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Original Article

Correlation of heart failure severity and N-terminal pro-brain natriuretic peptide level in children

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Abstract

Background Heart failure affects morbidity and mortality in children with heart disease. There is no single, specific test to diagnose heart failure. The modified Ross Reithmann scoring system has been used to classify heart failure severity, but it is limited due to its subjectivity. The N-terminal pro-brain natriuretic peptide (NT-proBNP) is secreted by the ventricles during heart failure. It has been suggested as a possible marker for diagnosing heart failure.

Objective To investigate the correlation between heart failure severity and plasma NT-proBNP concentration in children aged one month to 14 years.

Methods A cross-sectional study was performed in the Pediatrics Department of Mohammad Hoesin Hospital from July to September 2015 on children with congestive heart failure, aged one month to 14 years. Heart failure severity was assesed using the modified Ross Reithmann scoring system. Plasma NT-proBNP measurements were done in all subjects. Statistical analysis was done by Spearman's test.

Results Subjects' median plasma NT-proBNP concentration was 1,703 pg/mL (range 310-9,000 pg/mL). The NT-proBNP level and severity of heart failure had a significant, positive correlation ($r=0.87$; $P<0.001$). The NT-proBNP minimum levels in subjects with mild, moderate and severe heart failure were 310 pg/mL, 1,251 pg/mL, and 2,610 pg/mL, respectively.

Conclusion Plasma NT-proBNP level has a significant, positive correlation with the severity of heart failure in children. As such, NT-proBNP level may be useful as a biochemical marker for the diagnosis and grading of the severity of heart failure in children. **[Paediatr Indones. 2016;56:315-9. http://dx.doi.org/10.14238/pi56.6.2016.315-9]**.

Keywords: *Heart failure; NT-proBNP; modified Ross Reithmann score.*

Heart failure impacts morbidity and mortality in children with heart disease. Congenital heart disease occurs in around 8 per 1,000 live births. In addition, heart failure as a result of congenital defects was estimated to be 1 - 2 per 1,000 live births.[1] Diagnosis of heart failure in children is generally determined by history, physical examination, chest radiography, electrocardiography, and echocardiography.[2] There is no single, specific test to diagnose heart failure. However, one simple method to classify the symptomatic severity of heart failure in children is by a scoring system.[3,4] The Ross score, modified Ross Reithmann score, and *New York Heart Association* (NYHA) score are such methods, but these systems are limited by their subjectivity. A biomarker of heart failure would be less subjective and more useful for diagnosing heart failure in children. The N-terminal pro-brain natriuretic peptide (NT-proBNP) has been suggested as a biomarker of heart failure. The NT-proBNP is a sensitive and specific marker of ventricular

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dysfunction,[5] which is secreted by cardiac ventricular myocytes in response to an increase in left ventricular stretching or wall tension, and volume load.[6-9]

Past studies showed that increased NT-proBNP level was associated with increased heart failure severity, in congenital and acquired heart disease patients.[8-10] In Indonesia, studies on NT-proBNP levels in patients with heart failure generally have focused on adults, with only a few studies examining the role of NT-proBNP in pediatric patients.[11,12] The objective of this study was to examine for a correlation between NT-proBNP level and heart failure severity, based on the modified Ross Reithmann scoring system, in children aged one month to 14 years.

Methods

This cross-sectional study was done to investigate a correlation between heart failure severity and NT-proBNP level in children aged one months to 14 years. The study was conducted in the Pediatrics Department, Mohammad Hoesin Hospital (RSMH), Palembang, from July to September 2015. We recruited subjects by consecutive sampling. Inclusion criteria were all patients with congestive heart failure aged one month to 14 years who were admitted to RSMH and diagnosed to have heart disease by echocardiography. Exclusion criteria were children with renal failure and those who lacked parental consent.

