

Neutrophil-Lymphocyte Ratio as Predictor of Prognosis In Patient with Heart Failure with Reduced Ejection Fraction that Treated With Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Neprilysin Inhibitor: A Prospective Cohort Study in Aceh, Indonesia

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KEYWORDS

NLR, Prognosis, ACE-I, ARNI.

ABSTRACT

Introduction: Heart failure (HF) and inflammation are related. Angiotensin Converting Enzyme Inhibitors (ACE-I) and Angiotensin Receptor Neprilysin Inhibitors (ARNI) can reduce inflammation by lowering neutrophil counts. The neutrophil-lymphocyte ratio (NLR) is a simple marker of inflammation. There is a lack of studies showing that NLR can predict prognosis in patients with HFrEF, and further investigation is needed. **Objectives:** Investigating whether NLR could be a prognostic indicator for mortality and rehospitalization in patients with heart failure and reduced ejection fraction receiving treatment with ACE-I or ARNI.

Methods: A prospective observational cohort study with double-blind methods was conducted at Zainal Abidin General Hospital, Banda Aceh, Indonesia. Two groups, ACE-I and ARNI, each comprised 40 participants. Initially, blood sampling was performed to determine NLR. Participants were observed weekly for three months for prognosis outcomes (death and rehospitalization). After three months, the remaining participants were invited for re-evaluation of the NLR.

Results: This study found that pre-treatment NLR had a hazard ratio (HR) of 1.454 (95% CI: 1.266-1.670, $p < 0.001$). The risk ratio of abnormal pre-treatment NLR for rehospitalization was 6.56 in the ACE-I group and 8.33 in the ARNI group. Nevertheless, both ACE-I ($p = 0.014$) and ARNI ($p = 0.032$) decreased NLR levels.

Conclusions: High NLR could be as a predictor of prognosis in patients with heart failure with a decrease in left ventricular ejection fraction that treated with ACE-I or ARNI, also ACE-I and ARNI could reduce NLR levels.

1. Introduction

Heart failure (HF) is a multifactorial and life-threatening syndrome characterized by high morbidity and mortality rates, poor functional capacity and quality of life, and substantial treatment costs.[1] Based on one study, mortality remains high, particularly among elderly males and those with heart failure with reduced ejection fraction (HFrEF).[2] Data from the Indonesian Ministry of Health show that the prevalence of heart failure in Indonesia is 0.13%, while in Aceh province it is 0.1%.[3]

Heart failure and systemic inflammation are two processes that are interrelated, constantly evolving, occurring simultaneously, and exacerbating each other.[4,5] The initial hypothesis posited that endogenous cytokines trigger the development of heart failure. However, heart failure also induces inflammation, both in the myocardium itself and in other tissues and organs.[6,7] The three most important mechanisms associated with heart failure and inflammation involve the adrenergic nervous system, the Renin-Angiotensin-Aldosterone System (RAAS), and the increased production of antidiuretic hormones. Thus, heart failure could be worsened by the inflammatory response.[8]

Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor neprilysin inhibitors (ARNI) have markedly improved the clinical outcomes of patients with heart failure, including increased life expectancy and improved quality of life.[9] Based on this theory, ACE-I and ARNI further lower inflammation because they work directly to reduce neutrophils through the blockade of the renin-angiotensin-aldosterone system, thereby reducing the vasoconstrictive effect and sympathetic tone. Nevertheless, they could also reduce the

inflammatory response.[9]

Suppression of tumorigenicity 2 (ST2) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are popular modalities that can predict the prognosis of patients with heart failure but are known to be very expensive.[10–12] Besides being useful for determining prognosis, the measurement of ST2 and NT-proBNP in patients with chronic heart failure is also valuable in assessing the success of certain therapies.[13–15] Despite this, there is another simple modality to predict outcomes: the neutrophil-lymphocyte ratio (NLR).[16] It is a simple marker of inflammation obtained from a routine complete blood count and is more affordable.[17] A study has shown that an increased NLR is associated with worse outcomes in patients with heart failure.[18] The data is still lack for the study to reveal NLR could be a predictor of prognosis patient with HFrEF. The study related to how fast ARNI has a significant effect is still controversial. The ARTIM HF TRIAL study has proven that ARNI could reduce mortality within six months. [18] Thus, we assessed the effect of ARNI in a period of less than 3 months.

