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The Association between NTproBNP Biomarker Levels and Clinical Symptoms of Cardiac Septal Defects in Children

Ria Nova[1]*, Sukman Tulus Putra[2], Siti Nurmaini[3], Radiyati Umi Partan[4]

[1]Department of Child Health, Division of Pediatric Cardiology, Faculty of Medicine, Universitas Sriwijaya, Dr. Moh Hoesin Hospital, Palembang, Indonesia; [2]Department of Child Health, Division of Pediatric Cardiology, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia; [3]Intelligent System Research Group, Faculty of Computer Science, Universitas Sriwijaya, Palembang, Indonesia; [4]Department of Medicine, Faculty of Medicine, Universitas Sriwijaya, Dr. Moh Hoesin Hospital, Palembang, Indonesia

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***Correspondence:** Ria Nova, Department of Child Health, Division of Pediatric Cardiology, Faculty of Medicine, Universitas Sriwijaya, Dr. Moh Hoesin Hospital, Palembang, Indonesia. **E-mail:** rialuthfan@yahoo.com
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Abstract

BACKGROUND: In a cardiac septal defect, there is left-to-right shunt at the atrial, ventricle level, or both. This causes clinical symptoms of heart failure, pulmonary hypertension, or malnutrition. NTproBNP is synthesized and released into the circulation by the ventricular myocytes in response to pressure, volume overload, and increase in myocardial wall stress.

AIM: This study aims to evaluate relationship between NTproBNP levels and clinical symptoms of cardiac septal defect.

PATIENTS AND METHODS: This cross-sectional study was conducted from April to August 2021 at Moh Husin Hospital, Palembang, Indonesia. The presence of heart failure was determined using the modified Ross score. Nutritional status was defined on anthropometric measurement, and data were plot to weight to height Z-score chart. The presence of pulmonary hypertension was measured by Doppler echocardiography.

RESULTS: A total of 75 cardiac septal defect patients were included in this study. A similar plasma NTproBNP of 554 pg/ml was determined as the cut-off point for predicting heart failure and pulmonary hypertension, with a sensitivity of 57.1% and 54.5%, specificity of 85% and 80.9%, with area under receiver operating characteristic (ROC) of 0.706 and 0.716 respectively. For malnutrition, plasma NTproBNP of 429 pg/ml was found to have sensitivity, specificity, and area under ROC of 54.3%, 77.5%, and 0.640, respectively. The multivariate logistic regression showed that NTproBNP >554 pg/ml and >429 pg/ml had a 6-fold higher odds of having heart failure, an 8-fold higher odds of having pulmonary hypertension, and a 4-fold odds of having malnutrition.

CONCLUSION: NTproBNP is a biomarker that is strong enough to predict clinical symptoms of heart failure, pulmonary hypertension, and malnutrition in children with cardiac septal defect.

Introduction

Cardiac septal defect is a type of congenital heart disease (CHD) with a direct communication between the atrial cavities and or ventricle cavities that allow shunting of blood [1]. There are three type of cardiac septal defect, including atrial septal defect (ASD), ventricle septal defect (VSD), and atrioventricular septal defect (AVSD). Communication between the left side and the right side of the heart accounts for a left-to-right shunt in postnatal circulation [2].

In conditions with left-to-right shunt in cardiac septal defect result in increased pulmonary blood flow because of left-to-right shunting at the atrial and ventricular level [3]. This excess pulmonary blood flow results directly or indirectly in almost all of the significant clinical symptoms that characterize heart failure [4], [5], pulmonary hypertension [6], [7], and malnutrition [8], [9], [10], [11]. These overloads can result in necrosis, apoptosis, and mechanical stressors, such as direct pressure and stretching of myocardial cells, which are believed to cause myocardial damage and ventricular dysfunction [12].

