N Terminal-Pro B Type Natriuretic Peptide (NT- PRO BNP) levels and severity of disease in elderly with heart failure

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Original Article

ABSTRACT

Background: Heart failure is a major health problem in the world. It is associated with high morbidity and high mortality especially in elderly patients. Most studies reported that N terminal pro-B type natriuretic peptide (NT-proBNP) is used in the diagnosis of heart failure, but tests in determining severity levels of heart failure in the elderly remains unclear.
Objective: This study is to determine differences of NT-pro BNP levels based on severity of heart failure in elderly patients.
Methods: This was an observational study with a cross sectional design. Its subjects were patients with heart failure and age of ≥ 60 years. Patients were divided into two groups: mild and severe heart failure groups according to severity of heart failure based on New York Heart Association (NYHA). The NT Pro-BNP levels were measured for all subjects in both groups. All obtained data was analysed by using unpaired t test and was considered significant if p <0.05.
Results: This study involved 24 subjects. The mean age of the subjects was 64.50 ± 4.65 years with a minimum age of 60 years and a maximum age of 78 years. The NT pro-BNP levels in the severe heart failure group (1.2587.58 ± 574.85 pg/ml) was higher than the mild heart failure group (867.83 ± 333.27 pg/ml), andit was statistically significant with p = 0.040.
Conclusion: The levels of NT-pro BNP serum in the elderly patients with severe heart failure (NYHA III-IV) were significantly higher than in patients with mild heart failure (NYHA I-II).

Latar Belakang: Gagal jantung merupakan problem kesehatan mayor di dunia. Gagal jantung ini angka morbiditas dan mortalitasnya tinggi terutama pada usia lanjut. Penelitian sebelumnya menyatakan N Terminal pro Brain Natriuretic Peptide *(NT-pro BNP) dapat untuk diagnosis, tetapi perannya untuk membedakan tingkat keparahan gagal jantung pada usia lanjut belum sepenuhnya jelas.*
Tujuan: Mengetahui perbedaan kadar N Terminal pro B Type Natriuretic Peptides (NT pro BNP) berdasarkan derajat keparahan penyakit pada pasien gagal jantung usia lanjut.
Metode: Penelitian ini adalah observasional analitik dengan desain cross sectional. Subyek yang memenuhi kriteria (terdiagnosis gagal jantung, berusia ≥ 60 tahun) dibagi 2 kelompok berdasarkan derajat keparahan penyakitnya sesuai kriteria New York Heart Association (NYHA) dan dilakukan pemeriksaan kadar NT pro BNP. Analisis statistik menggunakan uji t tidak berpasangan dan dianggap bermakna bila p<0,05.
Hasil: Pada penelitian ini melibatkan 24 subyek penelitian, yang terdiri dari kelompok pasien gagal jantung ringan (NYHA kelas I-II) dan kelompok pasien gagal jantung berat (NYHA III-IV). Rerata usia subyek penelitian adalah 64,50±4,65 tahun dengan usia minimum 60 tahun dan maksimum 78 tahun.

Kadar NT pro BNP kelompok gagal jantung berat (1.2587,58± 574,85 pg/ml) lebih tinggi dibanding kelompok gagal jantung ringan (867,83 ± 333,27 pg/ml), secara statistik bermakna dengan p=0,040. **Kesimpulan:** *Kadar NT pro BNP pada pasien usia lanjut dengan gagal jantung berat (NYHA III-IV) lebih tinggi secara bermakna daripada pada pasien gagal jantung ringan (NYHA I-II).*

INTRODUCTION

Heart failure is a major health problem in Indonesia and on the global scale due to its high rates of morbidity and mortality. Prevalence of heart failure growing with increasing of age and mortality rates was found higher in elderly. Therefore, treatment for elderly heart failure patients needs special attention. Basic Health Research of the Indonesian Ministry of Health in 2018 calculated that the prevalence of heart failure based on a doctor's diagnosis is estimated at 1.5%. Yogyakarta has the most elderly population in Indonesia, so an increase in age-related problems including heart failure occurs.[1,2]

Heart failure is a neurohumoral complex syndrome and inflammation. Neurohumoral activation in heart failure is resulted from a dysfunction in a balance of a hormone system that causes vasoconstriction (antinatriuretic, antidiuretic, growth factors) and vasodilation (natriuretic, diuretic, antimitotic).[3] Early diagnosis and treatment of heart failure will prevent complications and reduce treatment costs. Echocardiography currently becomes a gold standard in the diagnosis of heart failure. However, due to its limited availability, specific tests are needed to aid diagnosis and avoid severity of heart failure. Therefore, examination of natriuretic peptide (NP) is considered to be beneficial in a heart failure diagnosis.[4]

