Acta Biomed 2025; Vol. 96, N. 5: 17961 DOI: 10.23750/abm. v96i5.17961

Original article

Angiogenic and inflammatory biomarkers in acute ischemic stroke: The prognostic role of vascular endothelial growth factor, neutrophil-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio in a cross-sectional study

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Abstract. *Background and aim:* Acute ischemic stroke (AIS) is a leading cause of morbidity and mortality, with a complex pathophysiological mechanism involving inflammation and angiogenesis. Vascular Endothelial Growth Factor (VEGF), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) are thought to play roles in determining stroke severity. *Methods:* This was an observational analytic study with a cross-sectional design conducted on AIS patients at Dr. Wahidin Sudirohusodo General Hospital, Makassar. Serum VEGF levels were measured using the ELISA method, while NLR, PLR, and LMR were calculated from routine blood tests. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) and categorized into two groups: moderate (0–15) and moderate-to-severe (16–42). Pearson correlation and linear regression analyses were performed to evaluate the relationships between variables. *Results:* A total of 50 patients met the inclusion criteria (54% male, 46% female). Correlation analysis showed a significant positive association between VEGF and NIHSS (r = 0.831; p = 0.000), as well as between NLR and NIHSS (r = 0.548; p = 0.000). LMR demonstrated a significant negative correlation with NIHSS (r = –0.549; p = 0.000). In contrast, PLR was not significantly associated with NIHSS (r = 0.228; p = 0.112). Multiple regression analysis identified VEGF and NLR as dominant predictors (R^2 = 0.735; p < 0.001). *Conclusions:* Serum VEGF, NLR, and LMR were significantly associated with the severity of AIS, whereas PLR was not. VEGF and NLR may be considered potential biomarkers for risk stratification in AIS patients. (www.actabiomedica.it)

Key words: acute ischemic stroke, VEGF, NLR, PLR, LMR, NIHSS

Introduction

Stroke is a major global health problem and one of the leading causes of death and disability. In 2019, stroke ranked third as the cause of death and disability worldwide, with a significantly increased burden since 1990. Recent data reported 12.2 million incident cases of stroke, 101 million prevalent cases, 143 million Disability-Adjusted Life Years (DALYs), and 6.55 million deaths due to stroke in that year (1). In the United States, more than 795,000 people suffer from stroke each year,

