

N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) in Stage 1 and Stage 2 Hypertension Patients

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Abstract

The increased levels of NT-proBNP in the blood occur when heart function, especially the left ventricular muscle chambers of the heart increase. Therefore, NT-proBNP is used as a biomarker to detect heart failure. The level of N Terminal – Pro Brain Natriuretic Peptide was independently associated with an increased risk of hypertension. This study aimed to determine the difference of NT-proBNP serum levels and the correlation between the levels of NT-proBNP in patients with stage 1 and stage 2 hypertension. This research was conducted at RSUP dr. Wahidin Sudirohusodo in August - September 2018. The study used a cross-sectional design with the total of 72 hypertensive patients, who had met the inclusive criteria. NT-proBNP levels were measured using the ELISA (Enzyme Linked Immunosorbent Assay) method. The collected data was processed using Mann Whitney Different Test and Spearman's rho Correlation Test. The study results indicated that the level of NT-proBNP in the hypertensive patients with stage 2 was higher and significantly different ($p = 0.001$) compared to stage 1 hypertensive patients. NT-proBNP levels were higher in the hypertensive group of ≥ 6 years than in the hypertensive group < 6 years. There were significant differences between the two groups statistically ($p=0.010$). It can be Conclude that there is a significant difference in the levels of NT-proBNP with a degree of hypertension where NT-proBNP levels were higher in patients with stage 2 hypertension compared to stage 1 hypertension, although there was not statistically significant correlation between levels of NT-proBNP with Hypertension degree. Further research was needed to determine the relationship of NT-proBNP levels with the degree of hypertension, which can confirm the diagnosis, especially in patients with hypertension. Also, it is suggested to consider the accuracy of the data length of a patient suffering from undiagnosed hypertension.

Keywords

NT-proBNP, hypertension, degree of hypertension, duration of hypertension

INTRODUCTION

Hypertension or high blood pressure is a global health problem, including in Indonesia because of the high prevalence, although different in various state. Hypertension does not give complaints and typical symptoms so many people do not realize it since it was dubbed as the silent killer (1). Hypertension is defined as someone who had a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, on repeated examinations (2). Hypertension is one of the most common diseases found in primary medical practice which is also a risk factor of myocardial infarction, stroke, acute kidney failure, and death (3).

According to NHLBI (National Heart, Lung, and Blood Institute), 1 in 3 (patients) suffers from hypertension. In a meta-analysis study that includes 61 prospective international studies in 1 billion patients, which was equivalent to 12.7 million person-years, it was found that a decrease in mean systolic blood pressure of 2 mmHg could reduce the risk of mortality from ischemic heart disease by 7% and reduce the risk of stroke mortality by 10%. Achieving the target of reducing blood pressure is very important to reduce cardiovascular events in hypertensive patients (4).

The Health Profile of South Sulawesi Province in 2016 showed the prevalence of hypertension in South Sulawesi Province obtained through population blood pressure

measurements at the age of > 18 years with a total of 142,571 cases (5). Based on data from the Makassar City Health Profile in 2016, hypertension was included in the top 10 cases of the highest cause of death in Makassar (6).

Primary hypertension is hypertension that does not have a known cause, faced by the majority (90%) of high blood pressure patients who come to the practice. Primary (essential) hypertension has several factors at play, namely hormonal factors in the renin-angiotensin and aldosterone system, autonomic nervous system, peripheral resistance, salt intake (NaCl), and others. Secondary hypertension can be determined as the cause which is generally experienced by a small percentage of patients (10%) with high blood pressure. The most common cause of secondary hypertension is chronic kidney disease. Other causes are obstructive sleep apnea, primary aldosteronism, renal artery stenosis, Cushing's syndrome, pheochromocytoma, hyperparathyroidism, coarctation of aorta, hypo and hyperthyroidism and drugs (1).

