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Original Article

Comparison of Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio as a Predictor of Clinical Outcome in Acute Ischemic Stroke

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Introduction: Stroke is a clinical syndrome characterized by neurological deficits lasting more than 24 hours or resulting in death, caused exclusively by cerebrovascular disease. Stroke is a leading cause of mortality, responsible for 7.8 million deaths worldwide each year and accounting for 13% of all deaths. Several studies have revealed the role of neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in predicting stroke. However, no study has directly compared NLR and PLR levels with the clinical outcomes of acute ischemic stroke (AIS). **Objective:** This study aims to compare the predictive value of the NLR and PLR with the clinical outcome of AIS based on the Modified Rankin Scale (mRS) and with the incidence of early neurological deterioration (END) based on NIHSS. **Method:** This was a prospective observational study. NLR and PLR values were obtained from routine blood examinations, and stroke outcome were assessed using the mRS. **Result:** A total of 125 ischemic stroke patients met the inclusion criteria. Chi-square test showed that NLR was associated with mRS outcomes, with an odds ratio (OR) of 6.1, while PLR was associated with mRS with an OR of 5.6. Fisher's exact test revealed a statistically significant association between NLR and the incidence of END (OR 19.26; p<0.001), as well as between PLR and END (OR 5.9; p=0.003). **Conclusion:** NLR and PLR have predictive value for both clinical outcome and the incidence of END in patients with acute ischemic stroke.

Keywords: Acute ischemic stroke. Modified Rankin Scale, Neutrophil-lymphocyte ratio, Platelet-lymphocyte ratio, Stroke ischemic outcome

Highlights
- NLR and PLR are associated with stroke outcomes.
- They may influence outcomes via thromboinflammatory pathways.

Introduction

Stroke is a clinical syndrome manifested as focal or global neurological deficits lasting more than 24 hours or resulting in death, caused by cerebrovascular disease.[1] Stroke causes approximately 7.8 million deaths worldwide each year, accounting for 13% of all deaths.[2] In Indonesia, based on the 2018 Basic Health Research, the prevalence of stroke reached 10.8 per 1000 population, with a mean age of 58.8 years. Stroke is the leading cause of death in Indonesia, comprising 15.4% of all mortalities, with the highest prevalence observed in East Kalimantan Province. According to the American Heart Association/American Stroke Association (2016), ischemic stroke accounts for

87% of all strokes, with hypertension being the most common risk factor, followed by old age, dyslipidemia, diabetes, heart disease, smoking, physical inactivity, family history, and obesity.[3]

One of the mechanisms that plays a role in the severity and clinical outcome of stroke is thromboinflammation—a complex process involving interactions between platelet-mediated thrombosis and immune-mediated inflammation, ultimately resulting in brain injury and increased stroke severity.[4,5] The neutrophil-lymphocyte ratio (NLR) is a marker of systemic inflammation and endothelial dysfunction derived from routine hematologic tests, making it easy to obtain and widely accessible.[6] Neutrophils, as part of the innate immune system, are the body's first line of defense during infection or ischemic injury. To fulfill this role, neutrophils deploy various chemical agents, including reactive oxygen species (ROS), proteases-containing vesicles, antibacterial biomolecules, and neutrophil extracellular traps.[7]

Neutrophils can also bind to platelets to form platelet-neutrophil aggregates (heterotypic aggregates) mediated by the interaction between P-Selectin (CD62P), expressed on the surface of activated platelets, and its leukocyte receptor, P-selectin glycoprotein ligand (PSGL-1).[8,9] This relationship then increases the expression of CD11b/CD18 (Mac-1) on leukocytes, promoting further binding to platelets via GpIIb/IIIa, thereby contributing to inflammation, thrombosis, and atherosclerosis.[10]

As an inflammatory marker, NLR helps explain the thromboinflammatory process, which exacerbates brain injury in ischemic stroke. Ischemia activates microglia, triggering both local and systemic inflammatory cascades. Neutrophils are among the first cells to infiltrate the brain (within 30 minutes to several hours, peaking at 24–72 hours) and are elevated during the early phase of stroke. This increase is associated with further brain cell damage, as neutrophils release neurotoxic enzymes, chemokines, and ROS or reactive nitrogen species (RNS). During the acute phase, a systemic immunosuppressive reflex also occurs, mediated by glucocorticoid release from the hypothalamic-pituitary-adrenal (HPA) axis. While this response helps limit excessive central inflammation, it causes a decrease in lymphocytes—especially T cells and natural killer cells. The imbalance between central inflammation and peripheral immunosuppression is thought to underlie elevated NLR levels.[6]

