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CORRELATION OF C3C COMPLEMENT, NT-PRO BNP AND LEFT VENTRICULAR EJECTION FRACTION IN HEART FAILURE

Julious[1], Jusak Nugraha[1], Aminuddin[2]

[1] Department of Clinical Pathology, Faculty of Medicine Airlangga University/Dr. Soetomo Hospital, Surabaya, Indonesia. E-mail: jusak.nugraha@yahoo.com
[2] Department of Cardiology, Faculty of Medicine Airlangga University/Dr. Soetomo Hospital, Surabaya, Indonesia

ABSTRACT

Heart failure is a health problem in Indonesia. The 2013 Basic Health Research Data showed that the estimated heart failure patients in Indonesia were 530,068 people. Echocardiography which has been a routine examination of heart failure patients is not widely available in all hospitals. Therefore, a more applicable and affordable alternative examination is needed. Previous studies have shown that an increase of C3c levels was associated with improved survival and better cardiac remodeling. On this basis, this research needs to be performed to determine the correlation between C3c complement levels, NT-proBNP and LVEF in heart failure patients. A cross-sectional study was conducted at the Dr. Soetomo Hospital starting from August to September 2018 with 30 samples in total. Samples were taken consecutively from patients with heart failure who were being treated at the integrated heart service center. Examination of C3c complement, NT-proBNP and echocardiography (LVEF data) was carried out in all patients. The result of this study showed no significant correlation between C3c complement and NT-proBNP (r = -0.253, p=0.177) no significant correlation between C3c complement and LVEF (r = -0.074, p=0.696), and a moderate correlation between NT-proBNP and LVEF (r = -0.444, p=0.014). The C3c complement could not be used as an alternative examination for NT-proBNP and LVEF. The limitations of the study were heterogeneous sample characteristics. A further study with more stringent criteria is needed to minimize the bias of examination results.

Key words: C3c complement, NT-proBNP, left ventricular ejection fraction, heart failure

INTRODUCTION

Heart failure is a global health problem. The American Heart Association (AHA) estimates the prevalence of heart failure in the Asian region is ranging from 1.26 to 6.7% with an estimated 9 million people in Southeast Asia suffering from heart failure.[1] The 2013 Basic Health Research Data showed there were 530,068 heart failure patients at age of 15 years in Indonesia. East Java is the province with the highest number of heart failure patients in Indonesia with 86,568 people.[2]

Heart failure consists of clinical symptoms, but only about 50% of patients are found with a decrease of left ventricle ejection fraction (LVEF) with clinical symptoms of heart failure. N-Terminal-pro B Type Natriuretic Peptide (NT-proBNP) is a marker to help diagnose heart failure.[3] NT-proBNP is mainly produced in the heart and circulates in the circulation in response to increased pressure on the heart wall.[4]

Chronic heart failure is still characterized by high rates of mortality and morbidity even though improvements in management of heart failure have been carried out. This shows that the pathogenic mechanism still occurs and has not been overcome by current treatment. Cytokines and other inflammatory mediators are assumed to play a role in this mechanism.[5] Several studies have shown the role of inflammation in the development of heart failure, but this mechanism is still unclear.[6]

Patients with heart failure often show chronic low activation of the immune system. This is indicated by increased levels of cytokines, chemokines, and inflammatory proteins. The immune system in people with activated heart failure is still not clearly understood for years. Research in recent years shows that the immune response may be due to activation of the innate immune system through endogenous signals. These endogenous signals are released by dead cells and several factors such as heat shock protein.[7]

The effect of immune system activation on the development of heart failure depends on the time. Activation of the innate immune system after the occurrence of acute cardiac injury (such as myocardial infarction) is aimed for healing, but the activation of the innate immune system in the long term causes remodeling of the left ventricle and

heart failure.[7]