NTproBNP is one of the cardiac peptides that increase in ventricular dysfunction. This substance is produced in the ventricle and released in the form of pre-pro brain natriuretic peptide (BNP), and finally becomes degraded enzymatically in response to ventricular dilation and pressure overload to pro-BNP [13]. Serum levels of NTproBNP have been used in assessing cardiac dysfunction in heart failure patients in the general population [14]. However, in CHD patients with heart failure, the diagnostic value of serum NTproBNP levels remains challenging. Heterogeneity in causes, and in clinical signs and symptoms as well as variation in sex, age, and comorbidities affect serum NTproBNP levels. As far as we know, there are few reports in the

literature comparing level of NTproBNP and clinical symptoms of cardiac septal defect. Therefore, the aim of this study was to evaluate the relationship between plasma levels of NTproBNP and clinical symptoms of cardiac septal defect in children.

Patients and Methods

This cross-sectional study occurred from April to August 2021 at Moh Hoesin Hospital, Palembang, Indonesia. Inclusion criteria were patients with ASD, VSD, or AVSD. The exclusion criteria were cardiac septal defect patients aged <2 months or over 10 years. Subjects were recruited using a consecutive sampling technique, and informed consent was obtained from parents at study admission. Clinical symptoms were assessed in each patient with cardiac septal defect. Clinical symptoms assessed included heart failure, pulmonary hypertension, and malnutrition. The presence of heart failure was determined using the modified Ross score [15]. Nutritional status was defined by anthropometric measurement of weight in kilograms and height in centimeters. Data were plotted on the weight-to-height Z-score (WHZ) chart and classified as malnourished if WHZ < -3SD, undernourished if WHZ -3SD to -2SD, well-nourished if WHZ -2SD to 2SD, or overweight if WHZ was more than 2SD [16]. The presence of pulmonary hypertension was measured by Doppler echocardiography using jet flow on tricuspid valve and pulmonary valves. Using velocity time integral (VTI) measured by Doppler echocardiography at the pulmonary and aortic valves, the Qp/Qs ratio was calculated using the following formula [17]:

$$QP = RVOT\,VTI \times \pi \times \left(\frac{RVOT^2}{2} \right)$$

$$QS = LVOT\,VTI \times \pi \times \left(\frac{LVOT^2}{2} \right)$$

QS/QP RATIO=QP/QS

According to Qp/Qs ratio, the severity of the disease was divided into two categories; mild to moderate (Qp/Qs <2), and severe (Qp/Qs>2).

Blood samples were collected in ethylenediaminetetraacetic acid (EDTA)-coated tubes and immediately placed in a cooling box at 4°C, followed by centrifugation. Plasma was stored at −80 C if the NTproBNP measurements could not be immediately performed. Plasma NTproBNP levels were measured using electrochemiluminescent immunoassay technique using kits that were manufactured Cobas e-411/e-601 with reagen proBNP II Cat.04842464 (Sandhofer Strasse, Germany).

Statistical analysis

Descriptive analysis were expressed in frequencies and percentages, while for quantitative variables, both the mean and the standard deviation were calculated. We calculated the receiver operating characteristic (ROC) curve to predict NTproBNP cut-off points for heart failure, pulmonary hypertension, and malnutrition in cardiac septal defect. Inferential analysis used the multivariate logistic regression analysis to determine the independent predictor (NTproBNP, size defect, type defect, ratio Qp/QS) associated with the clinical symptoms (heart failure, pulmonary hypertension, and malnutrition). All significant variables in the bivariate analysis were selected, entered into a multivariate regression, and reported as odds ratios and 95% confidence intervals. The significance for all categorical variables was assessed using the X^2 test and $p < 0.05$ was considered to indicate statistical significance. The analysis was performed with licensed software: Stata/BE 17. Ethical clearance for this study was granted based on the criteria of the Health Research Ethics Committee Dr. Moh Hoesin Hospital Palembang, Indonesia (No. 38/kepkrsmh/2021).