2. Objectives

The objective of this study was to investigate whether NLR could serve as a prognostic indicator for mortality and rehospitalization in patients with heart failure and reduced ejection fraction receiving treatment with ACE-I or ARNI. Furthermore, the study aimed to examine the effects of ACE-I or ARNI on lowering NLR levels in Aceh, Indonesia.

3. Methods

Study Design and Sampling

This study was a prospective observational cohort study undertaken at Zainal Abidin General Hospital in Banda Aceh, Indonesia. Eligible patients were required to be aged 18-75 years, have reduced LVEF (<50%), and be willing to participate in this research through informed consent. The exclusion criteria included patients with congenital heart disease, severe valvular heart disease, chronic obstructive pulmonary disease (COPD), hypotension, severe infections, immunological disorders, cancer, active smokers, those consuming antidepressant drugs, worsening heart failure, and chronic kidney disease (CKD).

Sampling was carried out using non-probability sampling techniques, specifically quota sampling with a double-blind method. The minimum sample size based on the Lamshow Formula for cohort studies was 25 samples. There were two groups: the ACE-I group and the ARNI group, each consisting of 40 samples. Initially, samples underwent an ejection fraction examination by echocardiography, along with blood sampling to determine NLR before the administration of ACE-I or ARNI.

During the three-month period, samples were monitored for rehospitalization and death through phone interviews and routine outpatient clinic visits every week. After three months, blood samples were taken again to evaluate NLR. A normal NLR was defined as below three, while a high NLR was defined as above three.

Ethic Statement

The study adhered to the principles outlined in the Declaration of Helsinki and received approval from the ethics committee of Zainal Abidin General Hospital (Approval No. 124/ETIK-RSUDZA/2023). Prior to participation in the study, all patients provided written informed consent, demonstrating their willingness to be included in one of the study groups. This information underscores the ethical considerations and regulatory approvals that were obtained before conducting the study, ensuring that patient rights and well-being were protected according to established guidelines. The requirement for informed consent signifies that participants understood the study's purpose, procedures, and potential risks, and voluntarily agreed to participate.

Procedures

All participants who met the inclusion and exclusion criteria were divided into two groups: the ACE inhibitor group and the ARNI group. Prior to this, blood sampling was performed to determine NLR. Blood sampling was conducted through aseptic venipuncture in the cubital fossa, collecting 10 cc of blood. During the three-month period, all samples were followed up periodically by the enumerator to monitor rehospitalization and mortality. Echocardiography was used to assess ejection fraction before treatment. After three months of follow-up, the remaining participants were invited for re-evaluation of the blood sampling procedure.

Statistical Analysis

Baseline characteristics were presented as counts (percentages) of patients for categorical variables and as means or medians for continuous variables. Bivariate analysis was conducted to compare ACE-I and ARNI in terms of their effect on reducing NLR levels, using the Mann-Whitney or Wilcoxon test due to the abnormal distribution of the data as indicated by normality tests. Statistical analyses were conducted using IBM SPSS Statistics version 25 (IBM Corp, Armonk, NY, USA). P-values less than 0.05 were considered statistically significant. This study also utilized STATA version 18 (StataCorp LLC, Texas, USA) for calculating the hazard ratio.

4. Results

Baseline Characteristic

The pre-NLR was distributed abnormally between groups; however, the other baseline characteristics were normally distributed. Except for the age variable, there were no differences between both groups for the other variables ($p > 0.05$), which means that the variables were homogeneous in both groups. The result of baseline characteristics are shown in table 1.