Complications of hypertension may affect various organs such as the heart (ischemic heart disease, left ventricular hypertrophy, heart failure), brain (stroke), kidney (renal failure), the eyes (retinopathy) also peripheral arteries (intermittent claudication). The damage of these organs depend in high blood pressure patients and the duration of the high blood pressure is not

controlled and untreated (4). The division of the severity of hypertension in a person is one of the basis for determining the treatment of hypertension according to The seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The classification of hypertension in adults divided into groups of normal, prehypertension, stage I hypertension and stage II hypertension. Systolic blood pressure is the main measurement that is the basis for determining the diagnosis of hypertension (2).

NT-proBNP test can be used as a new parameter to identify at an early stage and monitor the progress of side effects of chemotherapy on the heart, in addition to the measurement of left ventricular ejection fraction. Aside from being used as a biomarker for acute and chronic heart failure, NT-proBNP can also be used to protect against the decrease in left ventricular function of asymptomatic patients with risk factors for cardiovascular disease. Hypertension is one of the main risk factors for cardiovascular disease, such as heart failure, acute myocardial infarction and even sudden death. Patients with hypertension can control the abnormalities and heart functions such as left ventricular hypertrophy / LVH) and left ventricular systolic dysfunction (LVSD), and the effect of their use by the left ventricular hypertrophic response associated

with hypertension. Detection of this condition is very important in the management of hypertension (1).

Diagnosis of hypertension with the most accurate physical examination is by using mercury sphygmomanometer. You should do more than one measurement in a sitting position with your elbows bent on the table with your palms facing up and your arms should be at heart level. Measurements are made in a calm state. Patients are expected to not consume food and drinks that can affect blood pressure such as coffee, soda, foods high in cholesterol, alcohol and so on (7).

Biomarkers such as NT-proBNP has been investigated as a test that can help the diagnosis and management of heart failure at the same prognosis. Steffanus (8), also declared that there is a relationship between elevated levels of NT-proBNP with cirrhosis of the liver disease. Reseach conducted by Khairunnisa (9), stated that there is a relationship between increased levels of NT-proBNP and the impairment of left ventricular ejection fraction-proBNP. NT-proBNP different on various diseases, because it needs to do further research to determine differences in the levels of the various diseases that cause heart failure. However, other studies have suggested that the increased NT-proBNP was independently associated with an increased risk of hypertension (10). This makes the researcher interested to know the different levels of NT-

proBNP and NT-proBNP levels relationship with the degree of hypertension. The purpose of this study was to determine the differences in the levels of NT-proBNP in stage 1 hypertensive patients and stage 2 hypertension patients. Also, the researcher intended to know the relationship between the levels of NT-proBNP in stage 1 hypertension and stage 2 hypertension.

MATERIALS AND METHODS

This research was conducted in the Medical Record Room and Outpatient Installation of Dr. Wahidin Sudirohusodo General Hospital Makassar, August - September 2018. 72 sampel collected in the analysis in Research Unit at University RSPTN Hasanuddin. This research was a cross-sectional study. The population in this study were all patients with hypertension who underwent outpatient RSWs who aged > 30 years and suffering from hypertension stage I and stage II and has a systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg.

Data from medical records collected by age, sex, duration of hypertension and blood pressure are presented in tabular form to explain the characteristics of the study sample. The tools used in this study were ELISA (Enzyme-linked Immunosorbent Assays) Reader Organon model 680 (biorad) and microwell shaker tool (Incubator 1000 heidolph). NT-proBNP Levels in Patients

with Stage I and Stage II Hypertension previously done Kolgomorov-Smirnov test to determine whether the data have normal distribution. The mean of the two groups were then tested for statistical significance by Mann Whitney test and Spearman's rho. Results revealed significant when $P < 0.05$.