with 610,000 of these being first-time strokes and 185,000 recurrent strokes. Approximately 140,000 stroke-related deaths occur annually, accounting for 1 in every 20 deaths, making stroke the fifth leading cause of death in the country. In addition, stroke is the leading cause of long-term disability, with an annual healthcare cost burden of 34 billion dollars (2). Indonesia is currently facing a double burden of diseases, namely communicable and non-communicable diseases (NCDs). This epidemiological shift is influenced by environmental changes, community behavior, demographic transition, technology, economy, and socio-cultural factors. The increasing burden of NCDs is in line with higher prevalence of risk factors, such as hypertension, hyperglycemia, obesity, unhealthy diet, physical inactivity, smoking, and alcohol consumption. Stroke is one of the diseases with the highest mortality and healthcare costs in Indonesia. The 2019 Basic Health Research survey reported that the prevalence of stroke in people aged ≥15 years increased from 7 to 10.9 per thousand, with a total of 638,178 cases in 2023, predominantly in the 25–34 years age group, and more common in men than women. Stroke is defined as "rapidly developing clinical signs of focal or global neurological deficit due to cerebral, spinal cord, or retinal infarction, lasting more than 24 hours or leading to death, with no cause other than vascular origin" (3). Stroke is classified into ischemic stroke and hemorrhagic stroke. Ischemic stroke occurs due to reduced blood flow to the brain caused by narrowing or blockage of blood vessels, leading to decreased oxygen and nutrient supply to brain tissue. This condition triggers a complex inflammatory response characterized by the release of cytokines, chemokines, adhesion molecules, and proteolytic enzymes, which exacerbate tissue damage (4). Acute ischemic stroke (AIS) is a neurological emergency caused by obstruction of blood flow, usually due to thrombus or embolism, resulting in rapid brain tissue death. Clinical symptoms appear suddenly, such as hemiparesis, aphasia, and impaired consciousness, making immediate treatment critical since every minute of delay can result in the loss of millions of neurons (5). The post-ischemic inflammatory process involves multiple immune cells, including neutrophils, lymphocytes, and monocytes, as well as molecular mediators such as cytokines and Vascular Endothelial Growth Factor (VEGF) (6). VEGF is an angiogenic protein that enhances tissue perfusion through stimulation of angiogenesis, increases vascular permeability, and exerts neuroprotective effects. However, VEGF expression may be dualistic: in the early phase of stroke, it may aggravate cerebral edema through blood-brain barrier disruption, while in the subacute to chronic phases, it supports tissue repair via angiogenesis and neurodegeneration (7). In addition to VEGF, simple hematological inflammatory parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) have been studied as prognostic biomarkers in AIS. High NLR reflects the predominance of neutrophil-mediated inflammation and a decrease in protective lymphocytes, which is associated with blood-brain barrier (BBB) damage and poor prognosis (8). PLR reflects the balance between prothrombotic platelet activity and adaptive immune function of lymphocytes, with higher values associated with increased infarct volume and risk of complications (9). Meanwhile, LMR describes the balance between protective lymphocyte responses and proinflammatory monocyte activity, with lower values associated with more severe strokes and poorer clinical outcomes (10). Neutrophils in the early phase of stroke release proinflammatory cytokines and matrix metalloproteinase-9 (MMP-9) that damage the blood-brain barrier and stimulate VEGF release through interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) (11). This highlights the close interplay between systemic inflammatory responses and angiogenic pathways in determining the severity of acute ischemic stroke. Therefore, investigating VEGF, NLR, PLR, and LMR is important to understand their roles as inflammatory and angiogenic biomarkers and predictors of stroke severity.

Material and Methods

Study design

This study was an observational analytic study with a cross-sectional design conducted at Dr. Wahidin Sudirohusodo General Hospital, Makassar, and its

affiliated hospitals from June 2025 until the required sample size was achieved. The study population consisted of patients with AIS, with the accessible population being inpatients at the hospital. Samples were drawn from the target population who met the inclusion and exclusion criteria using a consecutive sampling method based on the order of hospital admission during the study period.

Sample criteria

The study population consisted of patients diagnosed with AIS who were admitted to Dr. Wahidin Sudirohusodo Central General Hospital, Makassar, and its affiliated healthcare facilities during the study period. Participants were consecutively recruited according to predefined eligibility standards. Eligible patients were adults aged 18–70 years with a clinically and radiologically confirmed diagnosis of AIS, with symptom onset between one and seven days. Only those with complete clinical and laboratory data who provided written informed consent, either personally or through a legal representative, were included. Patients were excluded if they had medical conditions that could influence biomarker levels or clinical outcomes, such as chronic kidney disease, chronic heart failure or severe cardiac disease, active infectious or autoimmune disorders, malignant disease, severe liver disease, or a history of myocardial infarction. Individuals who failed to complete all study procedures or who withdrew their participation after initial consent were classified as dropouts and excluded from the final analysis. These criteria were applied to reduce potential confounding factors and ensure a homogeneous sample, thereby allowing for a more reliable assessment of the prognostic role of VEGF and inflammatory hematologic ratios in AIS.

