictive value for acute HF compared to BNP
Schoonbeek et al. [23]	306 adult patients	≥125 pg/mL	In 44% of PVR patients
Westhoff-Bleck et al. [2]	81 patients, 26.3 ± 7.4 years of age	232-764 pg/mL 168 ng/L and ≥232 ng/L	In cumulative survival curves worse outcomes Specificity increased with increasing levels: from 75% to 85.3%
Baggen et al. [24]	595 patients, median age 33 years	<15.2 pmol/L >33.3 pmol/L	Cumulative proportion of death and HF of 1% Strongest association with cardiovascular events, death or HF
Eindhoven et al. [11]	770 patients, 4.2 to 30.9 years of age	18-231 pg/mL	Increased values compared to healthy controls (38-111 pg/mL)

HF – heart failure, BNP – brain natriuretic peptide, PVR – pulmonary valve replacement

However, in the total study population or in a subgroup of patients without prior PVR, the severity of PR was not related to NT-proBNP [22].

Schoonbeek et al., stated that 44% of the PVR patients presented with high NT-proBNP levels, ≥125 pg/mL. Additionally, an association between a higher age at the latest valve replacement and higher NT-proBNP levels was established [23].

Westhoff-Bleck et al. showed significantly worse outcomes in patients with NT-proBNP levels between 232-764 ng/L in cumulative survival curves. The emphasis was on the diagnostic power and utility of NT-proBNP in prediction of adverse clinical outcomes. Increasing levels had an association with increasing specificity. Cut-off of 168 ng/L yielded 84.5% sensitivity and 75% specificity, whereas NT-proBNP ≥232 ng/L resulted in 76.9% sensitivity with 85.3% specificity. NT-proBNP levels tended to increase with increasing NYHA class. NT-proBNP also remained as an independent predictor of all adverse events correlating with LV ejection fraction, mass, and end-diastolic and end-systolic volume indexes. During the follow-up patients receiving PVR tended to have higher NT-proBNP levels at the baseline [2].

According to Baggen et al., NT-proBNP >14 pmol/L identified those patients with the highest risk for cardiovascular events, death or HF. The strongest association was at >33.3 pmol/L. The risk of patients who presented with a high NT-proBNP level could be further evaluated by combining also hs-cTn to NT-proBNP testing [24].

Hs-cTn

In a study by Jabagi et al., hs-cTn level increased with increasing RV volume and worsening RV ejection fraction in adult patients with previous TOF repair. Predictive and diagnostic utility of this marker, measured in patients undergoing cardiac surgery, could provide information about the post-operative recovery. [12].

Rajpal et al. showed in a multivariable analysis how hs-TnT, including hs-cTn, was a predictive of the secondary end point; death or HF in adults. Primary end point, such as death, HF, hospitalisation, or arrhythmia, was no longer significant in multivariable adjustment. However, it was found more common in the highest hs-TnT quartile, with >7.7 ng/L, compared to the first quartile, with levels <3 ng/L [25].

Baggen et al. stated adults, with median age of 33, showing hs-cTn levels >14 ng/L faced the highest risk of cardiovascular events [24].

PVR

Yasukawa et al. showed how within 3 years after PVR, BNP was higher in the subnormal-stroke volume index group compared to normal stroke volume index group [26].

According to Kitagawa et al., BNP cut-off value considering PVR was 32.15 pg/mL [27].

Paolino et al. used a NT-proBNP cut-off value of 133.2 pg/mL predicting PVR, based on the RV end-diastolic and end-systolic values [21].

In a study by Peng et al., BNP was found to correlate with PR severity, and decreased significantly following PVR [10].

Nir et al. noted a significant increase in BNP levels in a small group of patients requiring PVR before the procedure. However, both BNP and NT-proBNP diminished in patients with significant PR following PVR [19].

Discussion

CHDs are widely recognised as causative agents of infant mortality as well as adverse outcomes later in life despite the early initial correction. Thus, for more precise clinical outcome prediction of TOF, more clinically applicable blood biomarker decision limits need to be established, which this review aimed for. Also, controversies related to PVR were under consideration.