Table 1. Baseline Characteristic

	ACE-I	ARNI	p-value
Age, mean (SD), years old	56 (11)	61,5 (9)	0,011
Sex			0,963
Women, n(%)	9 (22,5%)	8 (20%)	
Men, n(%)	31 (77,5%)	32 (80%)	
Body Mass Index, [mean (SD)], kg/m ²	25,39(2,33)	24,97(2,76)	0,48
Systolic Blood Pressure, [mean (SD)], mmHg	122,25 (23,77)	126,32 (23,71)	0,47
Diastolic Blood Pressure, [mean (SD)], mmHg	70,83 (10,96)	69,35 (10,23)	0,55
Baseline EF, [mean (SD)], (%)	40,6 (6,14)	39,65 (6,75)	0,692
NLR pre [median (min-max)]	2,95 (1,02-10,25)	2,70 (1,27-14,60)	0,494
T2DM, n(%)	9 (22)	10 (40)	0,796

SD: standard deviation

In terms of sex, the number of male samples was more dominant than female samples in both groups, with 31 males (77.5%) in the ACE-I group and 32 males (80%) in the ARNI group, resulting in a p-value of 0.963. Based on body mass index (BMI), the average BMI of samples in the ACE-I group was 25.39 kg/m², while the average BMI in the ARNI group was 24.97 kg/m² (p-value = 0.48). For systolic blood pressure (SBP), the average SBP in the ACE-I group was 122.25 mmHg, while the average SBP in the ARNI group was 126.32 mmHg (p-value = 0.47). Meanwhile, for diastolic blood pressure (DBP), the average DBP in the ACE-I group was 70.83 mmHg, and the average DBP in the ARNI group was 69.35 mmHg (p-value = 0.55).

Cohort Outcomes

The median post-NLR in the ACE-I treatment group was 1.95, while in the ARNI group it was 1.90. It can be concluded that the median post-NLR decreased in both groups compared to the median pre-NLR in each group. The p-value calculated for the post-NLR variable was $p = 0.964$. Regarding the incidence of rehospitalization, the number of rehospitalized samples in the ACE-I group was more dominant, with 7 samples (17.5%) in the ACE-I group and 6 samples (15%) in the ARNI group ($p = 0.955$). In terms of mortality, the percentage of deaths in the ACE-I group (11.1%) was higher than in the ARNI group (8.3%), with a p-value of 0.696. For death, rehospitalization, and post-NLR, the p-values were greater than 0.05, indicating that there were no significant differences in the incidence of death between the ACE-I and ARNI groups. Table 2 shows the resume of these findings.

Table 2. Study Outcomes

	ACE-I	ARNI	p-value
Death, n(%)	4 (11,1)	3 (8,3)	0,696
Rehospitalization, n(%)	7 (17,5)	6 (15)	0,955
NLR post, [median (min-max)]	1,95 (0,80-4,43)	1,90 (1,04-5,66)	0,964

Survival estimate in ACE-i and ARNI Group

Each patient was followed up for 12 weeks to determine the survival rate. There were 37 samples that survived in the ACE-I group and 36 samples in the ARNI group. Thus, the Kaplan-Meier curve illustrated the survival rates in both the ACE-I and ARNI groups.

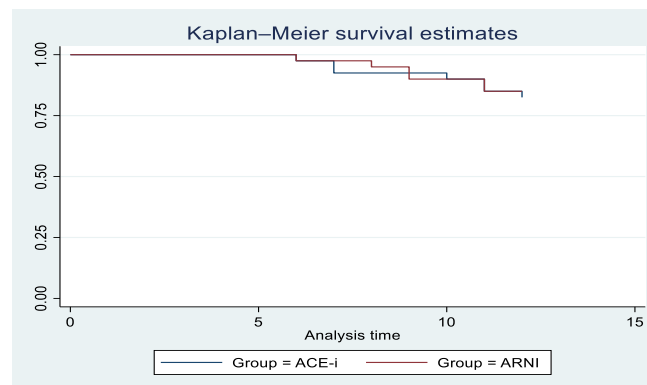


Figure 1. Estimation of Survival Rate in ACE-I and ARNI Groups

NLR as Mortality Predictor in ACE-i and ARNI Group

Hazard ratio (HR) for pre-NLR is 1.454, with a 95% confidence interval (CI) of 1.266-1.670, and a p-value < 0.001. It can be concluded that a high NLR predicts a 1.45 times increased risk of death in patients with heart failure and a reduced left ventricular ejection fraction.