Research procedure

Patients with suspected AIS who were admitted to Dr. Wahidin Sudirohusodo Central General Hospital, Makassar, and its affiliated hospitals were screened for eligibility. The diagnosis was established through clinical history, neurological examination, and non-contrast head computed tomography (CT) scans to rule out hemorrhagic stroke. Patients fulfilling the inclusion criteria and none of the exclusion criteria were consecutively recruited. Prior to enrolment, the study team explained the objectives and procedures in detail to patients or their families, and written informed consent was obtained. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) in patients with symptom onset between one and seven days. Following clinical assessment, routine hematological tests were performed, and venous blood samples were collected for biomarker analysis. Approximately 5 mL of venous blood was drawn under aseptic conditions into plain tubes for serum VEGF measurement, while NLR, PLR, and LMR were derived from routine blood counts. The serum samples were transported in a cool box maintained at 4 °C and processed at the Hasanuddin University Medical Research Center (HUMRC) Laboratory, Hasanuddin University Hospital. Serum VEGF concentrations were measured using enzyme-linked immunosorbent assay (ELISA) according to standardized protocols. All clinical, laboratory, and demographic data were recorded in a structured case report form, and the compiled dataset was subsequently analyzed to assess the relationship between VEGF, inflammatory hematologic ratios, and stroke severity.

Data and statistical analysis

All data were analyzed using SPSS version 27.0 software. The normality of continuous variables was tested with the Kolmogorov–Smirnov test, as the sample size was ≥ 50. A p-value of less than 0.05 was considered statistically significant. Correlations between serum VEGF, NLR, PLR, and LMR with stroke severity were assessed using Pearson's correlation test for normally distributed data and Spearman's rank correlation test for non-parametric data. Comparisons of biomarker levels across different categories of stroke severity (mild, moderate, and moderate-to-severe) were evaluated using analysis of variance (ANOVA) or the Kruskal–Walli's test, depending on data distribution. Furthermore, multiple linear regression analysis was employed to identify independent

predictors of stroke severity after adjusting for potential confounders.

Results

Baseline characteristics of the study population

A total of 50 patients with AIS who fulfilled the inclusion criteria were enrolled. The demographic characteristics are summarised in Table 1. Male patients were slightly more predominant (54%) compared with females (46%). The majority of patients were younger than 60 years (60%), while 40% were aged 60 years or older. Regarding stroke severity based on NIHSS, 10% were classified as mild, 40% moderate, 20% moderate-to-severe, and 30% severe. Hypertension was the most prevalent risk factor (62%), followed by smoking (22%) and diabetes mellitus (20%).

Distribution of inflammatory and angiogenic biomarkers

The descriptive statistics of VEGF, NLR, PLR, and LMR are presented in Table 2. Median VEGF was 163.36 pg/mL (range 51.21–517.09). The median NLR was 5.0 (1.3–36.6), PLR 28.2 (2.4–245.5), and LMR 2.05 (0.3–44.3).

Table 1. Demographic characteristics of research subjects

Characteristic	Category	n (%)
Gender	Male	27 (54)
	Female	23 (46)
Age	<60 years	30 (60)
	≥60 years	20 (40)
Stroke severity	Mild	5 (10)
	Moderate	20 (40)
	Moderate-severe	10 (20)
	Severe	15 (30)
Risk factors	Hypertension	31 (62)
	Smoking	11 (22)
	Diabetes Mellitus	10 (20)
Total		50 (100)

Primary data sources.

Comparison of VEGF, NLR, PLR, and LMR serum levels with stroke severity

Serum VEGF levels showed a marked increase with higher stroke severity. Patients in the moderate-to-severe group demonstrated significantly higher VEGF levels compared to those in the moderate group (269.6 ± 97.6 vs. 109.7 ± 39.1pgmL; $p < 0.001$). Similarly, NLR was significantly elevated in the moderate-to-severe group (median 7.0) compared to the moderate group (median 2.6; $p < 0.001$). LMR demonstrated the opposite trend, being markedly reduced in the moderate-to-severe group (median 1.0) compared with the moderate group (median 3.5; $p < 0.001$). In contrast, PLR showed only a non-significant tendency towards higher values in more severe cases (median 33.3 vs. 22.5; $p = 0.095$). The comparison of these biomarker levels across stroke severity is presented in Table 3.