The B-type natriuretic peptide (BNP) and the co-metabolite, N-terminal pro-B-type natriuretic peptide (NT-pro BNP) can be used to improve accuracy of heart failure detection. Brain Natriuretic Peptide is synthesized by myocytes and is released during hemodynamic stress, such as when there are dilation and ventricular hypertrophy or increased pressure on the heart wall. Plasma B-type natriuretic peptide (BNP) has a role as a diagnostic marker of heart failure with a sensitivity of 90%, specificity of 76%, and a predictive value of 83%.[5] Several studies have shown that a higher concentration of BNP and NT-pro BNP corresponds with shortness of breath symptoms caused by heart failure. Previous studies have also found that BNP and NT pro-BNP are associated with decreased ejection fraction and risk stratification of patients with heart failure.[6,7]

Levels of severity of heart failure is functionally established by the New York Heart Association (NYHA). This system divides 4 functional classes based on clinical symptoms: NYHA I if there are no symptoms, NYHA II refers to shortness of breath with strenuous activities, NYHA III represents shortness of breath during light activities, and NYHA IV is shortness of breath despite resting conditions. Previous studies in adult patients showed a significant increase of NT-pro BNP levels according to severity levels based on the NYHA. In addition, a significant correlation was found between NT-pro BNP levels in patients with morbidity and mortality of ventricular systolic dysfunction.[8,9]

NT-pro BNP levels in the elderly increase according to their age decade. The relationship between increased levels of NT-pro BNP and the severity of heart failure in the elderly is still obscure because elevated levels of NT-pro BNP is also influenced by age. However, in the elderly heart failure patients, an increase of plasma NT-pro BNP levels is higher but it can be influenced by other comorbidities other than chronic heart failure.[10-12] Therefore, NT-pro BNP levels cannot determine causes of shortness of breath in the elderly due to various factors including existence of comorbid diseases.[10] Furthermore, one study showed that BNP cannot differentiate between cardiac and respiratory causes in a population of very elderly patients with acute shortness of breath symptoms.[11] For that reasons, this study focuses on the relationship between the

levels of terminal pro Brain Natriuretic Peptides (NT- pro BNP) and the severity of elderly heart failure patients.

METHODS
Research design
This study was an observational analytic study with a cross-sectional design. The data collection time of NT-pro BNP levels and the severity of heart failure disease were conducted at the same time. The study was conducted for approximately 1 year in outpatient and inpatient institutions at Gramedika Hospital Yogyakarta.

Research Subjects
Inclusion criteria of this study were heart failure patients confirmed by an internal medicine specialist based on history taking, physical examination, laboratory and radiology examination. Subjects with age older or equal to 60 years agreed and signed an informed consent. Exclusion criteria for this study were patients with respiratory problems (COPD and Asthma). Severity of heart failure in this study was determined based on the NYHA criteria. This criteria divides 4 functional classes based on clinical symptoms as previously mentioned. In this study, the subjects were grouped into 2 groups: a group with mild heart failure consisting of NYHA I-II and a group with severe heart failure consisting of NYHA III-IV

Sample Calculation
Sample size of this study sample was calculated by using sample size formula for unpaired numerical analytic research

$$N_1 = N_2 = \left\{ \frac{(Z\alpha + Z\beta) S}{X_1 - X_2} \right\}^2$$

In this study, with an error rate of $\alpha = 5\%$, a two-way hypothesis test, then $Z\alpha = 1.64$. Meanwhile, with the research power of 80%, then $Z\beta = 0.842$. A previous research found that a mean standard deviation is 802.7, and

a significant difference in value was 1926.56. Hence, it was obtained N = 12 patients for each group. Determination of the research subjects used a non-probability sampling method with a consecutive sampling approach.[13,14]

Research Flow
Heart failure patients who met the inclusion and exclusion criteria were recorded in a study form. History taking, physical examination, chest radiograph, and electrocardiography (EKG) were performed, and the clinical severity of the disease was determined based on the NYHA classification. Venous blood in amount of 10 ml was withdrawn to check the levels of NT-pro BNP. N-Terminal pro-BNP (NT-pro BNP) was measured by using a Roche diagnostic immunoassay method. The independent variable was the level of NT-pro BNP, while the dependent variable is the clinical severity of heart failure.

Statistical analysis
This study used unpaired t-test to evaluate the relationship between NT-pro BNP levels and the severity of heart failure by evaluating the differences of NT-pro BNP levels in the mild heart failure (NYHA I-II) group and in the severe heart failure (NYHA III-IV) group. It is considered significant if $p < 0.05$. All analyses used a statistical software.

Ethical Clearance
This study ensured all the patients confidentiality and performed all procedures according to the research ethics. This study received approval from the ethics committee for biomedical research in humans from the Ethics Committee, the Faculty of Medicine, Universitas Islam Indonesia (No, 37/Ka.Kom. Et /70/KE/I/2016).