Table 3. NLR as Mortality Predictor

Serum	Hazard Ratio	p-value	CI 95%
NLR	1.454	0.000	1.266-1.670

The Role of NLR in Predicting Rehospitalization Incidence in ACE-I and ARNI Groups

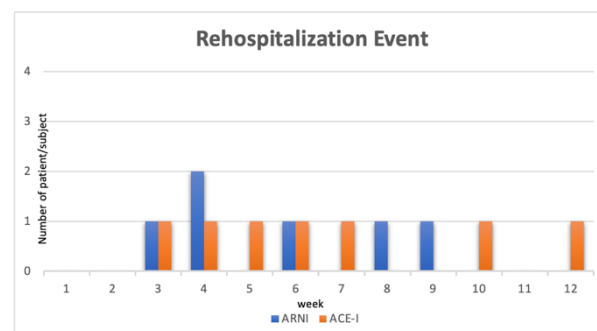


Figure 2. Rehospitalization event

Figure 2 showed the incidence of rehospitalization per week of monitoring. Rehospitalization in both ACE-I and ARNI groups began to occur in the third week. In the fourth week, the rate of ARNI rehospitalization was higher than that of ACE-I. In ARNI's group, there were no rehospitalization incident after 10 weeks. Nevertheless, the incident of rehospitalization was still on going after 10 weeks in ACE-I's group.

Table 4. The Role of NLR Pre as a Predictor of Rehospitalization in ACE-I vs ARNI

Intervention	Serum		Rehospitalization n, %	Risk Ratio
ACE-I	NLR Pre	Abnormal	6 (31,5%)	6,56
		Normal	1 (4,8%)	
ARNI	NLR Pre	Abnormal	5 (33,3%)	8,333
		Normal	1 (4%)	

We also reviewed the risk of rehospitalization in each group and its relation with pre-treatment NLR value. On ACE-I group, people who had abnormal NLR pre had a 6.56-fold risk of rehospitalization than people who had normal pre-treatment NLR value, whereas in the ARNI group, people who had abnormal value NLR pre had an

8.33 fold risk of rehospitalization than people who had normal pre-treatment NLR value. Table 4 shows the resume of these findings.

Comparison of NLR Pre vs Post in ACE-I and ARNI Group

From the monitoring results until the end of the period, the NLR value decreased in both groups; however, the decrease was more pronounced in the ACE-I group. The NLR level decrease from both group is shown in table 4.

Table 5 shows the results of the differences between pre-NLR and post-NLR in the ACE-I and ARNI groups, as analyzed using the Wilcoxon test. It can be concluded that there are significant differences in pre-NLR versus post-NLR in both the ACE-I and ARNI administration groups. This conclusion is supported by the p-value of pre-NLR versus post-NLR in the ACE-I group, which is $p = 0.014$, and the p-value for the ARNI group, which is $p = 0.032$. The results indicate that both ACE-I and ARNI treatments led to a decrease in NLR, demonstrating their effectiveness in reducing NLR levels.

Tabel 5. Comparison of NLR Pre vs Post in ACE-I and ARNI Group

Serum	Intervention	Mean (SD) Delta	P Value
Delta NLR Pre vs Post	ACE-I	-0.8667 (1.87)	0.014
Delta NLR Pre vs Post	ARNI	-0.6250 (1.73)	0.032

5. Discussion

Based on this research, NLR can predict mortality in heart failure patients with decreased left ventricular ejection fraction treated with ACE-I and ARNI. A high NLR is a sign of increased inflammation. The higher NLR in patients with heart failure is associated with increased all-cause mortality due to various potential mechanisms.[19] Firstly, NLR serves as an indicator of inflammation. [19] Secondly, it reflects sympathetic nervous system activity. NLR comprises neutrophils, which signify ongoing non-specific inflammation and a rapid response, and lymphocytes, which indicate regulatory pathways associated with a more adaptive immune response. [19] This combination underscores physiological stress in the body. [19] In contrast, lymphocytes are involved in immune system regulation. [19]

Elevated NLR in heart failure patients is a concerning sign, potentially reflecting heightened inflammation and sympathetic nervous system activity. The imbalance between neutrophils and lymphocytes may signify a disrupted immune response and increased physiological strain, contributing to poor outcomes in these patients. [19] Inflammation can lead to lymphocytopenia, which reduces the regulation of lymphocyte apoptosis, lymphocyte differentiation, proliferation, and neurohumoral activation.[20]

Lymphopenia, which refers to a lower-than-normal level of lymphocytes in the blood, has been identified as an independent prognostic factor associated with reduced survival rates in patients with heart failure.[21] This condition indicates a state in which fewer lymphocytes are available to perform their crucial roles in the immune system. [21] In patients with heart failure, lymphopenia may reflect underlying immune dysfunction or increased physiological stress, both of which can contribute to poorer outcomes and elevated mortality rates. [21] Therefore, monitoring lymphocyte levels could be important for assessing the severity and prognosis of heart failure patients.