Correlation of VEGF, NLR, PLR, and LMR serum levels with stroke severity

The relationships between stroke severity (NIHSS score) and inflammatory/angiogenic markers (VEGF, NLR, PLR, and LMR) are summarised in Table 4. Pearson's correlation was applied for VEGF, while Spearman's rank correlation was used for the hematologic ratios. A robust positive correlation was observed between VEGF and stroke severity ($r = 0.831$, $p < 0.001$), indicating that higher VEGF levels were associated with more severe neurological deficits. NLR also showed a significant moderate positive correlation with NIHSS ($r = 0.548$, $p < 0.001$), reflecting the role of neutrophil-driven inflammation in worsening clinical severity. In contrast, LMR demonstrated a moderate and statistically significant negative correlation with NIHSS ($r = –0.549$, $p < 0.001$), suggesting that lower LMR values were linked with greater stroke severity, likely due to the predominance of monocyte-mediated inflammatory activity. Meanwhile, PLR showed a weak positive correlation ($r = 0.228$) that did not reach statistical significance ($p = 0.112$). These findings

Table 2. Characteristics of serum VEGF, NLR, PLR, and LMR

Biomarker	Mean	SD	Median	Range
Vascular Endothelial Growth Factor (VEGF)	189.47	109.10	163.36	51.21–517.09
Neutrophil-to-Lymphocyte Ratio (NLR)	7.84	7.81	5.00	1.3–36.6
Platelet-to-Lymphocyte Ratio (PLR)	56.05	57.86	28.20	2.4–245.5
Lymphocyte-to-Monocyte Ratio (LMR)	3.78	6.78	2.05	0.3–44.3

Primary data sources

Table 3. Comparison of VEGF, NLR, PLR, and LMR serum levels with stroke severity

Characteristics	Severity		*p* Value
	Moderate Mean±SD	Moderate-severe Mean±SD	
Vascular Endothelial Growth Factor (VEGF)	109,70±39,05	269,63±97,57	*p* = 0,000*
Neutrophil-to-Lymphocyte Ratio (NLR)	2,6(1,3-26)	7(2,4-36,6)	*p* = 0,000**
Platelet-to-Lymphocyte Ratio (PLR)	22,5(2,4-147,5)	33,3(9,4-245,5)	*p* = 0,095**
Lymphocyte-to-Monocyte Ratio (LMR)	3,5(0,3-44,3)	1(0,3-4,9)	*p* = 0,000**

* *P* value with ANOVA test; ** *P value with Kruskal Wallis test.*

Table 4. Correlation of VEGF, NLR, PLR, and LMR with Stroke Severity

Biomarker	r	*p*-value	Strength of correlation	Interpretation
Vascular Endothelial Growth Factor (VEGF)	0.831	<0.001*	Very strong positive	Higher VEGF is associated with greater severity
Neutrophil-to-Lymphocyte Ratio (NLR)	0.548	<0.001**	Moderate positive	Elevated NLR linked to more severe strokes
Platelet-to-Lymphocyte Ratio (PLR)	0.228	0.112**	Weak positive (NS)	No significant correlation
Lymphocyte-to-Monocyte Ratio (LMR)	– 0.549	<0.001**	Moderate negative	Lower LMR is associated with greater severity

** P value with Pearson correlation test; ** P value with Spearman correlation test*

emphasise that VEGF and NLR are robust markers of clinical severity, while LMR provides an inverse reflection of disease burden, whereas PLR appears less informative in this cohort.

Multivariate regression analysis of the relationship of serum VEGF and NLR, PLR, and LMR levels with stroke severity

The results of regression analysis showed that VEGF levels and NLR, are presented in Table 5, had a significant relationship with the NIHSS score, which reflects the severity of AIS. VEGF was positively associated with NIHSS, meaning that the higher the VEGF levels, the more severe the stroke severity. This is in line with the role of VEGF as a mediator of angiogenesis, which increases in conditions of brain ischemia due to hypoxia. However, in the acute phase, it correlates with vascular damage and edema that aggravate clinical manifestations. Similarly, a high NLR reflects a predominance of neutrophil over lymphocyte inflammatory response, which significantly increases the risk of stroke severity. In contrast, PLR and LMR showed no significant association with NIHSS score.

