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Neutrophil Lymphocyte Ratio and Mortality in Patients with Acute Limb Ischemia

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Abstract

Acute Limb Ischemia (ALI) is a sudden decrease in limb perfusion with a potential of limb loss and is an indication for immediate vascular intervention. Apart from reducing the quality of life, the mortality rate in ALI is reported to be high, i.e., around 40%. Neutrophil Lymphocyte Ratio (NLR) can be used to reflect the inflammatory process in this condition. This study aimed to assess the correlation of NLR to mortality rate in ALI Rutherford Category III patients treated in Dr. Hasan Sadikin General Hospital Bandung, Indonesia. This was a cross-sectional analytical observative retrospective study on data collected from medical records of ALI Rutherford Category III patients treated in the hospital from 2019 to 2022. Sampling was performed consecutively and data were processed using the SPSS with univariate analysis and bivariate analysis using Kendall's tau b analysis test. Results demonstrated that of a total of 46 patients, the majority were female patients (n=31) and 28 patients died. The mean NLR levels in patients who survived was 5.8, in contrast with 9.7 observed among those who died. The statistical test results showed a significant correlation between the NLR and mortality rate of ALI Rutherford category III patients ($p<0.05$), albeit weak positive correlation (r value=0.35). The higher the NLR value was, the higher the risk of death. Hence, the NLR value could be used to recognize the risk of death among these patients.

Keywords: Acute limb ischemia (ALI), NLR, mortality rate

Introduction

Acute Limb Ischemia (ALI) is defined as a sudden decrease in limb perfusion that threatens limb viability.[1,2] The Rutherford classification system categorizes ALI into stages I, IIA, IIB, and III based on clinical presentation and prognosis.[3] In Rutherford category III, irreversible tissue damage has occurred, and amputation is often necessary.[3] ALI management depends on the cause and severity. Management of Rutherford category III Acute Limb Ischemia (ALI) emphasizes that reperfusion therapy cannot restore limb function, making amputation the primary option.[4, 5] Despite adequate therapy, ALI has a high mortality rate (around 40%), often attributed to underlying vascular disorders. [6,3,5] In Dr. Hasan Sadikin General Hospital, Bandung, from 2019–2022, 187 ALI cases were reported, with 60 categorized as Rutherford III.

Neutrophil-Lymphocyte Ratio (NLR) is a simple parameter used to assess an individual's inflammatory status. An elevated NLR reflects an increasing inflammatory process and is associated with a poor prognosis.[7] Research by Nuno H. Coelho and colleagues found a positive correlation between preoperative NLR values and 30-day mortality or amputation after revascularization in ALI Rutherford grade IIa and IIb. Higher pre-revascularization NLR values are linked to increased mortality or amputation. [8,9] Besides acute limb ischemia, NLR has long been used to predict mortality and survival in various diseases, including stroke, myocardial infarction, malignancies, and more recently, predicting mortality in COVID-19 patients. [9,10] NLR, as a mortality predictor in ALI patients, offers advantages such as efficient sample collection preoperatively, simple calculation based on complete blood count upon admission, and a straightforward process without requiring

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additional analyses or reagents, making it a relatively easy, cost-effective, and rapid test. [9,10]

Given the high mortality rate among patients with Rutherford category III Acute Limb Ischemia (ALI) at Dr. Hasan Sadikin Central General Hospital, the present study aims to investigate the association between the neutrophil-to-lymphocyte ratio (NLR) and mortality. Existing literature on the correlation between NLR, as an inflammatory marker, and the severity grading of ALI remains limited. The findings of this study may contribute to improved prognostication and inform treatment decisions for patients presenting with ALI.

Methods

This study is a retrospective cohort design. Data were collected through a review of medical records of patients diagnosed with Rutherford category III Acute Limb Ischemia (ALI) at Dr. Hasan Sadikin General Hospital, Bandung. The study population comprised patients with Rutherford category III ALI treated at the same hospital. Inclusion criteria were as follows: (1) age 18 years or older, (2) confirmed diagnosis of category III acute limb ischemia, and (3) presence of comorbidities such as diabetes mellitus, heart disease, or other vascular conditions. Patients were excluded if medical records indicated signs or evidence of infection, as this could influence neutrophil-to-lymphocyte ratio (NLR) values.

The sample was obtained through consecutive sampling based on the predefined inclusion and exclusion criteria. Subjects meeting the eligibility requirements were included continuously until the end of the specified study period, ensuring that the minimum required sample size was achieved. Data were collected during each patient's hospitalization. Variables were analyzed based on their type and distribution using either the Mann–Whitney U test or the unpaired t-test, as appropriate.

The strength of correlation between variables was assessed using Kendall's tau-b analysis.