Several other studies have shown that NLR can predict mortality. One study conducted in 2020 used NLR as a predictor of mortality over a 3-year period.[16] In another study conducted in 2023, it was found that NLR could predict mortality in heart failure patients treated with ACE-I, revealing a hazard ratio (HR) of 1.12; 95% confidence interval (CI) of 1.02–1.23; $p = 0.013$. [20] Additionally, the most recent research demonstrated that NLR could serve as a predictor of death in patients with acute heart failure who were hospitalized and treated with ACE-I, with an odds ratio of 1.156; 95% CI of 1.001–1.334; $p = 0.048$. [18]

Our study showed that post-treatment NLR decreased in the ACE-I group. One study revealed that NLR decreases when ACE-I is administered.[21] This reduction occurs because ACE-I blocks the angiotensin-converting enzyme, which converts angiotensin I to angiotensin II, thereby inhibiting the activation of the renin-angiotensin-aldosterone system. [21] A decrease in angiotensin II production plays a role in reducing inflammation.[16] In our study, we used NLR as a mortality predictor in heart failure patients treated with ARNI. There have been no previous studies reporting NLR as a mortality predictor in heart failure patients undergoing

ARNI treatment. This is a novel finding, as it indicates that NLR could be a mortality predictor in patients with heart failure with reduced ejection fraction (HFrEF) treated with ARNI. Our study also showed that post-treatment NLR decreased in the ARNI group. This research is the first to demonstrate that ARNI could reduce NLR. This finding is related to the theory that neprilysin increases the activation of neutrophils. Since ARNI acts as a neprilysin inhibitor, the decrease in neprilysin levels may lead to lower neutrophil counts.[21]

Currently, there are not many studies that use NLR as a predictor of rehospitalization in patients treated with ACE-I and ARNI. While the relationship between rehospitalization and increased NLR is closely associated with the degree of inflammation, NLR itself is a marker of inflammation; the higher the inflammation, the higher the risk of rehospitalization events.[16] A study conducted in 2021 by Angkananard et al. explored the role of NLR and platelet volume with lymphocyte ratio in acute adult heart failure patients, showing that high NLR values can increase the incidence of rehospitalization by 2.70 (95% CI, 1.58 - 4.61) compared to low NLR values.[19]

Research conducted by Maeda et al. in 2022 on heart failure patients, which combined FAN (Fibrosis Index, Albumin, NLR) values, also indicated that rehospitalization due to heart failure was more common in patients with higher FAN scores. This study showed a correlation between increased NLR values and the number of rehospitalizations, with a hazard ratio (HR) adjusted model of 1.43 (95% CI, 1.17-1.75; $p < 0.001$).[20]

In a meta-analysis of patients with thoroughly treated heart failure, NLR as a predictor of rehospitalization demonstrated a hazard ratio (HR) of 2.19 (95% CI, 0.94–5.09). [21] This rehospitalization event is related to the theory that active neutrophils release acid phosphatase, elastase, and myeloperoxidase, which are types of proteolytic enzymes that facilitate the destruction of cardiomyocytes. [21]

The study found that the NLR can be used as a predictive marker for mortality in patients with heart failure and reduced left ventricular ejection fraction who were receiving treatment with ACE-I and ARNI. Furthermore, the study demonstrated that ACE-I and ARNI therapy led to decreased NLR levels. This research suggests that monitoring NLR levels could help predict outcomes in heart failure patients on specific medication regimens. The observed reduction in NLR with ACE-I and ARNI treatment highlights a potential beneficial effect of these medications on inflammatory markers in this particular population.

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