Table 5. Relationship of serum VEGF and NLR, PLR, and LMR with Stroke Severity

NIHSS	Coefficient	t	P value (partial)	F	*p* value (Simultaneous)	R^2
(Constant)	2,986	1,853	0,070	31,187	0,000	0,735
Vascular Endothelial Growth Factor (VEGF)	0,060	9,757	0,000			
Neutrophil-to-Lymphocyte Ratio (NLR)	0,205	2,398	0,021			
Platelet-to-Lymphocyte Ratio (PLR)	-0,016	-1,374	0,176			
Lymphocyte-to-Monocyte Ratio (LMR)	-0,034	-0,339	0,736			

* *Linear regression test.*

Although in theory, PLR can describe the inflammatory process and platelet activation that play a role in stroke pathogenesis, in this study, its contribution to stroke severity was not proven to be significant. Similarly, LMR, although this ratio is often associated with immune response, did not have a significant effect on stroke severity in the analysis results. This suggests that not all inflammatory markers have the same predictive value for AIS severity. Simultaneously, the regression model involving VEGF, NLR, PLR, and LMR proved significant with an F value of 31.187 and $p < 0.001$, with a contribution of 73.5% ($R^2 = 0.735$) in explaining the variation of NIHSS scores. This means that most of the stroke severity can be explained by the combination of these biomarkers, especially VEGF and NLR, as the dominant factors. These results confirm that inflammatory markers and angiogenic factors have an important role in determining the severity of AIS, so that they can be considered as clinical and laboratory parameters in patient risk stratification. These patterns are illustrated in Figure 1, which presents scatter plots of the relationship of serum VEGF and NLR, PLR, and LMR with stroke severity.

Discussion

The results of this study suggest that demographic factors, vascular risk factors, and angiogenic and inflammatory biomarkers play an important role in determining the severity of AIS. Analysis of sample characteristics provides a basis for understanding the clinical context of patients, as well as providing a foundation for interpreting the relationship between serum VEGF levels and inflammatory parameters with NIHSS score as a measure of stroke severity. Sample characteristics showed that the prevalence of AIS was higher in men (54%) than in women (46%), in accordance with the report of Jiang et al., who mentioned the higher risk of stroke in men due to lifestyle factors such as smoking, alcohol consumption, and work stress (12). Pre-menopausal women tend to be protected by the protective effects of estrogen that maintain endothelial function, lipid profiles, and provide anti-inflammatory and anti-thrombotic effects, so stroke onset in women is more common after menopause when estrogen levels decrease. In addition, the age group <60 years dominated with 60%, indicating a shift in the trend of stroke incidence to younger ages, where pathophysiologic mechanisms are often related to cardiac abnormalities, vascular abnormalities, autoimmune diseases, or poor lifestyle factors (13). The main risk factors found were hypertension (62%), smoking (22%), and diabetes mellitus (20%). Hypertension remains the dominant factor that accelerates structural and functional vascular changes, increases arterial stiffness, and damages the endothelium, triggering atherosclerosis and thrombosis (14). Smoking contributes to vasoconstriction, oxidative stress, inflammation, and endothelial damage, further accelerating the process of atherosclerosis (15). Meanwhile, diabetes mellitus exacerbates stroke risk through chronic hyperglycemia that causes endothelial damage, accelerates atherogenesis, and increases platelet aggregation (16). The combination of these three risk factors predisposes patients to AIS events and worsens clinical