Patients were diagnosed to have heart disease by interviews, physical examinations, and echocardiography. A modified Ross Reithmann score was used for clinical evaluation of heart failure severity. Heart failure was defined as a modified Ross Reithmann total score >2. The symptoms of heart failure were graded on a scale of 0, 1, or 2 points, according to severity. This score was used to classify patients as having mild heart failure (3-6 points), moderate heart failure (7-9 points), or severe heart failure (10-12 points).[3] Blood specimens (2 mL) were preserved in in ethylenediaminetetraacetic acid (EDTA) for NT-proBNP quantification using *the Roche cardiac proBNP testing kit*.[13]

Descriptive data was presented as median with range and a normality test (*Shapiro-Wilk*) was performed on the data. Spearman's test was used to analyze for correlations of variables. The distribution of NT-proBNP level was illustrated by box-and-whisker plots. We analyzed all data with *SPSS 18.0 software*. The study protocol was approved by the Health Research Review Committee of Mohammad Hoesin Hospital.

Results

From July to September 2015, 30 patients with congestive heart failure met the inclusion criteria. Three patients were excluded because two had renal failure and one could not undergo NT-proBNP measurement. Subjects' median age was 12 months (range 2-162 months). Female to male ratio was 2:1. The majority of patients were well-nourished (17/30). In addition, most subjects were diagnosed with congenital heart disease (23/30). Characteristics of subjects are presented in **Table 1**.

The specific cardiovascular diseases diagnosed in our subjects are shown in **Table 2**. Most congenital heart disease patients had ventricular septal defects (14/30) and most acquired heart disease patients had rheumatic heart disease (3/30).

Patients were classified according to the severity of heart failure, based on the modified Ross Reithmann scores and underwent laboratory examinations of NT-proBNP levels. Nine patients with mild heart failure had a median NT-proBNP of 518 pg/mL (310-1,213 pg/mL); 12 patients with moderate heart failure had a median NT-proBNP of 1,703 pg/mL (1,251-9,000 pg/mL); and the 9 remaining patients with severe heart failure had a median NT-proBNP of 6,510 (2,610-9,000 pg/mL) (**Table 3**).

Table 1. Baseline characteristics of subjects

Characteristics	N=30
Gender, n	
Male	10
Female	20
Nutritional status	
Severely undernourished	5
Undernourished	8
Well-nourished	17
Heart disease	
Congenital	23
Acquired	7
History of heart disease	
Yes	11
No	19
Median age, months (range)	12 (2-162)

Table 2. Types of heart disease in subjects

Heart disease	N=30
Congenital	
VSD	8
VSD + PDA	3
VSD + cardiomyopathy	2
VSD + severe MR	1
PDA	2
PDA + ASD	1
ASD	2
AVSD	1
Pulmonary atresia+VSD+PDA +PFO	1
TAPVD+DORV+VSD+PDA+ASD	1
HLHS+PDA+ASD	1
Acquired	
Rheumatic heart disease	3
Cardiomyopathy	2
Rheumatic heart disease + cardiomyopathy	1
TR, MR, PR caused by pulmonal hypertension	1

VSD=ventricular septal defect; PDA=patent ductus arteriosus; MR=mitral regurgitation; ASD=atrial septal defect; AVSD=atrioventricular septal defect; PFO=patent foramen ovale; TAPVD=total anomalous pulmonary venous drainage; DORV=double outlet right ventricle; HLHS=hypoplastic left heart syndrome; TR=tricuspid regurgitation; PR=pulmonal regurgitation

Table 3. NT-proBNP level according to heart failure severity

Severity of heart failure	Median NT-proBNP (range), pg/mL
Mild (n=9)	518 (310-1,213)
Moderate (n=12)	1,703 (1,251-9,000)
Severe (n=9)	6,510 (2,610-9,000)
Total (N=30)	1,703 (310-9,000)

We found that NT-proBNP level increased with increased heart failure severity, except in the subjects with moderate heart failure, which had two extremes in the data (**Figure 1**). Also, median NT-proBNP level in congenital heart disease patients was higher than in those with acquired heart disease, except for one data outlier in the acquired group (**Figure 2**).

