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THE ROLE COMBINATION OF HIGH NEUTROPHIL LYMPHOCYTE RATIO (NLR) AND LOW ALBUMIN SERUM 24-HOURS AS PREDICTORS OF MAJOR CARDIOVASCULAR EVENTS (MACEs) DURING HOSPITALIZATION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCT

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ABSTRACT

Background: The inflammatory response is a key mechanism of the progressivity of atherosclerosis. While NLR is an inflammatory marker elevated in ACS, serum albumin decreased in inflammatory conditions during acute critical illness. The combination of these two inflammatory parameters in patients with ACS has not been widely studied.
Objective: To investigate the combination of NLR and albumin parameters in patients with NSTEMI and STEMI towards MACEs during hospitalization
Methods: A prospective observational cohort study was conducted at Prof. dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Bali, from October to December 2024. Observations were made during the hospitalization period to evaluate the occurrence of MACEs. Survival analysis was performed using Kaplan-Meier curves and Cox regression analysis on covariates. The MACEs parameters studied included all causes of death, acute stent thrombosis, cardiogenic shock, malignant arrhythmia, and pulmonary edema.
Results: This study included 124 patients with NSTEMI and STEMI. There were 66 observed cases of MACEs. High NLR value at admission was an independent predictor of MACEs (HR= 2.3, 95% CI 1.0-5.2, p<0.05). Low albumin at admission was not a predictor of MACEs (HR= 1.5, 95% CI 0.8-2.8; p value = 0.1). The combination of high NLR + low serum albumin was an independent predictor of MACEs (HR= 2.9, 95% CI 1.4-5.8; p value <0.05)
Conclusion: Combined score of high NLR + low albumin level was an independent predictor of MACEs in patients with NSTEMI and STEMI
Keywords: *acute coronary syndrome, neutrophil lymphocyte ratio, albumin serum, major adverse cardiovascular events*

INTRODUCTION

Coronary heart disease is known to be a global cause of death. Based on WHO data, an estimated 17.9 million people died from heart disease in 2019, representing 32% of global deaths. Of these deaths, 85% were due to acute coronary syndrome (ACS). The 2023 Indonesian Health Survey shows that the prevalence of cardiovascular disease in Indonesia reached 877,531 people, with the highest prevalence among men aged 25-34 years who live in urban areas[1].

Acute coronary syndrome refers to acute ischemia and necrosis of the myocardium, which can lead to acute inflammation and a stress response characterized by leukocyte mobilization in the area of myocardial necrosis. The white blood cell (WBC) count within 24 hours after admission is an independent predictor of mortality and MACEs in patients with acute myocardial infarction (AMI), and low lymphocyte counts are significantly associated with cardiovascular mortality. The neutrophil-to-lymphocyte ratio (NLR) is a more valuable inflammatory indicator than a single indicator for predicting the prognosis of patients with acute myocardial infarction. In non-STEMI patients, NLR is also valuable for predicting in-hospital mortality. In patients with STEMI, a high NLR is independently associated with the risk of death one year after percutaneous coronary intervention (PCI)[2].

Neutrophils secrete inflammatory mediators that can cause vascular wall degeneration. Conversely, lymphocytes play a role in regulating the inflammatory response and also act as anti-atherosclerosis agents. Based on this, NLR plays a role as an inflammatory biomarker and a potential predictor of the risk and prognosis of heart disease[3].

Serum albumin is the largest plasma protein in the human body. Serum albumin is also the main negative

acute phase reactant, whose levels decrease significantly in response to inflammation during chronic systemic diseases and acute critical illnesses. Several studies have shown that albumin has good predictive value in patients with cardiovascular disease[4,5]. Recent studies show an increased risk of cardiovascular events at albumin levels of 3.5–4.0 g/dL (HR 1.88, 95% CI 1.23 to 2.86, P = 0.003)[6,7].

The combination of NLR and albumin parameters, which indicate inflammatory predictors, has been extensively studied as a parameter for chemotherapy safety and a prognostic predictor in patients with malignancies. However, in the population of patients with AMI, the combination of these two inflammatory parameters has not been widely studied to assess the MACEs rate during the hospitalization period. The objective of this study was to determine whether a combination of high NLR and low serum albumin at admission is an independent predictor of MACEs during hospitalization in patients with NSTEMI and STEMI.