RESULTS
Characteristics of Research Data
This study involved 24 heart failure patients with a minimum age of 60 years its research subjects. The subjects consisted of 18 men

(75%), and 6 women (25%). The youngest patient was 60 years old and the oldest was 78 years old. The mean age of the patient was 64.50 ± 4.65 years. The subjects were divided into two groups: namely group A consisting of 12 mild heart failure patients (NYHA class I-II), and group B consisting of 12 severe heart failure patients (NYHA III-IV). Group A consisted of 7 men and 5 women, with 4 patients with NYHA I and 8 patients with NYHA II. Group B consisted of 9 male and 3 female patients, with 11 patient with NYHA III and 1 patient with NYHA IV. The subjects of this study mostly had comorbid diabetes mellitus, hypertension, coronary heart disease, and kidney disease. Data of the subject characteristics is presented in the Table 1.

Table 1. Basic characteristics of elderly patients with mild and severe heart failure

	Total (n=24)	Group A Mild Heart Failure (NYHA I-II) (n=12)	Group B Severe Heart Failure (NYHA III-IV) (n=12)	p value*
Sex				p>0,05
Male (%)	18 (75 %)	9 (75 %)	9 (75 %)	
Female (%)	6 (25 %)	3(25 %)	3 (3 %)	
Age (year)	64,50±4,65	63,67±3,82	65,33±5,40	p>0,05
Comorbid				p>0,05
Diabetes Mellitus (%)	9 (37,50 %)	5 (41,70 %)	4 (33,33 %)	
Hypertension (%)	8 (33,33 %)	4 (33,33 %)	4 (33,33 %)	
Coronary Heart Disease (%)	2 (16,70 %)	1 (8,30 %)	2 (16,70 %)	
Kidney Disease (%)	2 (16,70 %)	1 (8,30 %)	1 (8,30 %)	
Others	3 (12,50 %)	1 (8,30 %)	1 (8,30 %)	
Blood Pressure (mmHg)				
Systolic	135,42±27,34	134,17±25,39	136,67±30,25	p>0,05
Diastolic	78,33±11,67	75,83±9.00	80,83±13,79	p>0,05
Blood Sugar Level (mg/dl)	162,21±73,34	167,08 ± 77,47	157,33±72,05	p<0,05

*P-values obtained by the Mann-Whitney test for numerical variables and by chi-square or Fisher's exact test for categorical variables.

Table 1 shows that there was no significant difference in the variables of age, sex, systolic, and diastolic blood pressure between the two groups, with p> 0.05. Meanwhile, the blood sugar levels were significantly different between the two groups, with p <0.05. The blood sugar level of patients with mild heart failure was higher than in patients with severe heart failure.

The NT pro BNP level based on the severity of heart failure can be seen in Table 2. The NT pro BNP level in the severe heart failure group (NYHA III-IV) was 1.2587.58 ± 574.85 pg/ml.

Table 2. Basic characteristics of elderly patients with mild and severe heart failure

Variable	Group A Mild Heart Failure (NYHA I-II) (n=12)	Group B Severe Heart Failure (NYHA III-IV) (n=12)	p value*
NT-pro BNP (pg/ml)	867,83 ± 333,27	1.2587,58± 574,85	p=0,040

* P-values obtained by t test.

This level was higher than the NT pro BNP level (867.83 ± 333.27 pg/ml) in the mild heart failure group (NYHA I-II) which was statistically significant with p = 0.040.

Table 3 presents the differences of NT-pro BNP levels based on sex, age, and hypertension. The levels of NT-pro BNP based on age were divided into two groups, namely groups with ages ≥ 70 years and ages <70 years. There were 5 research subjects aged ≥ 70 years, and <70 years old were 19 people. NT pro-BNP levels in the age group ≥ 70 years were higher than those at <70 years old, but not statistically significant with p = 0.074. The levels of NT-pro

BNP based on gender were seen in the male group to be higher than that of the women, but there was no statistically significant difference with p= 0.988. Gender did not affect NT-pro BNP levels. To see differences of NT-pro BNP levels based on hypertensive conditions, the subjects were divided into two groups: namely the hypertensive group and the non-hypertensive group. There were 8 subjects with hypertension, and 16 subjects without hypertension. The NT-pro BNP level in the non-hypertensive group was higher than that in the hypertension group, but it was not statistically significant with p = 0.889.

