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TANAFFOS

Correlation of Pro-BNP Level with Echocardiographic and MRI Findings before Pulmonary Valve Replacement in Repaired Tetralogy of Fallot

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Background: This study aimed to determine the correlation between plasma Pro-BNP levels and MRI and echocardiographic findings in patients with repaired Tetralogy of Fallot (rTOF) undergoing surgical pulmonary valve replacement (PVR) to optimize valve implantation timing and reduce intervention costs.

Materials and Methods: Twenty-six patients who met the criteria for undergoing surgical pulmonary valve replacement at the tertiary medical center of Modarres Hospital from May 2019 to December 2023 enrolled in the study. We compared echocardiographic findings (LVEF, TAPSE, LVED diameter, Residual VSD, AI) and MRI data (right ventricular systolic and diastolic volume index, RV and LV ejection fraction) with Pro-BNP levels.

Results: This research studied 26 patients with a mean age of 16.5 ± 9.43 years. Plasma Pro-BNP levels ranged from 33.60 to 2095 pg/mL, with a mean ± SD of 212.15±395.22 pg/mL. Based on the results, there was no significant relationship between Pro-BNP level and RVESVI, LVEF, RVEF, TAPSE, RVEDVI, LVEDD, and Residual VSD. The results showed that there is a positive and significant correlation between Pro-BNP level and the age of the patients. According to the results of this study, there was a significant relationship between the incidence of aortic valve regurgitation (AR) and plasma Pro-BNP levels.

Conclusion: Regarding the results of the present study and the lack of a proven statistical relationship between the plasma Pro-BNP level and most of the findings of echocardiography and MRI, it can be concluded that serum Pro-BNP is not an acceptable measure to decide on PVR surgery, and MRI still determines the indication of PVR surgery.

Keywords: Pro-BNP; MRI; Echocardiography; Pulmonary valve replacement; Tetralogy of Fallot

INTRODUCTION

Tetralogy of Fallot (TOF) is the most prevalent cyanotic congenital heart disease, with an occurrence of 0.26–0.8 per 1000 live births (1). In recent times, long-term survival rates after surgical repair have been reported as 95% at 10 years and more than 90% at 25 years (2, 3). Regardless of reasonable survival rates, patients experience long-term complications, with nearly all patients having some degree of pulmonary regurgitation (4) due to right ventricular outflow tract reconstruction (2-5). Right ventricular (RV) dilatation and dysfunction as a result of constant substantial PR have demonstrated some adverse

consequences, including limitation of physical activities, left ventricular dysfunction, ECG abnormalities, and especially life-threatening atrial and ventricular arrhythmias associated with the development of sudden death (6). End-diastolic and end-systolic volumes after 1-year post-PVR (Pulmonary valve replacement) decreased by 30–50%; however, indications and timing of PVR are not well-established (7-10).

The best modality for the assessment of RV volumes and determining the degree of pulmonary and tricuspid regurgitation is cardiac magnetic resonance imaging (MRI) (9, 11). Among the disadvantages of MRI are the time-consuming analysis, multiphase data set, and cost (1).

N-terminal pro-brain natriuretic peptide (NT-Pro-BNP) is used as an FDA-approved marker of heart failure/function in children and adults with CHD (12, 13). The clinical diagnostic value of brain natriuretic peptide induced by atrial and ventricular stretch in children with heart failure, surgical repair of CHD, and pulmonary hypertension has been demonstrated in studies (14).

The goal of clinical management is to identify patients at risk who need intervention. The use of blood biomarkers, including plasma N-terminal pro-brain natriuretic peptide (NT-Pro-BNP), might be an emerging supplement to existing diagnostic methods to predict disease progression and thus identify appropriate patients for intervention.

We hypothesized that there is a relationship between RV volume, LV and RV ejection fraction, and plasma levels of Pro-BNP. Therefore, this study aimed to determine the potential prognostic value and association with adverse hemodynamic, echocardiographic, and MRI findings of Pro-BNP in patients with Tetralogy of Fallot (TOF).

MATERIALS AND METHODS

Between May 2019 and December 2023, 26 patients with a history of complete repair of tetralogy of Fallot at any age who underwent surgical pulmonary valve replacement were enrolled in the study. The indications for pulmonary valve replacement in our center are according to the internationally accepted guidelines and include the following: asymptomatic patients with moderate or severe pulmonary regurgitation ≥25% or if accompanied by at least two of the following criteria: right ventricular end-diastolic volume index (RVEDVI) >150 mL/m^2 or z score >4, right ventricular end systolic volume index (RVESVI) >80 mL/m^2, right ventricular ejection fraction (RVEF) less than 47%, left ventricular ejection fraction (LVEF) less than 55% via MRI, severe AR (aortic regurgitation), severe aortic dilation (diameter ≥ 5 cm), residual left to right shunts with pulmonary-to-systemic flow ratio ≥ 1.5, QRS duration >160 ms, sustained tachyarrhythmia related to right-sided heart volume overload in ECG, right ventricular outflow tract obstruction with right ventricular systolic pressure approaching 70% systemic pressure, in patients for whom catheter-based intervention is preferred over surgical intervention such as severe stenosis of branch pulmonary artery but not treatable by catheterization and/or greater than or equal to moderate tricuspid regurgitation. Patients ≥ 3 years at the time of repair for TOF, along with women with severe pulmonary regurgitation and RV dilatation at risk for pregnancy-related complications, would also be considered if they met one or more of the above-mentioned criteria. Symptomatic patients would be considered if they met one or more of the above criteria.