Results

This study was conducted with 75 subjects, consisting of 31 males and 44 females. The mean age of patients was 35.84 ± 29.19 months old. Among 75 patients with cardiac septal defect, 35 (46%) had clinical symptoms of heart failure, 33 (44%) had pulmonary hypertension, and 40 (53%) had malnutrition. Of those with heart failure, most (77.15%) were with mild heart failure (Ross score of 3–6). Symptoms of heart failure included diaphoresis, tachypnea, dyspnea, tachycardia, and hepatomegaly. The general characteristics of subjects with clinical symptoms are described in Table 1.

NTproBNP level was higher in cardiac septal defects with clinical symptoms of heart failure ($p = 0.002$), pulmonary hypertension ($p = 0.001$), and malnutrition ($p = 0.036$) than those without clinical symptoms (Figure 1).

According to ROC analysis, plasma NTproBNP 554 pg/ml was determined as the cut-off point for predicting heart failure with a sensitivity of 57.1%, specificity of 85%, positive LR of 3.8%, negative LR of 0.5%, area under ROC of 0.706, and for predicting pulmonary hypertension with sensitivity of 54.5%, specificity of 80.9%, positive LR of 2.8%, LR negative of 0.5%, and area under ROC of 0.716. For predicting malnutrition in patient with cardiac septal defect cut-off value NTproBNP was 429 pg/ml with sensitivity of 54.3%, specificity of 77.5%, positive LR of 2.4%, negative LR of 0.6%, and area under ROC of 0.640 (Figure 2).

Table 1: Baseline characteristics of subject with clinical symptoms

Characteristic	Heart failure, n (%)			Pulmonary hypertension, n (%)			Malnutrition, n (%)		
	Yes (n = 35)	No (n = 40)	p	Yes (n = 33)	No (n = 42)	p	Yes (n = 40)	No (n = 35)	p
Gender									
Male	13 (17.33)	18 (24)	0.490	13 (17.33)	18 (24)	0.762	13 (17.33)	18 (24)	0.490
Female	22 (29.33)	22 (29.33)		20 (26.66)	24 (32)		22 (29.33)	22 (29.33)	
Age (years)									
≤ 5	21 (28)	31 (41.33)	0.101	21 (28)	31 (41.33)	0.342	24 (32)	28 (37.33)	0.893
> 5	14 (18.66)	9 (12)		12 (16)	11 (14.66)		11 (14.66)	12 (16)	
Type of defect									
VSD	22 (29.33)	26 (34.66)	0.931	20 (26.66)	28 (37.33)	0.096	20 (26.66)	28 (37.33)	0.317
ASD	10 (13.33)	10 (13.33)		12 (16)	8 (10.66)		10 (13.33)	10 (13.33)	
AVSD	3 (4)	4 (5.33)		1 (1.33)	6 (8)		5 (6.66)	2 (2.66)	
Size of defect									
Small - moderate	9 (12)	25 (33.33)	0.001	7 (28)	27 (36)	0.0002	13 (17.33)	22 (29.33)	0.072
Large	26 (34.66)	15 (2)		26 (34.66)	15 (2)		23 (30.66)	18 (24)	
Qp/Qs ratio									
Mild-moderate (< 2)	2 (2.66)	18 (24)	0.0001	3 (4)	17 (22.66)	0.0023	7 (9.33)	13 (17.33)	0.2220
Severe (≥ 2)	33 (44)	22 (29.33)		30 (34)	25 (33.33)		28 (37.33)	27 (36)	

Chi-square test. ASD: Atrial septal defect, VSD: Ventricle septal defect, AVSD: Atrioventricular septal defect.