METHODS

This study was an observational analysis with a prospective cohort design. Data were collected prospectively, and blood samples were taken in the emergency room upon patient admission. MACEs monitoring was conducted in the ICVCU, HCU, and inpatient ward of the Pelayanan Jantung Terpadu and the Clinical Pathology Laboratory at Prof. dr. I G. N. G. Ngoerah General Hospital, Denpasar, Bali, from October 2024 to December 2024. The inclusion criteria for this study were patients aged ≥18 years who were hospitalized with NSTEMI or STEMI. Exclusion criteria for this study were patients with end-stage chronic kidney disease on hemodialysis, malignant tumors, severe infection or sepsis, coronary artery spasm, or other secondary causes of angina and myocardial infarction, severe heart disease (aortic dissection and hypertrophic cardiomyopathy), chronic inflammatory disease, and patients without serum albumin laboratory results.

This study began with measuring NLR and albumin values in 124 NSTEMI and STEMI patients treated at the hospital. A combination of high NLR and low albumin values was then determined as exposure. NSTEMI and STEMI patients were followed during hospitalization. Major cardiovascular events during hospitalization were assessed as study outcomes.

Data analysis was performed using SPSS 25.0. Bivariate analysis to compare the proportion of MACEs occurrence during hospitalization based on NLR, albumin, and the combination of high NLR + low serum albumin variables was performed by creating a two-by-two cross tabulation. The percentages shown are risk percentages. The measure of association calculated was the hazard ratio (HR). The statistical test used in the bivariate analysis was the Log-rank test. Survival analysis was performed to assess MACES outcomes based on high NLR, low serum albumin, and the combination of high NLR + low serum albumin using the Kaplan-Meier curve. Multivariate analysis used Cox regression to control for risk factors that were independently associated with MACEs. The Cox regression test was performed to determine the interaction between high NLR, low serum albumin, and the combination of high NLR + low serum albumin with covariates. The measure of association calculated was the adjusted hazard ratio. The confidence level in this study was set at 95%. Ho was rejected if the P value was < 0.05.

RESULTS

The basic characteristics of samples in the high NLR category showed no significant differences compared to the low-normal NLR category, as shown in Table 1. This study found that samples with high NLR were more likely to be male, have a diagnosis of STEMI compared to NSTEMI, have hypertension, and smoke. In the baseline characteristics of the serum albumin category, the low serum albumin category also showed no significant differences compared to the normal-high serum albumin category. The total number of MACEs observed during the study was 66 cases. The most common MACE event was acute pulmonary edema, with 59 cases.

In this study, it was found that the risk of major cardiovascular events in STEMI and NSTEMI patients was 2.3 times higher in patients with high NLR values compared to patients with normal-low NLR values (adjusted HR 2.3; 95% CI 1.1-4.8; p-value <0.05). Patients with high NLR had more MACEs events between 110 and 190 hours compared to patients with normal-low NLR, who had MACEs events later, between 190 and 250 hours hospitalization (Table 2 and Figure 1).

Table 2. Cox-regression analysis of high NLR with MACEs

Variable	*Adjusted HR*	CI 95%	p-value
NLR	**2,3**	**1,1-4,8**	**0,02**
DM type 2	1,1	0,6-1,9	0,6
Hypertension	0,8	0,5-1,4	0,6
Ejection fraction <50%	1,7	0,8-3,4	0,01

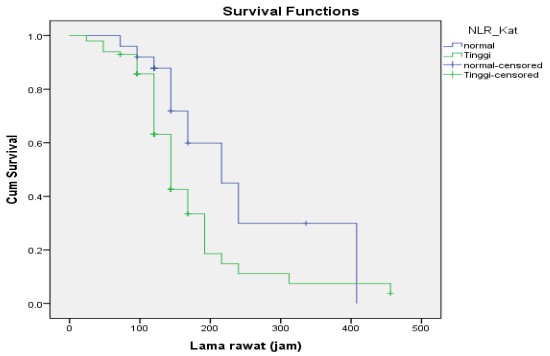
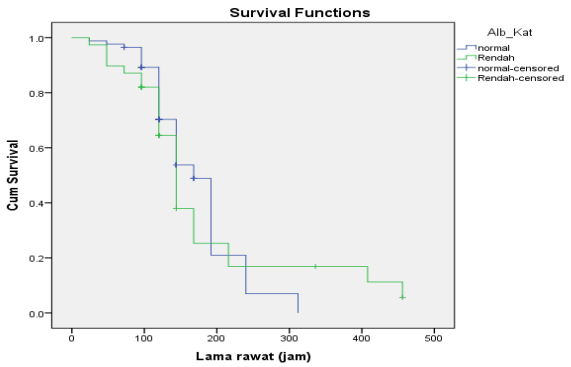


Figure 1. Kaplan Meier survival analysis curve of NLR category towards MACEs

Low serum albumin was not proven to be an independent predictor of MACEs (adjusted HR 1.5; 95% CI 0.8-2.8; p-value=0.1). Patients with albumin had a MACEs incidence rate that was not significantly different



at <200 hours during treatment in the low serum albumin and normal-high categories (Table 3 and Figure 2).