RESULTS

This study was conducted on 72 patients with hypertension based on blood pressure, hypertension degree and medical record data in the outpatient installation of RSUP Dr. Wahidin Sudiro Husodo. The research subjects were divided into 2 groups consisting of 36 patients per group with systolic blood pressure 140-159 mmHg; diastolic 90-99 mmHg (hypertension Stage 1) and systolic blood pressure ≥ 160 mmHg; diastolic ≥ 100 mmHg (Stage 2 hypertension).

The characteristics of sex of the subjects was illustrated on Table 1. The subject consisted of a total of 32 male patients and female 40 patients. based on the characteristics of the age, there was a total of 11 patients whose age below 45 years old (15.3%) and age greater than or equal to 45 years old amounted to 61 people (84.7%). Meanwhile, the total patients based on the characteristics of the length of hypertensive which less than 6 years was 56 patients (77.8%) and the number of hypertension patients which the length of hypertensive

greater than or equal to 6 years was 16 patients (22.2%). Lastly, the number of patients based on blood pressure

characteristics was 36 patients (50%) with first degree hypertension and 36 samples (50%) with second degree hypertension.

Table 1. Characteristics of Research Subjects

Characteristics		N	Percentage (%)	Min	Max	Mean
Gender	Male	32	44.4	-	-	
	Female	40	55.6			
Age (Year)	<45	11	15.3	32	80	56.17
	≥ 45	61	84.7			
Older Hypertension (Years)	<6	56	77.8	0	11	2.54
	≥ 6	16	22.2			
Blood pressure (MmHg)	Hypertension Stage 1	36	50	140/90	220/120	161.01/98.15
	Hypertension Stage 2	36	50			

Levels of NT-proBNP Analysis Based Research Subject Characteristics

The results of statistical analysis of the study subjects showed significant differences in the levels of NT-proBNP based on gender of patient suffering from hypertension (p=0.010) and degree of hypertension (p=<0.001).

in this study was 56.17 ± 10.35 years old with the largest age was ≥ 45 years old amounted to 84.7%, performed different tests based on the characteristics of the age of the patients (p=0,863). The test results showed statistically significant difference between the levels of NT-proBNP in patients with Stage 1 and Stage 2 hypertension (p=<0.001).

The results of statistical analysis in Table 2 showed that the average age of the subjects

Table 2. Analysis of Differences between NT-proBNP levels with Characteristics of The Research Subjects

Characteristics	NT-proBNP levels (ng / L)				p-value *	
	Min	Max	Mean	SD		
Gender	Male	5.47	250.22	51.49	48.51	0.803
	Female	3.46	1252.65	145.86	305.55	
Age (Year)	<45	10.60	128.55	46.77	35.10	0.863
	≥ 45	3.46	1252.65	114.22	252.24	
Older Hypertension (Year)	<6	3.46	1252.65	62.79	164.66	0.010
	≥ 6	16.65	1150.68	247.83	361.01	
Blood pressure (MmHg)	Stage 1	3.46	128.55	34.98	28.99	<0.001
	Stage 2	11.06	1252.65	172.85	316.26	

* Mann-Whitney (p=<0.05)

The results of statistical analysis in Table 3 is based on the characteristics of the study subjects which showed no correlation with the levels of NT-proBNP after Spearman's

rho test ($p < 0.05$) so that it can be concluded that there was no relationship between the levels of NT-proBNP with the degree of hypertension.

Table 3. Correlation Analysis Levels of NT-proBNP with Characteristics of Research Subjects

Characteristics		NT-proBNP levels (ng / L)				p-value*
		Median	Min	Max	SD	
Gender	Male	31.93	5.47	250.22	48.51	0.762
	Female	46.14	3.46	1252.65	305.35	
Age (Years)	<45	50.17	10.60	128.55	35.10	0.979
	≥ 45	36.20	3.46	1252.65	239.24	
Older	<6	32.32	3.46	1252.65	164.65	0.183
Hypertension (Years)	≥ 6	78.17	16.65	1150.68	361.01	
Blood pressure (MmHg)	Stage 1	24.33	3.46	128.55	28.99	0,862
	Stage 2	53.27	11.06	1252.65	316.26	