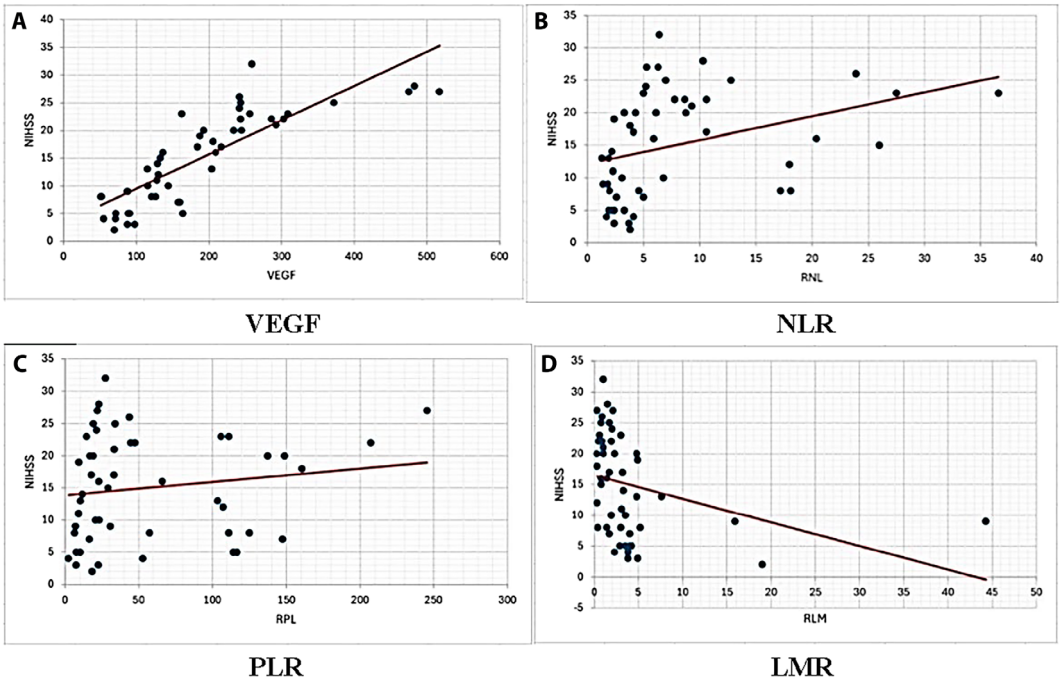

Figure 1. Graph of the relationship between serum VEGF levels (a); NLR (b); PLR (c); LMR (d) and the severity of AIS patients.

outcomes. In addition to risk factors, the distribution of NIHSS scores in this study, covering mild to severe degrees, shows the diversity of patients' clinical conditions. This is important as it shows the association of angiogenic (VEGF) and inflammatory (NLR, PLR, LMR) biomarkers with stroke severity in a broader spectrum (17). VEGF and NLR were shown to have significant associations with severity, illustrating the role of inflammatory and angiogenic mechanisms in exacerbating stroke brain damage (18). In contrast, PLR and LMR showed no significant association, suggesting that not all inflammatory markers have the same predictive value. These findings confirm the importance of understanding the distribution of patient characteristics to assess the validity of biomarker associations with AIS severity.

This study showed that serum VEGF levels increased significantly with increasing severity of AIS based on NIHSS score ($p<0.000$), triggered by hypoxia through activation of HIF-1α, which stimulates angiogenesis and tissue repair. However, in severe stroke, high VEGF levels also reflect extensive damage and potentially exacerbate cerebral edema due to increased vascular permeability, so that VEGF can be considered as a prognosis biomarker as well as a potential therapeutic target (19). In addition, NLR and LMR were shown to be significantly associated with stroke severity, where high NLR reflects the dominance of systemic inflammatory response and low LMR signifies the dominance of proinflammatory monocytes that aggravate blood-brain barrier damage. At the same time, PLR, although it tends to increase in severe stroke, did not show a statistically significant association, possibly due to sample limitation and confounding factors, thus NLR and LMR can be considered as potential hematological biomarkers in assessing the severity of acute ischemic stroke. At the same time, PLR still requires further studies for validation. The results of this study showed that serum VEGF levels were significantly associated with the severity of acute ischemic stroke, with a strong correlation ($r = 0.831$; $p = 0.000$), where increased VEGF was found in patients with higher NIHSS scores, reflecting activation of the hypoxic pathway via hypoxia-inducible factor 1α (HIF-1α) that stimulates angiogenesis, but at high levels also potentially increases vascular permeability and cerebral edema, thus associated with more