The complement system has more than 20 different serum proteins produced by various cells. These protein interactions are a gradual activation cascade. All cascade activations eventually meet C3 complement. C3 thus does not only seem as a good indicator of overall complement activation but may also have pathophysiological relevance in the cardiovascular system. Therefore, it is suspected that C3 will be a good marker for immune system activation and may also be associated with adverse cardiac remodeling and death in patients with stable heart failure.[7]

Study on C3c complement levels in patients with left heart failure and correlation analysis of C3c, NT-proBNP, and LVEF complement levels have not been carried out at Dr. Soetomo Surabaya Hospital until now. Echocardiographic examination which has been a routine test for patients with heart failure is not necessarily available in all hospitals. This is due to the need for cardiologists and expensive devices, suggesting need of a more applicable and affordable alternative examination. On this basis, this study needs to be performed to determine the correlation between levels of C3c complement, NT-proBNP and LVEF in patients with heart failure.

METHODS

This study was an observational analytic study with a cross-sectional approach in patients with heart failure. This study has been approved by the Dr. Soetomo Hospital Ethics Committee, Surabaya with no 0493/KEPK/VIII/2018. All patients filled out informed consent to participate in this study.

The sample size of this study was calculated based on the formula of the sample size for the correlation test and the number of research subjects obtained was 30 people.[8] The research subjects were taken by consecutive sampling in outpatient and cardiac arrest from August until September 2018 at the Dr. Soetomo Hospital, Surabaya. The inclusion criteria of the study were as follows: age ≥ 17 years, subjects were willing to fill out and sign an approval statement form to participate in the study, heart failure patients who met the criteria for diagnosis of Framingham receiving standard treatment for heart failure. Exclusion criteria were as follows: patients with heart failure who are at risk of HIV infection, patients with a history of autoimmune disease, patients with heart failure who were suffering from other inflammation (infection, trauma), receiving immunosuppressant or corticosteroid therapy.

Venous blood samples were taken as much as 5 mL and divided into 2.5 mL of blood in tubes with K2EDTA anticoagulants for NT-proBNP examination and 2.5 mL of blood in tubes without anticoagulants for serum C3c complement measurement. Measurement of C3c complement and NT-proBNP levels was carried out on the same day as blood sampling. C3c complement assay was carried out using serum sample by radial immunodiffusion (NOR-Partigen, Siemens, Germany) method. The reference range of C3c levels ranges from 50 to 120 mg/dL. NT-proBNP assay was carried out using a whole blood sample supplemented with K2EDTA anticoagulants by quantitative immunochromatography method (RAMP, Canada).

For statistical analysis, the SPSS program version 17.0 was used. Data were presented in mean±standard deviation and n (%). For the correlation analysis, the Spearman test was used. The p-value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

The number of study samples was 30 patients with heart failure. Characteristics of the subjects were presented in Table 1.

Table 1. Characteristics of heart failure patients

Characteristics	Heart Failure Patients (n=30)
Age (years)	
Mean ± SD	56.3 ± 13.84
Range	26-80
Sex (%)	
Male	13 (43.3)
Female	17 (56.7)
NYHA class (%)	
I-II	13 (43.3)
III-IV	17 (56.7)
Factors that cause heart failure (%)	
Coronary heart disease	11 (36.7)
Hypertension	11 (36.7)
Valvular heart disease	9 (30)
Cardiomyopathy	3 (10)
Medication (%)	
Diuretic	21 (45.7)
ACE inh/ARB	10 (21.7)
β-blocker	10 (21.70
Amiodarone	2 (4.3)
Digitalis	3 (6.5)
Comorbidities (%)	
Arrhythmia	6 (20)
Diabetes mellitus	6 (20)
Kidney disease	5 (16.7)
Cancer	3 (10)

Table 2. Mean, standard deviation, median, minimum and maximum value of NT-proBNP levels, C3c complement, and LVEF

	n	Mean±SD	Median (min – max)
NT-proBNP (ng/L)	30	12,209.87 ± 37,751.934	1439.5 (0 – 201070)
C3c complement (mg/dL)	30	164.17 ± 42.244	157 (64 – 238)
LVEF (%)	30	48.0 ± 14.92	43.5 (26 – 71)