*Correlation Spearman's rho

DISCUSSION

This research shows that there were more patients with hypertension in women than men and those whose age > 45 years old than those whose age < 45 years old. Age is an important factor of hypertension. When someone get older, the risk of hypertension is also higher. An increase in hypertension cases will develop in the fifties and sixties. Increase in blood pressure with the increase in age is a normal condition. However, if the change of blood pressure is too striking and accompanied by other factors, it triggers hypertension with its complications (11). According to Azhar (12), it was stated that hypertension is more common in women than in men, this happens because premenopausal

women are protected by the hormone estrogen which can increase the concentration of HDL and decrease LDL concentrations. However, when women experience menopause, estrogen will decrease. Mainly experienced by women who are elderly, so that the blood pressure in elderly women tend to be high (12).

As a biochemical marker that gives new hope to the cardiovascular field, the normal value of NT-proBNP still cannot be fully determined because it depends on the examination method and the time of sampling. However, the concentration mentioned can be influenced by age and sex, which tends to increase in older age and female sex. Some clinical conditions such as

acute coronary syndrome, kidney failure and diabetes mellitus can also increase the concentration of cardiac natriuretic peptides including NT-proBNP.

This study concluded that there was no difference in the levels of NT-proBNP in both men and women. These results are consistent with Renardi (2009) showed no significant difference between the groups in the study of sex where NT-proBNP levels were higher in men than in women. Meanwhile, in this study, NT-proBNP levels were higher in women than in male. This contradiction can be understood because it uses a different sample size and uneven distribution in the two groups of hypertension.

The results of another study showed that women and men have NT-proBNP concentrations were relatively the same. NT-proBNP concentration varies, depending on gender and age. In males, the NT-proBNP concentration increases with age as well as women's NT-proBNP plasma concentration relatively increases with age (9). This study also showed that there is no significant difference between age and levels of NT-proBNP. In contrast to these results, Sarzani et al (13), which an average age of study subjects is 88.1 ± 5.1 years concluded that there were significant differences between the age factor with NT-proBNP in patients with Heart Failure. This contradiction can be understood as research conducted on

different age groups and different groups of cases.

The average levels of NT-proBNP is based on the longtime characteristics of patients suffering from hypertension that concluded that there were differences in levels of NT-proBNP which was significantly longer based on the characteristics of hypertension. The results of statistical tests performed concluded that there was a significant difference between the levels of NT-proBNP in patients with stage 1 and stage 2 hypertension ($p < 0.001$). There was no significant (relationship) between NT-proBNP and sex of the subject. These results are consistent with the research conducted by Rosello et al (2012) which showed no significant relationship based on the characteristics of sex in hypertensive patients. There was no significant between age and levels of NT-proBNP.

Furthermore, there was no correlation between NT-proBNP levels were significantly associated with hypertension old. The results of this study for statistically consistent with research done by Munir & Sargowo (14), showed no significant correlation between levels of NT-proBNP with duration of hypertension (old hypertension) in patients with hypertension.

Statistical test results concluded that there was no significant correlation between levels of NT-proBNP in Degrees 1 and Degrees 2 Hypertension patients. Levels of

NT-proBNP is based on the characteristics of the systolic blood pressure 140-159 mmHg; diastolic 90-99 mmHg (Hypertension Grade 1) and systolic blood pressure ≥ 160 mm Hg; ≥ 100 mmHg diastolic (Hypertension Grade 2), after statistical correlation test value of $p = 0.862$ ($p = < 0.05$). This is consistent with the observation Asterina et al (15) also concludes that there was a significant relationship between levels of NT-proBNP in patients with hypertensive heart disease. This research agreement can be concluded there was no significant correlation between levels of NT-proBNP with the degree of Hypertension.

