Correlation Between Neutrophil to Lymphocyte Ratio (NLR) and Patient with Heart Failure: Haematology Variables in Patient with Heart Failure

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Abstracts

Heart failure is a condition of the heart that cannot pump blood adequately resulting in systemic tissue hypoperfusion. This situation will cause systemic inflammatory reactions. Neutrophil to Lymphocyte Ratio (NLR) is an inexpensive and easy parameter that can see inflammatory reactions. This research uses descriptive and analytical studies with cross-sectional studies. The number of samples was 67 heart failure patients who were treated at Atma Jaya Hospital. The statistical test used is unpaired T-test to see if there was a correlation between the NLR value in heart failure, after that NLR cut-off point will be analyzed using a receiver operating curve (ROC). Pearson correlation test was conducted to see the correlation of NLR with laboratory results, including haemoglobin, hematocrit, leukocytes, and platelet. The results showed a significant difference of NLR between controls and heart failure patients ($p = 1.0402^{-10}$). The cut-off point is 2.16 with an area under the curve of 86.4%, sensitivity 79.1%, and specificity 91%. Analysis of NLR data on heart failure with hemoglobin ($p = 0.108$), hematocrit ($p = 0.091$), and platelets ($p = 0.832$) showed no significant correlation, whereas showed a significant correlation with leukocytes ($p = 0.017$). This study shows a significant difference of NLR between control and heart failure therefore it can be used to predict the prognosis for heart failure. This study also found no significant correlation between NLR with the amount of haemoglobin, hematocrit, and platelets, while there was a correlation with leukocytes.

Keywords: Haemoglobin, Hematocrit, Leukocyte, NLR, Platelet

1. Introduction

Heart Failure is a condition where the heart is malfunctioning, that leads to the disturbance of blood circulation. Based on the American Heart Association in 2015, there are 26 million people that are diagnosed with heart failure, the CDC states that the 5 years survival rate is 50%.[1-3] Heart failure prevalance in Asia is up to 6,7%. In 2013, 0,3% (530,068 people) in Indonesia were diagnosed with heart failure, where most cases were seen in the age group between ages of 65-74 years old.[4,5] In order to decrease morbidity, early diagnosis is needed. There are many diagnostic examinations that can be used, such as N-terminal proB-type natriuretic peptide (NT-proBNP) examination, electrocardiography, and echocardiography. However, routine examination of NT-proBNP and echocardiography is expensive. Neutrophil to lymphocyte ratio (NLR) could be an alternative due to its cheaper and simple nature, but NLR cannot replace NT-proBNP and echocardiography as the gold standard for heart failure. NLR may be of use for evaluating prognosis. Therefore, this study's purpose is to discover the correlation of NLR and heart failure.[6,7]

In heart failure patients, there are rising levels of pro-inflammatory cytokines which are associated with NLR. In heart failure, there would be a delayed neutrophil apoptosis, causing increased neutrophil whilst the number of lymphocytes will go down, this is what is then calculated as a rise in NLR. A 2018 study in America shows that the average NLR in patients suffering heart failure is 2,15, other studies show that 1,95 is the average NLR in a healthy adult. It is also revealed that in chronic heart failure there is an increase in NLR value and mortality rates, it can be concluded that there is a positive correlation between NLR and chronic heart failure. Increased NLR value also indicates increased inflammation processes and worse heart conditions. Several other studies show that here are a little differences in prognosis of high NLR value in heart failure patient compared with high NT-ProBNP value, with a hazard ratio of 1,407 for NLR and 1,461 for NT-ProBNP.[8-13]

The hope of this study is to find correlation between NLR and heart failure, so it can be of use to prevent deteriorating conditions or as an option of examination for patient prognosis, therefore supporting early diagnosis and early treatment.