Thrombotic and inflammatory processes are key contributors to ischemic brain injury. In ischemic lesions, platelets aggregate and activated, causing secondary thrombosis. Simultaneously, ischemia triggers an inflammatory response that upregulates adhesion molecules and cytokines, leading to infiltration of leukocyte subsets. These interrelated processes are collectively termed thromboinflammation. Recent studies have identified Von Willebrand Factor (vWF) and glycoprotein Ib (GPIb) as potent inflammatory mediators that promote leukocyte adhesion and extravasation. vWF is secreted by the endothelium and platelets. Platelets also participate in acute inflammatory reactions by releasing mediators such as IL-1αβ, transforming growth factor β, histamine, serotonin, and CD40L—all of which contribute to ischemic injury.[4]

The platelet-lymphocyte ratio (PLR) is another inflammatory marker and a prognostic factor for cardiovascular disease. An elevated platelet count enhances platelet activation and aggregation, while a reduction in lymphocytes leads to systemic immunosuppression—together resulting in an increased PLR, which reflects the thromboinflammatory state. In a study by Perez *et al.*, PLR at admission correlated with stroke severity, as measured by National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS).[11] Similarly, Xu *et al.* found that higher PLR was independently associated with poor clinical outcomes and mortality at 3 months. Elevated PLR after endovascular therapy has also been linked to worse prognosis and inadequate recanalization.[12]

Objective

This study aims to compare the predictive value of the NLR and PLR with the clinical outcome of AIS based on the mRS as the primary outcome, and early neurologic deterioration (END) as the secondary outcome.

Methods

This study was a prospective observational study conducted at Wahidin Sudirohusodo Hospital, Makassar, from May to August 2021, using a consecutive sampling technique. The study subjects were hospitalized AIS patients. Ethical clearance was obtained from the Institutional Review Board Ethics Commission of Faculty of Medicine, Hasanuddin University (Approval No. 387/UN4.6.4.5.31/PP36/2021, dated June 11th, 2021).

Inclusion criteria were: first-time AIS, age 18-80 years, stroke onset less than 72 hours, and willingness to participate by signing informed consent. The exclusion criteria were stroke in posterior circulation, diagnosis of transient ischemic attack (TIA), brain infection, chronic kidney disease, any form of malignancy or autoimmune disease, and current or recent (within 7 days before onset) use of steroid or nonsteroid anti-inflammatory drugs.

Demographic data were collected using a subject biodata form. Clinical outcomes were assessed using the mRS at day 30 post-onset and the NIHSS to determine END. Clinical outcome was categorized into two groups: good (mRS 0-2) and poor (mRS 3-6). END was defined as an increase of more than 2 points in the NIHSS score on day 7 compared to day 1.

Blood samples were obtained via venipuncture from the subject's forearm. NLR and PLR were calculated within the first 24 hours of admission using Sysmex XN1000 flow cytometry method: NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, and PLR was calculated by dividing the platelet count by the absolute lymphocyte counts.

The data were analyzed using SPSS version 22.0. Results are presented in tables including percentages, means, medians, receiver operating characteristics (ROC), Chi-square tests, and Fisher's Exact tests.

Results

Characteristics of the subjects

A total of 125 subjects met the inclusion criteria, with 69 (55.2%) in the poor clinical outcome group and 56 (44.8%) in the good clinical outcome group The average age of the subjects was 57.8 years. Based on sex, there were more males than females (53.6% vs 46.4%). Most of the subjects were in the age range of 44-59 years (48%) (Table 1).

Table 1. Characteristics of the subjects

Characteristics	Total (n=125), n(%)	Outcome (1 month), n(%)		p-value
		Poor (n=69)	Good (n=56)	
Sex				
• Male	67 (53.6)	37 (53.6)	30 (53.6)	1.00[a]
• Female	58 (46.4)	32 (46.4)	26 (46.4)	
Age				
• 18-24 years	2 (1.6)	2 (2.9)	0 (0)	0.66[b]
• 25-43 years	11 (8.8)	5 (7.2)	6 (10.7)	
• 44-59 years	60 (48)	29 (42.0)	31 (55.4)	
• 60-74 years	42 (33.6)	25 (36.2)	17 (30.4)	
• ≥75 years	10 (8.0)	8 (11.6)	2 (3.6)	
Risk Factors				
• Hypertension	100 (80)	55 (79.7)	45 (80.4)	1.00[a]
• Diabetes	43 (34.4)	23 (33.3)	20 (35.7)	0.85[a]
• Dyslipidemia	57 (45.6)	37 (53.6)	20 (35.7)	0.05[a]
• Heart disease	26 (20.8)	15 (21.7)	11 (19.6)	0.82[a]
• Smoking	24 (19.2)	11 (15.9)	13 (23.2)	0.36[a]
NLR, median (range)	3.0 (1.0–42.4)	4.4 (1.2 – 42.4)	2.3 (1.0 – 11.5)	<0.001[c]*
PLR, median (range)	133.9 (68.1 – 1014.3)	161.5 (69.1 – 1014.3)	117.2 (68.1 – 253.6)	<0.001[c]*
NIHSS admission, median (range)	9.0 (2.0 – 30.0)	13.0 (4.0 – 30.0)	5.0 (2.0 – 15.0)	<0.001[c]*
NIHSS day 7, median (range)	7.0 (1.0 – 32.0)	11.0 (5.0 – 32.0)	4.0 (1.0 – 8,0)	<0.001[c]*
END	17 (13.6)	17 (24.6)	0 (0)	<0.001[b]*