All blood biomarkers showed increased values in TOF patients compared to healthy individuals and decreased following PVR throughout the cohort of studies. The higher the presented cut-off values were, the higher was the probability and severity of adverse outcome presentation. For the most severe outcome, death, prediction BNP cut-off values varied between >78 pg/mL in paediatric patients and >100 ng/L in adults. NT-proBNP >33.3 pmol/L had the strongest association with cardiovascular events, HF or death, in adult patients. All-cause mortality was increased at NT-proBNP levels 147 pg/mL in paediatric patients. Hs-cTn levels >14 ng/L had the highest risk of cardiovascular events. The data clearly shows the age-dependent variation of these blood biomarkers. NPs additionally proved to be useful in the paediatric patients in diagnosing and differentiation of pathologies. In gen-

eral, the acute adverse clinical outcomes, such as acute HF, showed significantly higher values throughout in comparison with chronic stages like cardiac overload. Notable is how even relatively small increases above the baseline can be clinically significant. Thus, before the occurrence of a more systematic treatment plan, every patient should be periodically evaluated, combining laboratory results with imagistic methods. Consequently, declining in the condition could be recognised, for example by clearly changed blood biomarker values, enabling prompt and correctly timed intervention.

Based on literature, blood biomarkers are already relatively extensively utilised for assessing the patients with different cardiac diseases. In case of CHDs, biomarker ranges, which respect different types of pathologies, age and gender, need to be outlined for more systematic treatment. Additionally, more correlations between blood biomarkers and other clinical evaluation methods, such as cardiac magnetic resonance imaging, should be established.

This review, as many others, have been greatly limited by the small population size and heterogeneity of the age groups in the studies. Physiological BNP level variation complicated the interpretation of the results regarding the long-term outcome prediction. Due to these factors, the indications and correct timing for PVR remain controversial, however, with wide range of possibilities. For instance, the potential of hs-TnT in CHD patients is clearly recognised but not yet widely utilised. Additionally, POF presenting lower prevalence compared to TOF, the aforementioned limitations are even more weighted, requiring special attention.

Blood biomarkers are unlikely able to act alone in outcome prediction. However, the results are promising in combination with imagistic methods, other biomarkers and parameters, such as cardiac magnetic resonance imaging, cardiopulmonary exercise testing and heart volume and function tests. Certain studies are already establishing relationships between echocardiographic findings and natriuretic peptides. With complex multifactorial CHDs easily measurable, affordable, sensitive, and specific parameters combined are most likely to yield the best possible results.

The future holds many promising directions concerning the clinical outcome prediction. Firstly, deepening the knowledge on already discussed blood biomarkers and establishing their relationship with other evaluation methods is essential. Establishing the trends of biomarker profile associated with clinical declining could prompt more effective assessment, yielding an algorithm of NPs in relation to the common interventions. Also standardisation of different commercial assays is needed [16][19]. Additionally, highly sensitive troponins are less used in CHD patients: they could offer information independently from, and additive to NPs in various outcomes. Secondly, the emergence and interpretation of more sensitive early biomarkers, such as copeptin, MR-proANP and GDF-15, may elucidate the approach to unique problems faced by CHD patients [19].

The differential gene expression in rTOF is already demonstrated with RNA sequencing, which could be utilised in studying genotype-phenotype relationships. This could be demonstrated by the genotype of patients originally with significant pulmonary stenosis in relation with later developed PR or gene expression pre-intervention versus post-intervention in PVR [6].

Conclusion

Advanced surgical repair techniques in infancy have increased patient survival into adulthood. Hence, adverse clinical outcomes concern not only children but also adult patients, enabling the outcome occurrence at any point of life. Periodical blood biomarker measurements in addition to other diagnostic methods should be performed to detect significant changes in blood biomarker values. This could possibly prevent adverse clinical outcomes also in the long-term setting and detect the most suitable timing for PVR for each patient individually. To aid in prevention and correctly timed interventions, more standardised guidelines considering age-dependency should be established. Also, the possible emergence of new blood biomarkers and thus new combinations with imagistic and other parameters would create more systematic treatment for these patients.

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Conflicts or competing interests

None to declare.

Authors' contribution

MK (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Validation; Visualization; Writing – original draft; Writing – review & editing)

IBK (Conceptualization; Investigation; Methodology, Validation; Visualization, Supervision; Writing – review & editing)

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