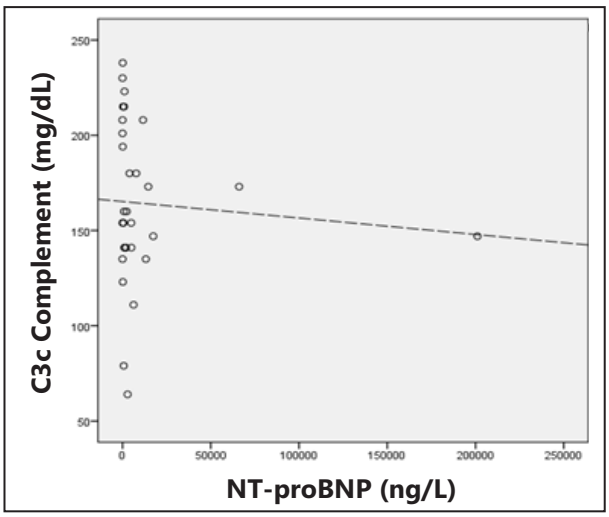

Figure 1. Correlation between C3c complement and NT-proBNP levels

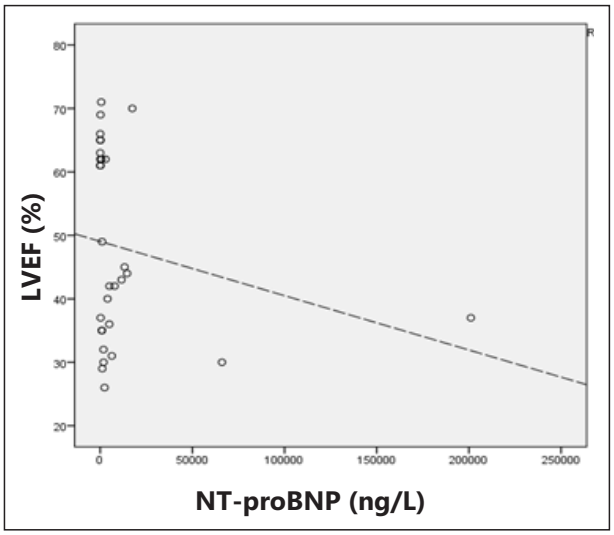

Figure 2. Correlation between LVEF and NT-proBNP levels

Mean, standard deviation, median, minimum and maximum value of NT-proBNP levels, C3c complement, and LVEF can be seen in Table 2.

The analysis showed that there was no statistically significant correlation between the C3c complement and NT-proBNP levels with r = -0.253 (p=0.177) (Figure 1), While the correlation obtained a significant negative correlation between LVEF and NT-proBNP levels r = - 0.444 (p = 0.014) (Figure 2), and no statistically significant correlation between C3c complement and LVEF with r = -0.074 (p = 0.696) (Figure 3).

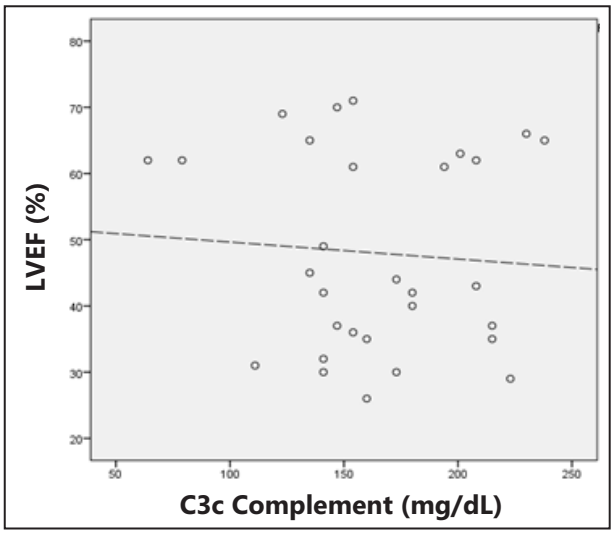

Figure 3. Correlation between LVEF and C3c complement levels

In this study, the mean age of patients was 56.3 years. Most patients were in the age group of 45-54 years with a total of 10 people (30%). This was in accordance with the 2013 Basic Health Research Data showing that heart failure patients were based on the highest age group of the 45-54 year age group.[2]