Table 1Characteristics of the Research Subjects

Characteristics	Total n=46	Alive Patients n=18	Deceased Patients n=28	p-value*
Sex				0.57
Male	15	5 (27.8%)	13 (72.2%)	
Female	31	10 (35.7%)	18 (64.3%)	
Age (year)				0.12
Mean	64	63	65	
Range	58-73	58-69	59-73	
Median	64	64	65	
Onset				
<6 hour	9	2 (22.2%)	7 (77.8%)	0.25
6–24 hour	19	10 (52.6 %)	9 (47.4%)	
24–48 hour	18	6 (33.3 %)	12 (66.7 %)	
>48 hour	0	0	0	
Comorbidity				0.25
Atrial Fibrillation	3	0 (0)	3 (100 %)	
Hypertension	14	4 (28.6 %)	10 (71.4%)	
Diabetes mellitus	12	6 (50%)	6 (50%)	
Hypercholesterolemia	11	6 (54.5%)	5 (45.5%)	
Kidney Failure	6	2 (33.3%)	4 (66.7%)	
Covid +	0	0	0	
Other disease	0	0	0	

*Uji Mann-Whitney

Table 2 Laboratory Characteristics of the Study

Characteristics	Total (n=46)	Alive Patients (n=18)	Deceased Patients (n=28)	p-value*
Hb				0.15
Mean	11.67	11.76	11.61	
Range	10.00–14.30	10.00–14.30	10.20 – 13.60	
Median	11.75	11.85	11.70	
Leukosit				0.01
Mean	13.93	10.15	16.37	
Range	2.40–29.74	2.40–21.63	4.39–29.74	
Median	11.94	9.210	15.28	
Trombosit				0.08
Mean	393.17	331.67	432.71	
Range	117–1195	117–674	148–1195	
Median	331	288	372	
Laktat				<0.01
Mean	3.76	3.64	3.84	
Range	0.80–21.50	0.80–21.50	0.80 – 21.50	
Median	1.850	1.85	2.00	
Base Excess				
Mean	- 8.66	- 0.24	-14.07	<0.01
Range	- 860–4.60	-8.60–6.50	-260.00–4.60	
Median	- 3.250	1.40	-5.85	
Ureum				<0.01
Mean	47.70	42.63	50.96	
Range	8.20–193.40	8.20–174.30	5.30–193.40	
Median	34.65	33.80	34.75	
Kreatinin				<0.01
Mean	1.60	1.46	1.69	
Range	0.45–6.17	0.45–1.40	0.34–6.17	
Median	1.02	1.01	1.10	
Neutrofil				0.03
Mean	12.75	10.35	14.29	
Range	2.45–33.90	2.45–14.24	3.62–33.90	
Median	11.92	7.84	14.30	
Limfosit				
Mean	1.96	2.16	1.82	0.04
Range	1.05-–9.16	1.05–5.98	0.62–9.16	
Median	1.87	1.94	1.50	

* Mann-Whitney

Table 3 Analysis of the Relationship Between NLR and Mortality in Rutherford Category III ALI Patients

Variable	Total (n=46)	Alive Patients (n=18)	Deceased Patients (n=28)	p*	r*
NLR				<0.01	0.35
Mean	8.4	5.8	10.1		
Range	0.5–23.3	0.45–22.92	1.54–23.29		
Median	7.0	3.89	9.71		

*Kendall's Test

Ethical approval for this study was granted by the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung (Approval Number: LB.02.01/X.6.5/249/2023).

Results

As presented in Table 1, the majority of patients (67.4%) were female, with a mean age of 69 years. Among the study population, 18 patients survived or showed clinical improvement, while 28 experienced deterioration and died. The most frequent onset of symptoms occurred within 6 to 24 hours prior to hospital admission. Common comorbidities included hypertension, hypercholesterolemia, and diabetes mellitus. Comparison between the surviving and deceased patient groups revealed no statistically significant differences in age, gender, symptom onset, or comorbidities. These findings were confirmed using the Mann–Whitney U test for non-normally distributed numerical data and categorical variables ($p>0.05$).

Table 1 presents the laboratory results for patients with Rutherford category III ALI, including the mean values for various clinical parameters. A Shapiro-Wilk test confirmed that all numerical data ($n<50$) were non-normally distributed ($p>0.05$). As a result, the Mann-Whitney U test was applied to compare unmatched groups. The analysis revealed no significant differences in hemoglobin and platelet levels between the groups. However, significant differences were observed in leukocyte count, lymphocyte count, lactate levels, neutrophils, neutrophil-to-lymphocyte ratio (NLR), base excess, urea, and creatinine levels. Specifically, patients who passed away had lower lymphocyte levels and higher neutrophil levels compared to survivors.

Table 3 shows that the overall mean neutrophil-to-lymphocyte ratio (NLR) was 8.4. The mean NLR among surviving patients was 5.8, while the mean NLR among deceased patients was 10.1, indicating an elevated NLR in the latter group. A Kendall's tau-b correlation test revealed a statistically significant association between NLR and mortality in patients with Rutherford category III Acute Limb Ischemia ($p<0.05$). The correlation coefficient indicated a weak positive correlation ($r=0.2–0.4$), suggesting that higher NLR levels were associated with increased mortality.