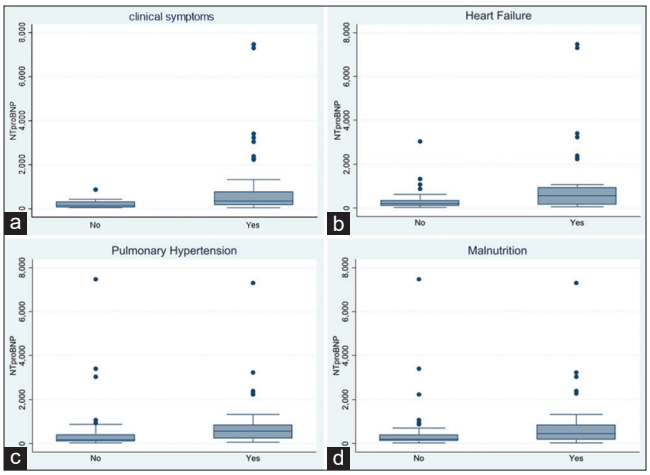

Figure 1: Box plots showing the relationship between NTproBNP and clinical symptoms, heart failure, pulmonary hypertension and malnutrition. Box show the interquartile range and the median. The comparison uses the Man–Whitney U-test. (a) p = 0.001. (b) p = 0.002. (c) p = 0.001. (d) p = 0.036

To assess the clinical symptoms (heart failure, pulmonary hypertension, and malnutrition) and NTproBNP levels in cardiac septal defect, we performed a logistic regression analysis. In the multivariate analysis, the variables that remained as the independent predictor for heart failure in cardiac septal defect were NTproBNP and Qp/Qs ratio. The independent predictors for pulmonary hypertension were NTproBNP, the type of defect, and size of defect, and predictor for malnutrition in cardiac septal defect was NTproBNP (Table 2).

Table 2: Multivariate logistic regression analysis according to heart failure, pulmonary hypertension, and malnutrition

Variable	Coefficient	SE	Z	p	OR	95% CI	
						Lower	Upper
Heart failure							
NTproBNP	1.84	3.87	3.03	0.002	6.35	1.92	20.98
Qp/Qs ratio	2.41	9.37	2.89	0.004	11.21	2.18	57.66
Pulmonary hypertension							
NTproBNP	2.08	6.03	2.76	0.006	8.01	1.83	35.08
Type of defect	−4.02	0.02	−3.09	0.002	0.01	0.00	0.22
Size of defect	2.00	4.59	3.24	0.001	7.42	2.20	24.95
Malnutrition							
NTproBNP	1.40	2.07	2.77	0.006	4.09	1.50	11.07

Adjusted for NTproBNP and heart failure. Pseudo R^2 = 0.26; Hesmer-Lemershow goodness-of-fit χ^2, 0.02; p = 0.8758. Adjusted for NTproBNP and pulmonary hypertension. Pseudo R2 = 0.31; Hesmer Lemershow goodness-of-fit χ^2, 6.26; p = 0.0438, Adjusted for NTproBNP and malnutrition. Pseudo R^2 = 0.07; Hesmer-Lemershow goodness-of-fit χ^2, 0.0; p = -. SE: Standard error, CI: Confidence interval, OR: Odds ratio.

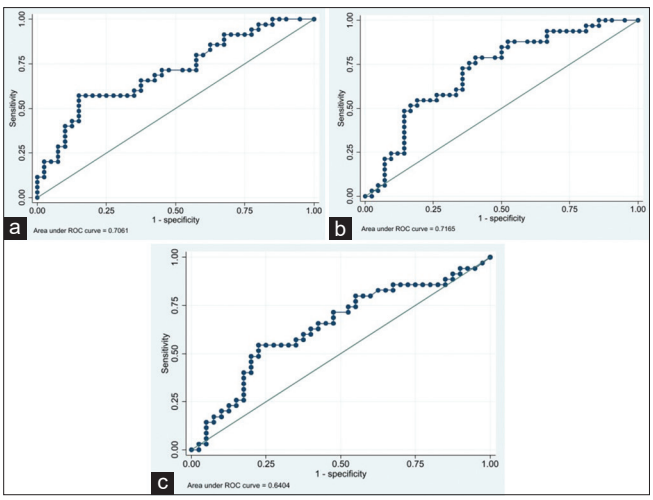

Figure 2: Receiver operating characteristic (ROC) curve of NTproBNP for predicting heart failure and pulmonary hypertension in cardiac septal defect with a cut-off point of 554 pg/ml, and malnutrition in cardiac septal defect with a cut-off point of 429 pg/ml. (a) ROC heart failure. (b) ROC pulmonary hypertension. (c) ROC malnutrition