2. Method

This study used a descriptive analytic research design with a cross sectional study. This study was conducted at Atma Jaya Hospital from January 2019 to August 2019 with a sample of 67 patients with heart failure. The inclusion criteria were adult patients (19-65 years) with chronic heart failure, following the American Heart Association definition, who were treated as an outpatient at a cardiology clinic. Exclusion criteria in this study were heart failure patients with immune system disorders, hematological disorders, patients with infections, malignancy, and patients taking anti-inflammatory drugs. This study correlates the NLR value in heart failure patients with the control NLR value. The control NLR value was obtained from the research of Ariesta et al.[22] This study will look for the cut-off point of the NLR in heart failure patients using the Receiver Operating Curve (ROC). This study also looks for correlations between NLR values and hematological variables such as hemoglobin, hematocrit, platelets, and leukocytes. The correlation test used is the Pearson correlation test with a significance limit of 95%.

3. Results

Characteristics of patients obtained based on data from 67 samples consisted of patients with heart failure, both chronic heart failure with NYHA I – NYHA IV and acute decompensated heart failure (ADHF). The percentage of patients with chronic heart failure is as much as 91,04%, while acute heart failure is 8,96%. In this study 55,22% of the samples were male and 44,78% of them were female. The hematological variables studied had an average of 12,7 g/dL for hemoglobin, 37,32% for hematocrit, 9,66 thousand/uL for leukocytes, 65,38% for neutrophils, 23,14% for lymphocytes, and 271.460 /uL for platelets (presented in Table 1)

Table 1. Average value (Mean) of hematological variables in this study

Variables	Heart Failure
Hemoglobin (g/dL)	12,7
Hematocrit (%)	37,32
Leukosit (thousand/μL)	9,66
Trombosit (/μL)	271.460
Neutrophil (%)	65,38
Lymphocyte (%)	23,14

The normality test of the data used is the Kolmogorov-Smirnov normality test. In the test, normal data distribution was obtained on the NLR value in controls ($\alpha = 0,05$ and $p = 0,200$; $p > \alpha$) and the NLR value in adult heart failure in sig. of 0.065 ($\alpha = 0,05$ and $p = 0,065$; $p > \alpha$). Normal value distribution was also found in hemoglobin, leukocytes, and platelets, while hematocrit had an abnormal distribution of data. This study also obtained an average NLR value of 1,68 for controls and 3,60 for adult heart failure. In addition, the average NLR value for each class of heart failure according to the NYHA are: 2,83 for CHF NYHA II, 3,59 for CHF

NYHA III, 2,97 for CHF NYHA IV (presented in Table 2).

Table 2. Average (Mean) NLR scores for each heart failure according to NYHA criteria

CHF NYHA I-IV	Mean
I	-
Ii	2,83
Iii	3,59
IV	2,97

The correlation between NLR values and hemoglobin, hematocrit, and platelets resulted in an insignificant correlation, while the correlation between NLR values and leukocytes resulted in a significant correlation ($\alpha = 0,05$ and $p = 0,200$; $p > \alpha$). The non-independence T test in this study showed the difference between the NLR of Heart Failure and the NLR of Normal People ($\alpha = 0.05$ and $p = 1.0402^{-10}$; $p < \alpha$). The cut-off point of NLR in patients with heart failure that was obtained from this study is 2,16 with a sensitivity of 79.1% and a specificity of 91% with an area under curve (AUC) of 86.4%. (Presented in Figure.1)
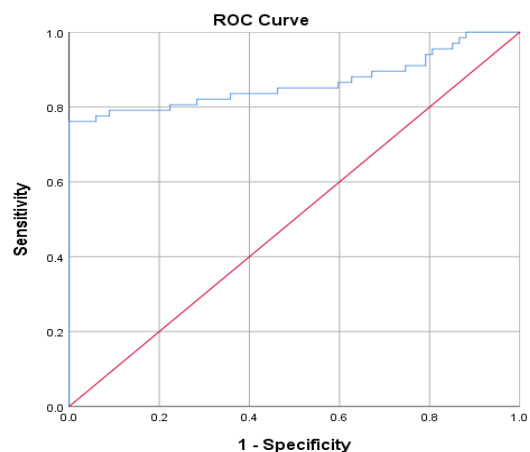

Figure 1. Reception Operation Curve used to see the intersection with sensitivity and specificity.