Subjects with moderate heart failure were divided into congenital and acquired heart disease groups. The median NT-proBNP level in those with congenital heart disease was higher than in those with acquired heart disease, except in two cases with data extremes (**Figure 3**). Likewise, subjects with severe heart failure were divided into congenital and acquired heart disease groups. The median NT-proBNP level in

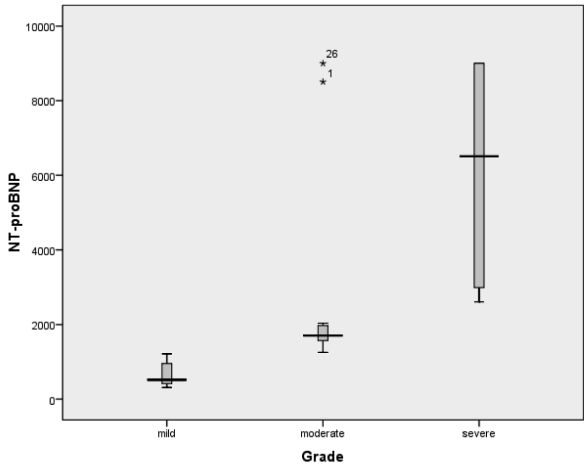

Figure 1. Median (range) NT-proBNP level according to heart failure severity

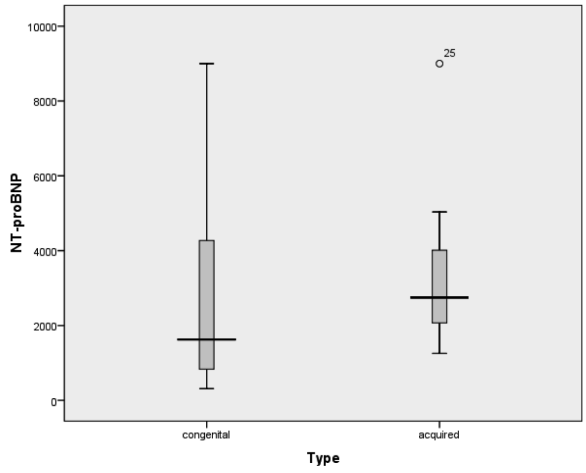

Figure 2. Median (range) NT-proBNP level according type of heart disease

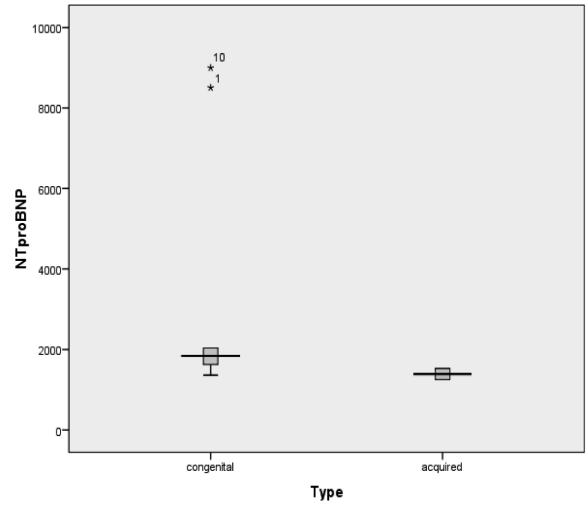

Figure 3. Median NT-proBNP level in subjects with moderate heart failure according to type of heart disease

those with congenital heart disease was higher than in those with acquired heart disease, except in one data outlier (**Figure 4**). In our study, congenital heart disease consisted of cyanotic and acyanotic subjects, of whom there were 3 cyanotic subjects and 20 acyanotic subjects. The median NT-proBNP level in cyanotic subjects was higher than in acyanotic subjects, as 2 cyanotic subjects had high NT-proBNP (9,000 pg/mL) and one cyanotic subject had NT-proBNP of 1,359 pg/mL. Median NT-proBNP level and heart failure severity had a significant, positive correlation (r=0.87; P=0.000).