[a]Using Chi-square test, [b]Fisher-Exact test, [c]Mann-Whitney U Test; *p<0.05
END: Early Neurologic Deterioration, NIHSS: National Institutes of Health Stroke Scale, NLR: Neutrophil-Lymphocyte Ratio, PLR: Platelet-Lymphocyte Ratio

ROC curve analysis

ROC curve analysis showed that the area under the curve (AUC) for NLR was 78% and for PLR was 71%. This indicates that, if NLR is used to predict poor outcomes in 100 patients with acute ischemic stroke, the prediction would be accurate in 78 cases. Similarly, PLR can correctly predict poor outcomes in 71 out of 100 cases. NLR demonstrated a slightly higher predictive value than PLR for one-month clinical outcomes in acute ischemic stroke patients (Figure 1).

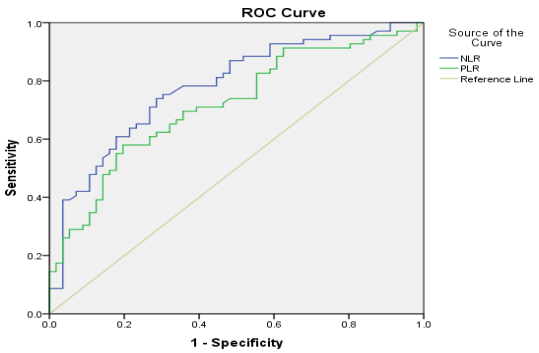

Figure 1. ROC curve of NLR and PLR relationship to clinical outcome

Relationship of NLR and PLR to Clinical Outcome

Using the Chi square test, NLR was significantly associated with mRS scores at one month (p < 0.001) with an odds ratio (OR) of 6.125 (Table 2). The PLR was also significantly associated with one-month mRS scores (p < 0.001) with an OR of 5.643 (Table 3).

Table 2. Relationship of NLR and mRS

Variable	Clinical Outcome, n(%)		p-value	OR
	Poor	Good		
NLR ≥ 3	49 (71.0)	16 (28.6)	<0.001*	6.125
NLR <3	20 (29.0)	40 (71.4)		
Total	69	56		

*p<0.05
NLR: Neutrophil-Lymphocyte Ratio, OR: Odds Ratio

Table 3. Relationship of PLR and mRS

Variable	Clinical Outcome, n(%)		p-value	OR
	Poor	Good		
PLR ≥ 150	40 (58.0)	11 (19.6)	<0.001*	5.643
PLR <150	29 (42.0)	45 (80.4)		
Total	69	56		

*p<0.05
OR: Odds Ratio, PLR: Platelet-Lymphocyte Ratio

Relationship of NLR and PLR to Early Neurological Deterioration (END)

Seventeen subjects (13.6%) experienced END. The relationship between NLR and PLR values and the occurrence of END is presented in Tables 4 and 5.

Table 4 shows that 16 (94.1%) patients who experienced END had an NLR value > 3, while 1 (5.9%) had an NLR value < 3. Among patients who did not experience END, 49 (45.4%) samples had an NLR value > 3, while 59 (54.6%) samples had an NLR value < 3. Fisher's exact test also found a statistically significant relationship between NLR and the incidence of END (OR 19.26; p <0.001).

Table 4. Relationship of NLR to END

Variable	END, n(%)		p-value	OR
	Yes	No		
NLR ≥ 3	16 (94.1)	49 (45.4)	<0.001*	19.26
NLR <3	1 (5.9)	59 (54.6)		
Total	17	108		

*p<0.05
NLR: Neutrophil-Lymphocyte Ratio, OR: Odds Ratio

Table 5 shows that 13 (76.5%) subjects who experienced END had a PLR value > 150, while 4 (23.5%) had a PLR values <150. In the group without END, 38 (35.2%) had a PLR value > 150, while 70 (54.6%) had a PLR value <150. Fisher's exact test also found a statistically significant relationship between the PLR and the incidence of END (OR=5.9; p=0.003).