Discussion

Acute Limb Ischemia (ALI) is a sudden decrease in arterial perfusion to the extremities, characterized by pallor, cold skin, decreased sensitivity, muscle weakness, claudication, and absence of distal pulse from the occlusion site. ALI is a medical emergency with an incidence of 3–14 per 100,000 people per year and a high rate of amputation (12–50%) and mortality (20–40%) without revascularization. The neutrophil-to-lymphocyte ratio (NLR) has been associated with specific cardiovascular disease manifestations and prognosis, but knowledge about predictive factors is still limited. [11,12]

The study included 46 patients with ALI Rutherford category III who met the inclusion criteria. The majority of patients were female, totaling 31 individuals (67.4%). This finding aligns with a study by Chihade et al., indicating a higher risk of death in female ALI patients. The prevalence of vascular disease increases in women after menopause, and their risk is determined by postmenopausal risk factors. In the United States, 67% of women have one or more major vascular risk factors at menopause, and this percentage increases with age. Hyperlipidemia, diabetes mellitus, hypertension, smoking history, and obesity are strong risk factors for developing vascular diseases. [13]

The mean age of patients in this study was 69 years, consistent with research by Daly[14]

where the average age of ALI patients was also 69 years. Another study by Kulezic et al. showed a median age of 74 years for ALI patients (IQR 66–84 years). The study found a mortality rate of 60.7%, in line with research by Sharath et al.[15] indicating a higher risk of death in patients with ALI Rutherford category III, around 20–50%. [15]

Recent studies indicate a correlation between a high neutrophil-to-lymphocyte ratio and mortality in patients with critical/acute ischemia due to the inflammatory response triggered by ischemic tissue, mediated by neutrophils. [16,17,18] Arbanasi et al. (2022) stated that increased NLR and PLR values before surgery are indicators of poor outcomes in patients with ALI Rutherford category II and III. Ergelen et al. showed that a high NLR (>6.97) is associated with increased in-hospital and long-term cardiovascular death in patients undergoing primary angioplasty. Additionally, NLR is reported as a strong independent predictor of clinical outcomes, including long-term cardiovascular mortality and morbidity after coronary artery bypass grafting and major vascular surgery. [19–21]

Spark et al. indicated that an NLR >5.25 is an independent predictive factor for all-cause mortality (HR 2.3, 95% CI 1.2–4.2; $p < 0.01$) in 149 patients diagnosed with critical limb ischemia (CLI). [22] King et al. suggested that a preoperative NLR >4 is an independent prognostic factor associated with high mortality ($p<0.05$) and low amputation-free survival ($p<0.01$) in 488 patients undergoing percutaneous intervention for femoropopliteal disease.[23] In this study, in line with previous research, the mean NLR value in the group that died or worsened after treatment was 13.75. The correlation test in this study also showed a high correlation between NLR and mortality. Thus, it can be concluded that the higher the NLR value, the higher the mortality rate.

Atherosclerotic disease and chronic inflammation are closely related, with a high white blood cell count associated with negative outcomes in patients with arterial disease. Neutrophils significantly affect the evolution of atherosclerotic plaques, while lymphopenia is a common inflammatory marker. The ratio can provide further information about the number of individual cells, neutrophilia, and lymphopenia. The inflammation imbalance expressed by neutrophils can explain different outcomes despite similar clinical presentations. Acute limb ischemia presents medical and surgical challenges, and decision-making remains difficult even after endovascular therapy. An individualized approach is needed, possibly using a more aggressive strategy for those with high initial neutrophil levels. Considering ease and cost, NLR can be used in preoperative patient stratification into risk groups, correlated with Rutherford classification, for better patient management and predictive hypothesis formation. Moreover, we consider that NLR increases clinical vulnerability to poor outcomes after revascularization, making it the first line in a series of predictable biochemical surveillance. This study suggests calculating NLR before and after thrombectomy and bypass is recommended for vascular care.

The study identified an uneven distribution of data, particularly in laboratory results between the surviving and deceased patient groups. This variability may be attributed to the relatively small sample size, indicating the need for future research with a larger cohort to enhance statistical power and generalizability.

Findings from this study demonstrated a correlation between NLR values and mortality in patients with Rutherford category III ALI. Higher NLR values were associated with an increased risk of death, emphasizing the need for timely clinical intervention. NLR may serve as a valuable tool in preoperative risk stratification, complementing the Rutherford classification to improve patient management and inform predictive modeling. Additionally, elevated NLR levels may reflect increased vulnerability to adverse outcomes following revascularization, supporting its use as an initial marker in biochemical surveillance. Further research involving a larger population and controlling for potential biases is recommended to build upon these findings and refine prognostic assessments.

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