The limitations of this study include inaccurate data and information regarding the length of time patients suffer from hypertension because some patients do not remember clearly, other patients are late to check up on health facilities so it is difficult to determine the duration of suffering from true hypertension.

CONCLUSIONS

It can be concluded that there was a significant difference in the levels of NT-proBNP with a degree of hypertension, found NT-proBNP levels were higher in patients with grade 2 hypertension compared to group 1 degree hypertension, although it was not

statistically significant correlation between levels of NT-proBNP with Hypertension degree. Further research are needed to determine the relationship of NT-proBNP levels with the degree of hypertension, which can confirm the diagnosis, especially in patients with hypertension and to consider the accuracy of the data length of a patient suffering/undiagnosed hypertension.

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CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Rilantono LI. Cardiovascular disease. Jakarta: Faculty of Medicine, University of Indonesia; 2016.
2. Cardiovascular Specialist Doctors Association of Indonesia (CSDAI). Hypertension Management Guidelines on Cardiovascular Disease. Issue I. Jakarta: Cardiovascular Specialist Doctors Association of Indonesia; 2015.
3. *Joint National Committee (JNC) 8. The Eighth Joint National Committee, Hypertension: The Silent Killer: Update JNC-8 Guideline*; 2015.
4. Muhadi. Evidence-based Guideline. Handling Hypertension Adult Patients. (Online). 2016;43(1).(www.cdkjournal.com/index.php/CDK/article/, Accessed January 14, 2018).
5. South Sulawesi Provincial Health Office. Health Profile of South Sulawesi Province in 2015. Makassar: South Sulawesi Provincial Health Office; 2015.
6. Makassar City Health Office. 2015. 2015 Makassar City Health Profile Makassar: Makassar City Health Office.
7. Hulaima, I.S. 2017. Factors Associated with Control of Blood Pressure in Hypertensive Patients at the Kedaton City Bandar Lampung Health Center. Bandar Lampung: Faculty of Medicine, University of Lampung.
8. Steffanus M, Wibawa IDN, Nadha IKP. Positive correlation between degree of liver cirrhosis and N terminal-Pro brain natriuretic peptide (NT-pro-BNP).
9. Khairunnisa. Correlation Levels of NT - proBNP with Left Ventricular Ejection Fraction Function in Children Heart Failure. Padang: Graduate Program in Biomedical Sciences - Medical Specialist Education Program UNAND - RS. M. DJAMIL; 2017.
10. Bower et al., .N-terminal pro-brain natriuretic peptide (NT-proBNP) and Risk of Hypertension in the Atherosclerosis Risk in Communities (ARIC) Study.American Journal of Hypertension. 2015;28(10):1262-1266.
11. Hikmah, N. Relationship between Smoking Time and Hypertension in Rannaloe Village, Buntaya District, Gowa Regency. Makassar: Faculty of Medicine and Health UIN Alauddin; 2017.
12. Azhar I. Hypertension Patient Characteristics picture in Sleman Gamping Puskesmas Yogyakarta. Yogyakarta: College of Health Sciences of the University General Achmad Yani Yogyakarta; 2017.
13. Sa'ani R. et al. NT-proBNP and Its Correlation Hospital Mortality of the Very Elderly without and Admission Diagnosis of Heart Failue.PLOS Journals.2016;11(4): e0153759.
14. Munir A,Surgowo N. N Terminal Pro Brain Natriuretic Peptide as Indicator of Left Ventricle Hypertrophy In Hypertensive Patients Compared with Left Ventricle Mass Index in Echocardiography. Jurnal Kardiologi Indonesia. 2010;31(2):87-98.
15. Asterina F, Nasution B, Akbar N. The Level of N Terminal-Pro Brain Natriuretic Peptide in Hypertensive Heart Disease Patients. Indonesian Journal of Clinical Pathology and Medical Laboratory. 2007;14(1):42-46.

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