Table 5. Relationship of PLR to END

Variable	END, n(%)		p-value	OR
	Yes	No		
PLR ≥ 150	13 (76.5)	38 (35.2)	0.003*	5.9
PLR <150	4 (23.5)	70 (64.8)		
Total	17	108		

*p<0.05
END: Early Neurologic Deterioration, OR: Odds Ratio, PLR: Platelet-Lymphocyte Ratio

Table 5 shows that 13 (76.5%) subjects who experienced END had a PLR value > 150, while 4 (23.5%) had a PLR values <150. In the group without END, 38 (35.2%) had a PLR value > 150, while 70 (54.6%) had a PLR value <150. Fisher's exact test also found a statistically significant relationship between the PLR and the incidence of END (OR=5.9; p=0.003).

Discussion

This research is a prospective observational study aimed at determining the relationship between NLR and PLR values and clinical outcomes based on the mRS, with END as a secondary outcome.

A total of 125 subjects met the inclusion and exclusion criteria, with 69 categorized in the poor clinical outcome group, and 56 in the good clinical outcome group. The average age of patients in this study was 57.8 years, with the majority aged between 44 and 59 years. These findings are consistent with research by Akbar *et al.*, who analyzed 2,065 stroke patients across 28 hospitals in Indonesia and reported an average stroke age of 58.8 years.[3] Males were more prevalent than females (53.6% vs 46.4%), which aligns with epidemiological research by Aliah *et al.*, indicating that strokes generally occur after age 40 and are more common in men.[3]

The most frequently reported risk factor in this study was hypertension (80%), followed by dyslipidemia (45.6%), diabetes mellitus (34.4%), heart disease (20.8%) and smoking (19.2%). This aligns with findings by Akbar *et al.*, who also identified hypertension as the most common risk factor (73.9%), along with smoking (20.4%), heart disease (19.9%), prior stroke (19.9%), and diabetes (17.3%).[3] Differences in frequency of other risk factors may stem from population variations and timing of data collection.

ROC curve analysis showed the AUC for NLR was 78%, and for PLR, 71%. NLR showed a higher predictive value than PLR for one-month clinical outcomes in AIS patients, although both parameters had a moderate predictive strength. The cutoff value for NLR was 3.0, with a sensitivity of 71.0% and specificity of 73.2%. For PLR, the cutoff was 150.8, with a sensitivity of 58.0% and specificity of 80.4%.

These findings are comparable to results by Chen *et al.*, who reported an NLR cutoff of 3.51 with a sensitivity of 64.6% and a specificity of 81.8% (AUC: 0.776, 95% CI: 0.727-0.825, p <0.001), and a PLR cutoff of 141.52 with a 69.2% sensitivity and 62.9% specificity (AUC 0.695, 95% CI: 0.641-0.753, p <0.001).[13] These values are similar to other biomarkers such as CRP and D-dimer. In a study by Bian *et al.*, CRP levels were independently associated with poor outcomes at three months post-stroke, with an AUC 0.829 (95% CI: 0.772-0.887, p<0.001), and a cutoff of 6.34 mg/L (68.2% sensitivity, 85.7% specificity).[14]

The median NLR in the poor outcome group was 4.4 (range: 1.2 – 42.4), compared to 2.3 (range: 0.95 – 11.5) in the good clinical outcome group. Chi-square testing showed a significant association between NLR and one-month mRS (OR 6.125, p = <0.001). Similarly, the median PLR value in the poor clinical outcome group was 161.5 (69.1 – 1014.3), and 117.2 (68.1 – 253.6) in the good outcome group (OR 5.643, p <0.001). Both markers were independently associated with one-month stroke outcomes, with nearly equivalent odds.