Table 3. Cox-regression analysis of low albumin serum with MACEs

Variabel	*Adjusted HR*	CI 95%	p-value
Low albumin serum	**1,5**	**0,8-2,8**	**0,1**
Age >60 yo	0,9	0,2-1,2	0,9
Male	0,5	0,2-1,2	0,1
DM type 2	1,0	0,5-1,8	0,8
BMI >23,0 kg/m2	1,2	0,7-2,2	0,4
Creatinine serum > 1,2 mg/dL	0,5	0,2-1,1	0,1
Ejection fraction <50%	1,5	0,7-3,0	0,1

Figure 2. Kaplan Meier survival analysis curve of albumin serum towards MACEs

However, the combination of high NLR and low serum albumin was proven to be an independent predictor of major cardiovascular events in STEMI and NSTEMI patients (adjusted HR 2.9; 95% CI 1.4–5.8; p <0.05) (Table 4).

Table 4. Cox-regression analysis of combination high NLR+low albumin serum with MACEs

Variable	*Adjusted HR*	CI 95%	p-value
Combination High NLR+Low Albumin Serum	**2,9**	**1,4-5,8**	**0,02**
Age >60 yo	0,8	0,4-1,5	0,5
DM type 2	0,9	0,5-1,6	0,8
Hypertension	0,8	0,4-1,4	0,4
BMI >23,0 kg/m2	1,2	0,6-2,1	0,5
Ejection fraction <50%	1,5	0,7-2,9	0,2

DISCUSSION

Various emerging evidence has implicated inflammatory processes in the pathogenesis of AMI involving local immune cells in the coronary arteries that produce inflammatory[8]. Activation of local inflammatory processes will result in endothelial damage. This mechanism causes endothelial dysfunction, altering its antithrombotic properties[8].

The formation of a "necrotic core" observed in atheroma occurs due to the accumulation of macrophages and their debris that are not phagocytosed, making the lesion more prone to rupture. Another cell promoting plaque development, destabilization, and thrombosis is the neutrophil. They achieve this state through the release of neutrophil extracellular traps (NETs), secretion of reactive oxygen species, and their capacity to attract proinflammatory monocytes to the arterial wall[9].

This study shows that high NLR values are proven to be predictors of in-hospital MACES in patients with STEMI and NSTEMI. In this context, the neutrophil-to-lymphocyte ratio is an easily obtainable, inexpensive, and credible indicator of systemic inflammation, and has therefore been evaluated in studies as a potential biomarker for predicting cardiovascular outcomes in the hospital and long term[10]. This results was consistent with studies by Arbel et al[11], Zhang et al[12], and Wei et al[13]. A study by Arbel involving a population of STEMI patients undergoing primary PCI found that a high NLR (>6.5) was associated with a higher 30-day mortality rate (OR=15.8, 95% CI 1.6–154, p=0.018) and was independently associated with a lower ejection fraction (OR=1.93, 95% CI 1.3–2.9, p=0.001), a higher incidence of cardiogenic shock (n=6%, p=0.005), and a higher incidence of acute kidney injury (n=12%, p=0.02) during hospitalization. A study by Zhang[10] found that a high NLR (>7) increased the risk of acute heart failure in STEMI patients (HR = 2.928, 95% CI: 1.393–6.158, P = 0.005) and NSTEMI (HR = 2.336, 95% CI: 1.236–4.416, P = 0.009). Similar findings were also obtained by Wei[13], where the group with high NLR values was associated with a higher incidence of MACEs compared to the group with normal-low NLR values. After myocardial infarction, myocardial necrosis can cause an inflammatory storm that

can further disrupt myocardial homeostasis, potentially leading to adverse cardiovascular events[10]. The combination of neutrophil and lymphocyte parameters has better prognostic value than each parameter separately.

Table 1. Sociodemographic and clinical characteristics of samples based on NLR and serum albumin categories