This study has been reviewed and approved by the School of Medicine, Shahid Beheshti University of Medical Sciences (no. IR.SBMU.MSP.REC.1398.409). Patients were included after signing the written informed consent.

Blood samples for Pro-BNP measurement were obtained from a peripheral vein. The cutoff of 46 pg/mL for pro-BNP was selected based on the classification of patients into two approximately equal groups. All participants underwent cardiac magnetic resonance (CMR) and a transthoracic echocardiographic examination before pulmonary valve replacement. Echocardiographic findings (LVEF, TAPSE, LVED diameter, Residual VSD, AR) and MRI data (right ventricular systolic and diastolic volume

index, RV and LV ejection fraction) were compared to Pro-BNP levels.

Statistics

Continuous variables were summarized as mean±standard deviation (SD). Categorical variables were presented as numbers and percentages. Between-group differences were analyzed by Student's *t*-tests, chi-squared tests, and ANOVA.

Pearson correlation test was used to investigate the relationship between Pro-BNP and echocardiographic findings or cardiac MRI-derived volumes. Correlations are reported as Pearson correlation coefficient (R-value) and p-value. A P-value <0.05 was considered statistically significant.

RESULTS

During the study period, 26 patients who met the criteria for undergoing surgical pulmonary valve replacement enrolled in the study. Clinical characteristics, cardiac MRI (CMR) results, and echocardiographic findings are presented in Table 1. The median age was 16.58 years, ranging from 5 years to 41 years. Sixty-five percent were male (n=17).

Table 1. Demographics, cardiac MRI, and echocardiographic characteristics of included patients

Variable	Median (Range)
Age (years)	16.58 (5-41)
Female N (%)	9 (35)
Weight (Kg)	46.73 (16-80)
Height (cm)	147 (105-180)
RVESVI (mL/m²)	102.66 (54-163)
RVEDVI (mL/m²)	167.47 (60-237)
RVEF (%)	42.70 (31-55)
LVEF (%)	50.88 (45-65)
TAPSE (mm)	11.85 (8-15)
LVEDD (mm)	31.61 (26-38)
Pro-BNP (pg/mL)	212.15 (33.60-2095)

RVESVI: Right Ventricular End-Systolic Volume Index, **RVEDVI**: Right Ventricular End-Diastolic Volume Index, **RVEF**: Right Ventricular Ejection Fraction, **LVEF**: Left Ventricular Ejection Fraction, **TAPSE**: Tricuspid Annular Plane Systolic Excursion, **LVEDD (m**: Left Ventricular End-Diastolic Diameter

RVESVI ≥85 mL/m² was observed in 18 patients (69.2%). RVEDVI ≥ 150 mL/m² was also detected in 17 patients (65.40%). Only three patients (11.5%) showed mild tricuspid regurgitation. Residual VSD was seen in 4 patients (15.40%) on echocardiography.

The plasma Pro-BNP level ranged from 33.60 to 2095 pg/mL, with a mean ± SD of 212.15 ± 395.22 pg/mL.

According to Table 2, there was only a statistically significant and positive relationship between patients' age and serum level of Pro-BNP. There was no statistically significant difference between the serum levels of Pro-BNP based on gender.

Table 2. Biomarker correlation to cardiac MRI and echocardiographic measurements

	r	P-value
Age	0.42	**0.03**
Weight	0.24	0.23
RVESVI	0.31	0.12
RVEDVI	0.27	0.18
TAPSE	-0.34	0.08
LVEDD	-0.14	0.46
LVEF	0.03	0.86
RVEF	-0.25	0.21

RVESVI: Right Ventricular End-Systolic Volume Index, **RVEDVI**: Right Ventricular End-Diastolic Volume Index, **TAPSE**: Tricuspid Annular Plane Systolic Excursion, **LVEDD**: Left Ventricular End-Diastolic Diameter, **RVEF**: Right Ventricular Ejection Fraction, **LVEF**: Left Ventricular Ejection Fraction

Based on the findings of Table 3, there is a statistically significant relationship between the incidence of aortic valve insufficiency and serum Pro-BNP levels.