4. Discussion

Heart failure is a clinical syndrome caused by impaired heart function to fulfil the needs of circulation to various organs of the body.[1] Heart failure is closely related to inflammation, both as a cause and as a result, this cause a chronic cycle between heart failure and inflammation.[14] Chemical compounds from damaged cells or tissues such as prostaglandins (PGs), leukotrienes (LTs), histamine, bradykinin, and other pro-inflammatory compounds are released in inflammation, it will result in leukocyte infiltration which increases the number of neutrophils and lymphocytes. Neutrophils and macrophages themselves are the first leukocytes that appear in the inflammatory response, then it will release proinflammatory cytokines and chemokines, which will induce T cells which are one form of lymphocytes. [15-17] Lymphocytes themselves will decrease in the acute phase due to the release of cortisol from the adrenal cortex. Conversely, in the chronic inflammatory phase, cortisol dysfunction will cause the increase of the lymphocytes.[20] In heart failure, inflammation occurs systemically so that it will affect the number of leukocytes in the blood. Heart failure itself will cause inflammation in several organs and tissues such as the heart, striated muscles, and gastrointestinal tract.[14] Neutrophil to Lymphocyte Ratio (NLR) is the ratio of the number of neutrophils and lymphocytes. Therefore, calculating the NLR value will be highly correlated with the state of heart failure, especially the severity of the heart condition in heart failure itself.

This study associated NLR values with patients with heart failure. The cut-off point of NLR for heart failure in this study was 2.16. This cut-off value has an area under curve (AUC) of 86.4%, a sensitivity of 79.1%, and a specificity of 91%. AUC of 86.4% has shown good results. The NLR value in this study was influenced by several factors, including age and current medical history (diabetes, hypertension, and coronary heart disease). In Diabetes Mellitus (DM), blood vessel damage is caused by hyperglycemic conditions which will cause inflammation that affect the NLR value in heart failure.[20] Vinita et al. In this study, the cut-off point value for the control NLR value for type 2 DM group was 1.74, and this value exceeded the average control NLR value in Ariesta et al. from 1.64.[21-22] In hypertension there is also damage to the endothelial cells of the blood vessels so that it will cause inflammation.[24] Atherosclerosis occurs In coronary heart disease which results in heart muscle cell infarction, this condition will result in the death of heart muscle cells and cause an inflammatory reaction.[24] In the study of Cahyadi et al. , The limit point for the control NLR value with the NLR of myocardial infarction was 2,5.[25]

The onset of heart failure also affects the NLR value. Acute heart failure will increase NLR values more than chronic heart failure, this happens because in the acute phase, the stress response during inflammation will stimulate the amygdala to activate the HPA axis which signals the hypothalamus to release corticotropin-releasing hormone (CRH). CRH will stimulate the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, then it stimulates the release of cortisol in the adrenal cortex. This cortisol will inhibit lymphocytes so there is a decrease in the number of lymphocytes in the acute phase. In the chronic phase, there is excessive cortisol binds to the glucocorticoid receptor, which will result in glucocorticoid receptor resistance, resulting in a regulation that results in a decrease in cortisol so that the number of lymphocytes will increase by.[19] Both of these show differences in NLR in the acute phase with the chronic phase, but in

this study the comparison the number of patients with acute and chronic heart failure is still not balanced so that researchers cannot continue to look for differences in the cut off point value of the NLR between acute and chronic heart failure. In the research of Caterina et al.,[26] NLR values in heart failure are highly correlated with the severity of heart failure and associated diseases. For example, an NLR > 3 cut-off point was associated with heart failure that correlated with kidney disease with a sensitivity of 68% and a specificity of 75%. The study also stated that the NLR cut-off point > 4.78 correlated with acute heart failure with a sensitivity of 66.7% and specificity of 60.5% while the NLR cut-off point for chronic heart failure had a lower value, > 2 ,74. Gender factor was not taken into account in this study because there was no significant difference between male and female NLR scores. In the research of Ariesta et al.,[21] the mean value of NLR for men and women is 1.64, so there is no difference between men and women.