These findings are supported by meta-analyses and systematic reviews by Zhang *et al.* and Song *et al.*, which confirmed that elevated NLR is associated with worse 3-month outcomes and increased risk of intracerebral hemorrhage, particularly in Asian populations.[15,16] Perez *et al.* also found that both NLR and PLR correlated with stroke severity and prognosis.[11] In AIS patients treated with intravenous thrombolysis, elevated PLR was associated with poor outcomes and mortality at three months.[12]

In AIS, platelet dysfunction and overactivation can drive thrombosis and release inflammatory mediators that exacerbate brain injury.[17] This study further reinforce the role of thromboinflammation in stroke pathophysiology. DAMPs released during infarction activate microglia activation and initiate peripheral inflammation. Neutrophils infiltrate the brain within 30 minutes to a few hours, peaking at 1–3 days post-stroke.[18] Early neutrophilia correlates with larger infarcts and higher stroke severity.[19] Neutrophils cause neurotoxicity by releasing proteolytic enzymes.[20] NETs (neutrophil extracellular traps),

composed of chromatin and granules, contribute to stroke-induced inflammation and injury via NETosis, involving HMGB1 and ATP. Excessive NETs promote microvascular thrombosis, endothelial death, and resistance to tissue plasminogen activator (tPA).[21,22]

Lymphocytes, in contrast, exert varied effects in thrombo-inflammation. They arrive later (3–6 days post-stroke), and their subsets (e.g., Th1, Th17, γδT cells) are proinflammatory, while regulatory T and B cells are neuroprotective.[23,24] Lymphopenia in AIS correlates with poor outcomes, possibly due to stress-induced HPA axis activation and elevated cortisol, which suppresses lymphocyte levels.[25]

Platelets also modulate thrombo-inflammation. Upon vascular injury, they form aggregates with leukocytes, aiding thrombus formation. Platelets promote inflammation by enabling immune cell adhesion and participate in atherosclerosis. They also interact with adaptive immunity, influencing T cell activation and function.[5]

In this study, 17 subjects (13.6%) experienced END, consistent with reported ranges (5–40%) depending on definition. The variation in numbers is caused by differences in the definition of END. Siegler *et al.* noted that using NIHSS score changes >2 is more sensitive in predicting poor outcomes than >4.[26] Geng *et al.* found END, defined as NIHSS increase >2, was a strong predictor of poor long-term outcomes.[27] We analyzed END because it reflects dynamic neurological changes unrelated to initial infarct size and offers insight into the mechanisms linking NLR/PLR to stroke outcomes.[28]

Unlike late neurological deterioration, END is driven by stroke pathophysiology, such as failed collateral circulation, thrombus progression, recurrent stroke, cerebral edema, hemorrhagic transformation, or vessel re-occlusion. In contrast, late deterioration is typically due to infections, metabolic disturbances, or vascular complications.[29]

Thrombo-inflammation can promote secondary thrombosis and inflammation via platelet microparticles and cytokines (IL-1α, IL-1β, TGF-β, histamine, serotonin, CD40). The Kinin contact pathway also plays a key role in ischemic and reperfusion injury.[30] This supports the conclusion that NLR and PLR predict clinical outcomes due to their association with stroke-related deterioration rather than complications like infection or metabolic imbalance.

Large vessel atherosclerosis may influence NLR/PLR through larger infarcts and stronger inflammatory responses. Identifying END early enables targeted intervention to mitigate deterioration via anti-inflammatory or antithrombotic strategies.

This study has several limitations. First, we excluded patients who were candidates for thrombolysis and thrombectomy, although these groups are also susceptible to deterioration due to the neuroinflammatory process triggered by reperfusion injury. Second, we did not measure serial NLR and PLR values, limiting analysis of NLR and PLR dynamics to the outcomes. Third, we lacked vascular imaging to determine the stroke subtypes based on TOAST. Fourth, we did not assess patients' emotional stress, which may influence immune response. Fifth, multivariate regression was not conducted to adjust for confounders such as age, initial NIHSS, and vascular risks. Lastly, we recommend future analysis of NLR/PLR by ischemic stroke subtype and using serial measurements to explore their temporal correlation with END.

Conclusion

In this study, there was a relationship between NLR and PLR and the clinical outcome of AIS. NLR had a higher predictive value compared to PLR. Both NLR and PLR also predicted END in AIS. Future research is needed to explore the relationship between NLR and PLR and each subtype of ischemic stroke, as well as their association with other neuroinflammatory markers such C-reactive protein or calcitonin.

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Conflict of interest
All authors declare no conflict of interest.

Ethic consideration
This study had received ethical clearance from the Institutional Review Board Ethics Commission of Faculty of Medicine, Hasanuddin University (Approval No. 387/UN4.6.4.5.31/PP36/2021, dated June 11th, 2021).

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Author contribution
Anthony Gunawan: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Writing–Original Draft. **Ashari Bahar:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Supervision, Writing–Original Draft, Writing–Review and Editing. **Irbab Hawari:** Validation, Visualization, Writing–Review and Editing. **Wijoyo Halim:** Validation, Visualization, Writing–Review and Editing.

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