Table 3. Association of plasma Pro-BNP level with qualitative variables

Pro-BNP			
Variable		**Median**	**P-value**
Gender	Female (n=9)	74.73	0.2
	Male (n=17)	274.90	
Residual VSD	Positive (n=4)	130.25	0.66
	Negative (22)	227.04	
AR	Positive (20)	840	0.002
	Negative (23)	130.26	

Table 4. Association of the two qualitatively classified groups of Pro-BNP levels with patient gender and AR

Variable		Pro-BNP <46 N (%)	Pro-BNP >46 N (%)	P-value
Gender (n)	Female (9)	8 (89)	1 (11)	0.009
	Male (17)	6 (35)	11 (65)	
AR	Positive (3)	0 (0)	3 (100)	0.047
	Negative (23)	14 (61)	9 (39)	

Twelve patients (46.20%) exceeded the upper limit of normal of 46 pg/mL. The results showed that among all of the studied variables, patients' gender and aortic regurgitation had a significant relationship with serum Pro-BNP levels according to a cutoff of 46 pg/mL. The number of male patients in the Pro-BNP group above 46 was significantly higher than that of female patients. All patients with aortic regurgitation had Pro-BNP levels >46 pg/mL, which was statistically significantly higher than those in patients without aortic regurgitation (Table 4).

Figure 1 indicates a weak negative correlation between Pro-BNP levels and RVEF. As RVEF increases, Pro-BNP levels slightly decrease.

Figure 2 suggests a weak negative relationship between Pro-BNP and LVEDD. As LVEDD increases, Pro-BNP levels tend to decrease slightly. However, the relationship is not strong.

Figure 3 shows a positive linear trend between Pro-BNP and RVESVI. As RVESVI increases, Pro-BNP levels tend to increase as well, although the relationship appears weak.

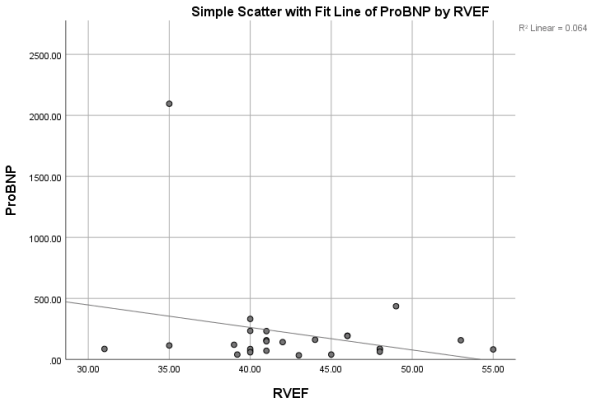


Figure 1. A scatterplot with a fit line illustrating the relationship between Pro-BNP and RVEF

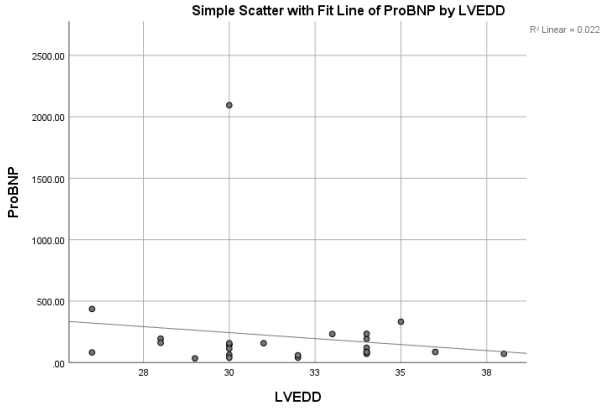


Figure 2. A scatterplot with a fit line illustrating the relationship between Pro-BNP and LVEDD

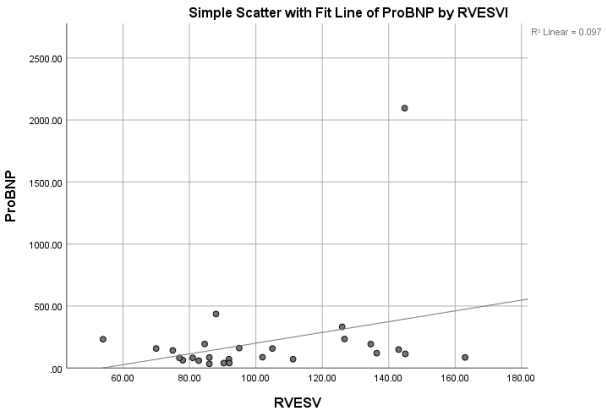


Figure 3. A scatterplot with a fit line illustrating the relationship between Pro-BNP and RVESVI

DISCUSSION

Although NT-Pro-BNP has been used in clinical practice for patients with structural congenital heart disease, there is insufficient evidence regarding its ability to reflect cardiac hemodynamics in patients with CHD to support its routine use as an adjunctive tool.