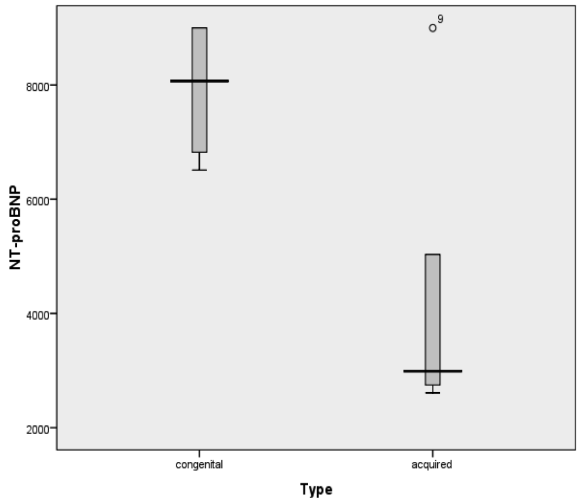

Figure 4. Median NT-proBNP level in subjects with severe heart failure according to type of heart disease

Discussion

N-terminal pro brain natriuretic peptide (NT-proBNP) has been suggested as a biomarker of heart failure. The NT-proBNP is secreted by cardiac ventricular myocytes in response to increased left ventricular stretching or wall tension, and volume load.[5-8] Recent studies evaluated for a correlation between heart failure severity in pediatric patients and NT-proBNP levels.[9,14,17] As reported in adults, heart failure severity and NT-proBNP level have a significant, positive correlation.[11,12] Few studies have been performed in children with heart failure, especially in Indonesia, so we conducted this study in pediatric patients to assess NT-proBNP levels and heart failure severity, as classified by modified Ross Reithmann scores.

Heart failure is a common clinical syndrome, but there is no single, specific test to diagnose heart failure. Clinical scores are generally used to classify the symptomatic severity of heart failure in children, one of which is the modified Ross Reithmann score.[3,4] In our study, plasma NT-proBNP increased as heart failure severity increased. The NT-proBNP level in subjects with severe heart failure was higher than in those with moderate or mild heart failure, in agreement with previous findings.[9-10,14-16] As such, NT-proBNP may be useful as a biochemical marker for the diagnosis and grading of heart failure severity in pediatric patients.

We found that plasma NT-proBNP levels correlated to heart failure severity, with higher NT-proBNP levels in those with more severe heart failure (r=0.87; P=0.000). Similar findings were reported by Sarangnga (r=0.74; P<0.0001), Sugimoto *et al.* (r=0.65; P<0.001 for children below 3 years old and r=0.47; P<0.001 for above 3 years old), and Baghdady *et al.* (P<0.0001).[9,14,17]

Our subjects had either congenital or acquired heart disease. The plasma NT-proBNP levels in congenital heart disease patients were higher than in subjects with acquired heart disease. Law *et al.* found that BNP is a reliable test to diagnose significant structural or functional heart disease in children. They found that BNP in those with anatomic defects was higher than in those without anatomic defects.[18] In our severe heart failure group, plasma NT-proBNP in those with congenital heart disease was higher than in those with acquired heart disease, except in one subject with complications of cardiomyopathy. In that subject, the complication of disease may have decreased cardiac function and muscle contraction resulting in increased NT-proBNP level. [19-20]

Our congenital heart disease patients consisted of cyanotic and acyanotic subjects. Plasma NT-proBNP levels were higher in in cyanotic patients than in acyanotic patients. Moses *et al.* found that NT-proBNP level in cyanotic subjects (mean 1,023 pg/mL) was higher than in acyanotic subjects (mean 372 pg/mL).[21] One subject of our three cyanotic subjects had lower NT-proBNP than the other two subjects, possibly due to drug therapy for heart failure. It has been well established that NT-proBNP level decreases in most patients who receive drug therapy

for heart failure.[8] Cyanotic heart disease patients often have more complex defects, compared to acyanotic patients, and they usually have more than one defect that tends to be complicated and severe. The complexicity of defects in cyanotic subjects increases both the risk of heart failure and the severity of heart failure compared to acyanotic subjects. Differing NT-proBNP levels between cyanotic and acyanotic heart disease patients can help us to differentiate the disease, but in practical terms, pulse oxymetry is easier, faster, and less expensive than NT-proBNP tests.

A limitation of this study was the small sample size of our subgroup of subjects with cyanotic and acyanotic heart disease, as well as the subgroups of subjects with congenital and acquired heart disease. In conclusion, NT-proBNP level had a significant, positive correlation to the severity of heart failure in children. As such, NT-proBNP level may be useful as a biochemical marker in the diagnosis and grading of heart failure in children**.**

Conflict of interest

None declared.

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