Table 3. NT-pro BNP levels based on age, sex, and hypertension

NT-pro BNP level based on age

	Age ≥ 70 tahun (n= 5)	Age < 70 tahun (n= 19)	p= value*
NT-pro BNP (pg/ml)	1.401,00 ± 647,80	934,58 ± 454,61	p=0,074

NT-pro BNP level based on sex

	Male (n= 18)	Female (n=6)	p value*
NT-pro BNP (pg/ml)	1.078,67±21,08	1.074,83±2018,01	p=0,988

NT-pro BNP level based on hypertension

	Hypertension (n= 8)	Not hypertension (n= 16)	p value*
NT -pro BNP (pg/ml)	1.009,25 ± 480,22	1.043,00±556,15	P=0,889

* P-values obtained by t test

DISCUSSION

In this study, of 24 elderly heart failure patients, 75% were male and 25% were female patients. These results are in agreement with two previous studies conducted in Indonesia.[14,15] On the contrary, a study in Scandinavia stated that prevalence of elderly heart failure patients based on gender is almost similar, but it was slightly higher in female patients.[2] Likewise, a study in Italy showed that both sexes were almost same, but it was slightly higher in women. In its theory, prevalence of heart failure in the elderly will be same for men and women. This is because hormonal protective factors in women

have been reduced due to menopause.[2,12] In this study, the number of patients with advanced heart failure was higher in male patients than in female patients.

Our study showed that NT-pro BNP levels were significantly higher in elderly patients with severe heart failure (NYHA III-IV) (p <0.005) than those with mild heart failure (NYHA I-II). A previous study in adult heart failure patients stated that the NT-pro BNP NYHA III-IV levels were higher than those in NYHA I-II.[14] Previous studies at Cipto Mangunkusumo Hospital obtained NT-proBNP levels in NYHA III and IV subjects with EF <40% (7316 pg/

mL) were higher than subjects with EF> 40-50% (2797 pg/mL), although statistically not significant (p> 0.05). Alhuselny et al. (2012) conducted a study which showed that serum NT-proBNP levels were inversely correlated (r = -0.339, p <0.001) with cardiac ejection fraction. However, the peptide level was inconsistently associated with the E/A ratio as assessed by Doppler indicating functional disability.[9,14]

In our study, male NT-pro BNP levels were higher than female patients, and NT pro-BNP levels in those aged>70 years were higher than those aged less than 70 years. Previous studies reported that levels of NT pro BNP were influenced by age and gender, however both factors were not statistically significant (p> 0.05). This result was influenced by the limited number of samples and the unequal sex and age among groups. A study in a general population of Copenhagen found that levels of NT-pro BNP increased with advancing age, and levels of NT-pro BNP in women were higher than in men.[9,16] Patients with systolic heart failure in the older age group ≥ 77 years had higher NT-pro BNP levels than other elderly age groups.[17]

In very elderly heart failure patients, the NT-proBNP value was related to disease severity or organ failures such as decreased eGFR, reduced albumin, and increased CRP.[12] NT-proBNP values > 1800 pg/ml were significantly associated with hospital mortality and were not affected by comorbidities and laboratory parameters. The NT-proBNP examination is highly recommended for the elderly who are hospitalized because it may predict heart failure which has a significant high impact on mortality in the hospital. This is in line with the results of this study, that further heart failure levels of NT pro-BNP are higher. Furthermore, NT pro BNP examination can identify underlying cardiac involvement and the efficacy of its treatment.[12,18]

In agreement with these results, a study conducted by Januzzi et al., (2010) showed that patients with a decrease in NT-proBNP levels experienced a greater quality of life improvement, a greater relative increase in LV ejection fraction, and a better left ventricular end-systolic and diastolic volume index. This suggests that improvement of severity is associated with a decrease of the patient's NT- pro BNP levels. Another study of elderly people in India stated that the NT-proBNP value increased significantly as the functional severity of heart failure (HF) increased (P <0.001). The mean NT-proBNP level was 1503.33 pg/mL. Patients with dyspnea had a mean NT-proBNP level of 309.28 pg/mL with a normal LV function. Increased levels of NT-proBNP NT were strongly correlated with worsening of LVEF.[19,20]

Based on the blood pressure condition of the patients, this study suggests that the NT pro BNP levels were found to be higher in those without hypertension, but this result was not statistically significant. This finding is contrary with previous studies which stated that NT pro-BNP levels were increased in hypertensive patients. This could be happened due to the limited sample size or imbalance between patients with hypertension and patients without hypertension. Previous studies showed that NT-proBNP levels in patients with grade 2 hypertension were higher and significantly different (p = <0.001) compared to grade 1 hypertension. Besides, there was a significant difference between the two groups (p = 0.010). Other studies suggest that an increase in NT-proBNP was independently associated with an increased risk of hypertension.[21,22]

This study has several limitations in the study design, sampling and data collection. This study is a cross-sectional design with a one-time collection, and this study does not exclude or consider other comorbid due to incomplete data on clinical conditions, supporting examinations, and other laboratory parameters.

CONCLUSION

It could be concluded that the levels of NT-pro BNP in elderly patients with severe heart failure (NYHA III-IV) were significantly higher than the levels of NT-pro BNP in patients with mild heart failure (NYHA I-II).

CONFLICTS OF INTEREST

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