We hypothesized that cardiac heart failure biomarker proteins such as NT-Pro-BNP would reflect MRI and echocardiographic findings in patients with tetralogy of Fallot and intention to treat with pulmonary valve replacement. So, Pro-BNP serum levels can be used for better disease management, optimize the timing of valve implantation, and reduce treatment costs. To achieve the aims of the research, 26 patients who met the criteria to enroll in the study were evaluated. Most of the patients in the study (21%) were male gender.

Investigations showed that there is a positive and significant correlation between the Pro-BNP level and the age of the patients. Meanwhile, in Adrish et al.'s study, no significant relationship was reported between age and the serum level of Pro-BNP. Although in the mentioned research, the serum level of Pro-BNP was categorized qualitatively (normal or increased), the difference in the results may be due to the difference in the analysis approach (15). In the study of Zegelbone et al., NT-Pro-BNP significantly correlated positively with age (0.6, p = 0.009). This finding potentially limits NT-Pro-BNP as a predictor of right heart hemodynamics in adult CHD (7).

Based on the results of the present study, there was a significant relationship between the incidence of aortic valve insufficiency (AR) and Pro-BNP levels, so that the serum level of Pro-BNP in patients with mild aortic valve insufficiency was much higher than in patients without AR. This relationship maintained its significance with reanalysis by categorizing Pro-BNP into two qualitative groups.

A weak positive correlation (R^2 = 0.097) between Pro-BNP and RVESV was observed in our study, suggesting that higher RVESV might be modestly associated with increased Pro-BNP levels. However, the relationship lacks statistical strength, indicating other factors likely contribute to Pro-BNP variability. Also, A weak negative correlation (R^2 = 0.064) was observed between Pro-BNP and RVEF, indicating a slight tendency for Pro-BNP levels to decrease as RVEF increases. However, this association is also limited in its predictive value.

The only difference in the results when analyzing the quantitative and qualitative levels of Pro-BNP was observed in the gender variable. Despite the fact that there was no significant relationship between gender and the quantitative level of Pro-BNP, the present research showed that the gender variable has a significant relationship between the two qualitatively classified groups of Pro-BNP level. So, Pro-BNP>46 was significantly higher in male patients than in female patients.

A study conducted by Khositseth et al. in 21 patients with TOF after total correction and a mean age of 12.06±2.54 years revealed a cut-off of 115 pg/mL for NT-Pro-BNP level for predicting RV dysfunction, providing sensitivity of 71% and specificity of 71% (AUC = 0.75). Linear correlation demonstrated a fair to good correlation between NT-Pro-BNP and RVEDVI (1).

Van den Bosch et al. in 2022, in 137 Fallot patients with a median age of 19.2 years, demonstrated that NT-Pro-BNP levels were associated with the composite endpoint (cardiac death, hospitalization for arrhythmias or cardioversion/ablation for arrhythmias or reaching a cardiopulmonary exercise test (CPET)) and VO_2 max below 65% in univariable analysis. However, when corrected for age at baseline, NT-Pro-BNP lost its predictive value (16).

In a study by Heng et al. in 83 patients over a median follow-up of 10 years, BNP was significantly related to all-cause mortality (AUC 0.68, p=0.04) (17).

Alborikan et al., in a systematic review in 2021, showed a statistically significant association of elevated NT-Pro-BNP levels with RV size and right ventricular end-diastolic volume (RVEDV), with a correlation coefficient of 0.41 (95% CI 0.32-0.48, P<0.001). Also, they indicated there was a statistically significant association between NT-Pro-BNP and the severity of pulmonary regurgitation, with a pooled correlation coefficient of -0.54 (95% CI -0.60 to -0.36) (18).

The limitation of this study was its small sample size. Due to the limited sample size, we may have missed the associations between biomarkers and hemodynamic findings. Detecting biomarker cut-off values for clinical use was not part of the current study, and further research is necessary to determine the potential role of the observed biomarkers in clinical practice.

Also, this study did not include catheterization data or detailed right ventricular (RV) echocardiographic parameters, such as RV end-diastolic volume (RVEDV), RV end-systolic volume (RVESV), RV fractional area change (RV-FAC), or RV ejection fraction (RVEF). Additionally, 3D echocardiography, which provides a more accurate assessment of RV function, was not utilized due to the study's retrospective nature. Future prospective studies incorporating catheterization data and advanced RV imaging techniques are warranted to enhance the understanding of this population.

CONCLUSION

In conclusion, according to the results of the present study and the lack of proof of a statistically significant relationship between serum Pro-BNP level and echocardiographic and MRI findings, it can be concluded that the serum Pro-BNP level is not an acceptable criterion to optimize the timing of valve implantation. Therefore, cardiac MRI still determines the indication of surgical PVR.

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