In this study also obtained the mean NLR value based on the classification of CHF according to the New York Heart Association (NYHA), an average of 2,83 for NYHA II, an average of 3,59 for NYHA III, and an average of 2,98 for NYHA IV. Delcea et al. it was found that the higher the NLR value, the greater the risk of a poor prognosis, at an NLR value >2,26 there can be a decrease in heart function and an NLR value > 4,4 will increase the risk of death in heart failure patients.[26] Values the average NLR will increase following the NYHA classification, except in this study the average NLR value of CHF NYHA IV is lower than CHF NYHA III, this is because the sample obtained for CHF NYHA IV is small so it cannot be used to accurately present NLR values in CHF NYHA IV patients.

This study shows that there is no relationship between NLR with hemoglobin and hematocrit values. In heart failure, the etiology of anemia can be influenced by several things. When heart failure occurs, cardiac output will decrease, resulting in renal hypoperfusion, then it will activate the renin-angiotensin-aldosterone system (RAAS) so that fluid retention will occur which results in hemodilution resulting in anemia.[27] Other conditions also occur in the condition of the heart muscle which is under stress so that it releases pro-inflammatory compounds. The release of these proinflammatory compounds will result in a decrease in erythropoietin secretion and a decrease in bone marrow response so that there will be a decrease in erythrocyte production which will cause anemia. Research Wisniacki et al,[28] showed the prevalence of heart failure with anemia by NYHA group as follows: 0% in class I, 36.4% in class II, 52% in class III, and 65.9% in class IV, while different results were obtained in the Tanner study. et al.[42] prevalence was found: 7% in class I, 9% in class II, 17% in class III, and 26% in class IV. According to the American Heart Association, a linear correlation between a decrease in hemoglobin and heart failure can only be achieved when the hemoglobin value is <13 g/Dl.[29] The NLR value is smaller than the cut-off point that has been studied previously, which is 2,16, this indicates that the decrease in hemoglobin and hematocrit levels in heart failure is not significant.

This study also show there was no relationship between NLR and platelet values in heart failure. In heart failure, the platelet value will change due to several factors. Ventricular dysfunction that occurs in heart failure will increase the amount of fibrin D-dimer and fibrinogen. Angiotensin II, which is part of the RAAS that occurs in heart failure, also increases plasma thromboglobulin and platelet fibrinogen binding. In this study, the absence of an

association between NLR and platelet count was influenced by several things, such as drug interventions such as diuretics (hydrochlorothiazide, furosemide, spironolactone, and indapamide) that could suppress the production of thromboxane A2. Beta receptor blocking drugs such as propranolol can reduce platelet aggregation. ACE inhibitors can also inhibit platelet aggregation.[30]

There is a relationship between the NLR value and the number of leukocytes in this study. An increase in the number of leukocytes is a sign of acute and chronic systemic inflammation. In heart failure, systemic inflammation occurs which can cause inflammation in several organs such as the gastrointestinal tract, striated muscles, and the heart itself and a decrease in cardiac output results in systemic inflammation in these organs resulting in a stress response that will result in the release of proinflammatory. cytokines. This proinflammatory cytokine will stimulate leukocyte invasion to the site of inflammation.[18] An increase in the number of leukocytes in heart failure was also supported in the study of Gunnar et al. In this research, the relationship between the concentration of leukocytes and the incidence of heart failure in the hospital was 2,53.[31]

5. Conclusion

Neutrophil to Lymphocyte Ratio (NLR) values can describe the inflammation that occurs in patients with heart failure. In heart failure, systemic inflammation occurs, which increases the number of leukocytes and increases the NLR value, especially in acute heart failure. The NLR cut off point obtained in heart failure is 2.16 and based on the Area Under Curve (AUC) obtained from the Receiving Operating Curve (ROC), this cut off point has

good results to help estimate the prognosis for heart failure.

NLR value of heart failure also has a relationship with several variables, including haemoglobin, hematocrit, and platelets, it's just that the relationship of NLR with these variables does not correlate because of several things one of them is drug intervention.

Furthermore, the data obtained from this study can be developed for further research, especially in determining the prognosis of heart failure.

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