The mean of C3c complement levels in patients with heart failure was 164 mg/dL with a standard deviation of 42.24 mg/dL. The normal range of C3c complement in Clinical Pathology Laboratory Dr. Soetomo is 50 - 120 mg/dL. The mean C3c complement level of the results was higher than the normal range of C3c complement. Among the samples, twenty-seven (90%) samples showed an increase of C3c complement levels and only 3 (10%) samples showed normal C3c complement levels. The increased C3c complement levels in 90% of samples supported the theory of immune system activation in patients with heart failure, especially the innate immune system characterized by increased complement.[7]

From the NT-proBNP levels measurement, it was obtained the mean of 12,209.87 ng/L with a standard deviation of 37,751.94 ng/L. The highest level of NT-proBNP in this study was 201,070 ng/L. This result was obtained with a ten-fold dilution because the highest detectable level of the device was 35,000 ng/L. Patients with a diagnosis of stage five chronic kidney disease and stage four cervical cancer. A study by Bando *et al*. showed that plasma NT-proBNP was significantly higher in patients with cancer and there was a significant positive correlation between NT-proBNP levels and CRP in cancer patients. These findings suggested that NT-proBNP levels may increase due to cancer-related inflammation. NT-proBNP levels increase in advanced stages of cancer (stage IV), possibly associated with systemic inflammation.[9]

This study also found a very high NT-proBNP level of 66,040 ng/L in patients with acute heart failure and acute kidney injury. NT-proBNP is excreted through the kidneys inactive form, without prior metabolism process.[10] Decreased glomerular filtration rate in acute kidney injury disrupted NT-proBNP excretion resulting in NT-proBNP retention in the blood.[11]

In this study, there were 5 patients with NT-proBNP levels ≤ 5 ng/L. This remarkably low NT-proBNP level was found in heart failure patients with co-morbidities severe preeclampsia, hypertension heart failure, anterior and lateral chronic myocardial infarction. Low NT-proBNP levels can be found in patients with ischemia.[12] Zheng *et al*. also found low NT-proBNP levels in patients with acute heart failure at the onset of symptoms and NT-proBNP levels increased according to symptoms and worsening of the symptoms.

There was no significant correlation between C3c complement levels and LVEF and the correlation of C3c complement levels with NT-proBNP in this study were not statistically significant. This was presumably caused by the influence of many factors to the C3c complement and unspecific parameter of heart function leading to bias. Five heart failure patients with a concomitant diagnosis of diabetes mellitus were found to have elevated levels of C3c complement. In patients with diabetes mellitus inflammation was frequently found and resulted in activation of the complement system.[13]

NT-proBNP examination has been widely used to diagnose acute heart failure. A study by Belagavi *et al.* showed that there was a moderate negative correlation between NT-proBNP levels and LVEF (r=-0.444).[14]

CONCLUSION AND SUGGESTION

The results of this study indicated an increase of C3c complement levels in most heart failure patients, but there was no statistically significant correlation between the C3c complement levels and LVEF and between the C3c complement and NT-proBNP levels. The C3c complement could not be used as an alternative examination for NT-proBNP and LVEF. However, in this study, there were several limitations such as heterogeneous subject characteristics that caused bias in the results, and no control or measurement of all factors that potentially affected the C3c complement and NT-proBNP levels. Further study with more samples and focused on factors that can influence C3c complement and NT-proBNP was needed. Kidney disorder and malignancy should be included in the exclusion criteria.

CONFLICT OF INTERESTS

The authors declared no conflict of interest in this study.

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