Discussion

In the present study, there was an association between NTproBNP and clinical symptoms in cardiac septal defect. The NTproBNP levels were elevated significantly in patients with heart failure compared with those with no heart failure (p = 0,002), patients with pulmonary hypertension compared with those with no pulmonary hypertension (p = 0.001), and patients with malnutrition compared with those with no malnutrition (p = 0.036) while also having a cardiac septal defect. This finding is similar to that reported by Koura *et al*. that NTproBNP levels are high in patients with CHD if there is a significant left-to-right shunt [15]. The significant left-to-right shunt may cause increased pulmonary blood flow leading to dilatation of cardiac chambers, heart failure, pulmonary hypertension, and malnutrition [16]. Ozyurt *et al*. demonstrated that

NTproBNP levels ⩾113.5 pg/ml was associated with high specificity and sensitivity for determining the significant shunt for VSD [17].

A previous study proposed that NTproBNP levels of >598 ng/l predicticted of pediatric heart failure [18]. Isah *et al*. reported that NTproBNP levels of 315 pg/ml have a sensitivity of 77.8% and specificity of 57.9% when identifying children with heart failure [19]. In the present study, the cut-off point for NTproBNP levels was determined at 554 pg/ml in cardiac septal defect with heart failure, with sensitivity and specificity of 57.1% and 85%, respectively. These findings demonstrate that NTproBNP may be more useful for predicting heart failure in children who are already diagnosed as having a cardiac septal defect. The multivariate logistic regression showed that patients with NTproBNP >554 pg/ml had a 6-fold higher odds of having heart failure.

Pulmonary hypertension that is secondary to CHD with a left-to-right shunt may be the result of chronic changes in the pulmonary vasculature, with endothelial dysfunction, and vascular remodeling, which leads to a further increase in mean pulmonary artery pressure (mPAP) and an increase in pulmonary vascular resistance [20]. Our findings indicate that NTproBNP levels at the cut-off point 554 pg/ml in patients with a cardiac septal defect with pulmonary hypertension, with sensitivity and specificity of 54.5% and 80.9%, respectively. The multivariate logistic regression showed that patients with NTproBNP >554 pg/ml had an 8-fold higher odds of having pulmonary hypertension. Deng's study reported that NTproBNp > 300 pg/ml predicts a poor prognosis in adult CHD with pulmonary hypertension [21].

In this study, the levels of NTproBNP were significantly different between cardiac septal defects with malnutrition and no malnutrition. The cut-off point for NTproBNP levels was determined at 429 pg/ml in patients with a cardiac septal defect with malnutrition, with sensitivity and specificity of 54.3% and 77.5%, respectively. The multivariate logistic regression showed that patients with NTproBNP >429 pg/ml had a 4-fold odds of having malnutrition. In a previous study, malnutrition was accompanied by volume overload and was associated with increased NTproBNP levels. In accordance, studies done by Ducros *et al*. reported that in hemodialysis patients with protein energy-wasting had a 14-fold higher odds of having high values of NTproBNP [22]. Kim *et al*. reported that the prognostic value of NTproBNP was greater in heart failure patients with BMI < 23 kg/m than in those with BMI >23 kg/m [23]. This result provides additional evidence regarding an influence of BMI on the utility of the NTproBNP assay for the prognosis of patients with heart failure.

This study has some limitations, including small number in each subgroup which may limit the accuracy of sensitivity and specificity of NTproBNP as biomarker of clinical symptoms of cardiac septal defect. Most of the subjects had mild heart failure, which may also reduce sensitivity. Large, multi-center, prospective studies are required on this subject in the future. Another limitation of this study that we did not analyze is the correlation between NTproBNp and cardiac function parameters. Therefore, whether NTproBNP levels are affected by cardiac function parameters cannot be discussed.

Conclusion

NTproBNP is a biomarker that is strong enough to predict clinical symptoms of heart failure, pulmonary hypertension, and malnutrition in children with cardiac septal defect. As a result, it is a major contributor for such predictions.

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