Characteristics	NLR value		Albumin Serum	
	High (≥3,13) (n=99)	Low-normal (<3,13) (n=25)	Low (<3,4) (n=39)	Normal-high (≥3,4) (n= 85)
Age (years)	60,2±10,2	60,2±11,2	63,2±9.6	58,9±11,4
Sex (n, %)				
Male	84 (84,8)	21 (84,0)	31 (79,5)	74 (87,1)
Diagnosis (n, %)				
STEMI	71 (71,7)	17 (68,0)	26 (66,7)	62 (72,9)
NSTEMI	28 (28,3)	8 (32,0)	13 (33,3)	23 (27,1)
Diabetes (n, %)	32 (32,3)	7 (28,0)	17 (43,6)	22 (25,9)
Hypertension (n, %)	56 (56,6)	15 (60,0)	22 (56,4)	49 (57,6)
Smoker	58 (58,6)	17 (68,0)	19 (48,7)	56 (65,9)
BMI (kg/m2)	25,6±3,5	25,2±4,7	24,0±3,6	26,2±3,6
Length hospitalization (hours)	132±61,9	153±75,2	150±99,8	130±39,1
Ejection fraction (%)	44,0±10,9	46,2±9,1	42,0±12,4	45,6±9,5
Creatinine Serum (mg)	1,3±1,1	1,1±0,4	1,3±0,7	1,2±1,1
Hs-Troponin I (pg/mL)	20.904±36.155	14.547±36.843	24.604±39.435	17.294±34.652
LDL (mg/dL)	121,7±44,4	116±41,2	98,5±40,3	130,9±41,5
Angiography result (n, %)				
Single vessel disease	28 (28,3)	5 (20,0)	3 (7,7)	30 (35,3)
Multi vessel diseases	63 (63,6)	19 (76,0)	31 (79,5)	51 (60,0)
MACEs occurence (n,%)	57 (57,6)	9 (36,0)	27 (69,2)	39 (45,9)

Another substance that has been extensively studied and plays a role in the development of atherosclerosis and its rupture process is serum albumin. Serum albumin, the main protein found in the extracellular fluid compartment, contributes to maintaining various physiological functions. It has been studied that serum albumin is associated with atherosclerosis through mechanisms that may include responses to inflammation, fibrinolysis and hemostasis, possible inhibition of platelet aggregation, antioxidant capacity, blood hyperviscosity, and nutritional status[14]. Although in this study, low serum albumin has not been proven to be a predictor of MACEs, different results were obtained from studies by Polat et al[15] and Yoshioka et al[16]. The study by Polat found that a population with low serum albumin (< 3.5 g/dL) was an independent predictor of increased mortality in patients with unstable angina pectoris/NSTEMI (OR: 2.764, 95% CI: 1.165-6.561, P =.021). The study by Yoshioka found that low serum albumin levels (<3.8 g/dL) during hospitalization were an independent predictor of the development of heart failure or cardiovascular death in the early phase after acute myocardial infarction (HR: 4.89, 95% CI: 1.64-6.67, P <0.001). The findings in these studies are assumed to differ from the results of the current study because the observation period in those studies was quite long, exceeding one year of observation for the occurrence of MACEs. The prognostic importance of hypoalbuminemia in patients with ACS may be due to the fact that hypoalbuminemia is associated with other comorbidities such as inflammation, malnutrition, and cachexia[15]. Plasma albumin levels decrease in inflammatory conditions.

This study shows that the combination of high NLR + low serum albumin is a proven predictor of in-hospital MACES in patients with STEMI and NSTEMI. The findings of this study are in line with the study by Wei et al[13] which studied 1,744 samples with STEMI undergoing

primary PCI. The samples were categorized into the high NLR + low albumin model (NLR >2.6, albumin <4.07 g/dl). After observing MACES for 446 days, it was found that the group with a high NLR + low albumin model had a higher incidence of MACES and was proven to be a predictor of MACES with a 2-fold increase in MACES risk (HR = 2.1; 95% CI = 1.3-3.4; p = 0.002) for each increase in the combination score of these parameters. From the other study, Li et al[17] showed that low albumin levels and high NLR levels were identified as risk factors for patients with poor prognosis undergoing surgical treatment for endometrial cancer.

Therefore, from the current study, it was concluded that NLR combined with albumin improves the prognostic value for inflammatory biomarkers.

Some limitations of this study are that it was based on a study conducted at only one center and the observation period was relatively short, so long-term survival could not be observed. This study also only evaluated NLR and albumin values at admission without evaluating the dynamics of parameter changes during hospitalization. Data on albumin prior to hospitalization was also not available, making it impossible to evaluate whether low albumin levels had occurred before the sample experienced SKA or not.

1. Conclusion

Combined score of high NLR and low albumin level was an independent predictor of MACEs in patients with NSTEMI and STEMI. Based on the results of the study, NLR and albumin testing can be used as a simple, widely available, and cost-effective modality for risk stratification of MACEs in patients with NSTEMI and STEMI during hospitalization. Therefore, monitoring of biomarkers that receive intervention during treatment should also be performed so that the significance of MACEs assessment can be improved.

Ethics statement

The studies involving humans were approved by Ethics Committee of Medical Faculty Udayana University Bali (No:2517/UN14.2.2.VII.14/LT/2024). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Disclosures

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