severe stroke. In addition, the NLR showed a significant moderate positive correlation (r=0.548; p=0.000), confirming its role as a simple inflammatory biomarker that may reflect the degree of systemic inflammation in the acute phase of stroke. In contrast, PLR showed only a weak positive correlation (r = 0.228; p = 0.112) that was not statistically significant, making it unreliable as a marker of stroke severity. Meanwhile, the LMR showed a significant moderate negative correlation (r = -0.549; p = 0.000), indicating that higher LMR values were associated with lower NIHSS scores and milder stroke severity, in accordance with the concept that the balance between lymphocyte protective immunity and monocyte proinflammatory responses affects the degree of brain damage. These findings reinforce the potential of VEGF, NLR, and LMR as important biomarkers in assessing the severity of acute ischemic stroke, whereas PLR has predictive limitations. The results of regression analysis in this study showed that VEGF levels and NLR were significantly associated with NIHSS score, confirming that both biomarkers play an important role in determining the severity of acute ischemic stroke, where elevated VEGF in addition to supporting angiogenesis also reflects vascular damage and cerebral edema, while high NLR illustrates the predominance of inflammatory responses that exacerbate brain damage; In contrast, PLR and LMR showed no significant association, signifying not all inflammatory biomarkers have the same prognostic value, and simultaneously the regression model with VEGF, NLR, PLR, and LMR contributed 73.5% in explaining the variation of NIHSS score, thus confirming that the combination of angiogenic and inflammatory factors can be a meaningful clinical risk stratification tool. This study has advantages in the form of topic relevance, comprehensive biomarker analysis, and patient-based data that reflect real conditions, but also has limitations in the form of limited sample size, cross-sectional design that only shows associative relationships, potential bias from confounding factors such as infection or comorbidity, and does not evaluate long-term outcomes, so further research is needed with larger samples, longitudinal designs, and tighter variable control to strengthen scientific evidence and support the clinical application of VEGF and NLR biomarkers as predictors of AIS prognosis.

Conclusions

This study concludes that serum VEGF levels and NLR were shown to be significantly associated with the severity of AIS based on the NIHSS score, so they can be considered as clinically valuable prognostic biomarkers, while PLR and LMR showed no significant association. These findings confirm the importance of the combination of angiogenic and inflammatory factors in assessing the condition of patients in the acute phase of stroke, while opening up opportunities for the development of more targeted diagnosis and therapy strategies in the future.

Ethic Approval: All research designs were reviewed and approved by the Health Research Ethics Committee of Dr Wahidin Sudirohusodo Hospital, Faculty of Medicine, Hasanuddin University (601/UN4.6.4.5.31/PP36/2025) on August 20, 2025.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: MYA, MA, AKB, MNM (Concept, Design, Supervision, Resources, Materials, Data Collection and Processing, Analysis and Interpretation, Literature Search, Writing Manuscript), UA, MYA, DAN (Concept, Design, Analysis and Interpretation, Literature Search, Writing Manuscript). All authors read and approved the final version of the manuscript.

Declaration on the Use of AI: None.

Consent for Publication: All subjects have provided consent for publication.

Acknowledgments: The authors would like to express their sincere gratitude to Dr. Wahidin Sudirohusodo Hospital and its network hospitals in Makassar for providing the facilities and support

required for this study. We also thank all the medical staff and colleagues in the Department of Neurology for their valuable assistance during patient recruitment and data collection. Our deepest appreciation goes to the patients and their families for their participation and cooperation, without whom this research would not have been possible.

Funding: This research received no external funding.

Data Availability Statement: All the data are available from the corresponding author upon a reasonable request (MYA).

Abbreviations

NCDs: Non-communicable diseases
AIS: Acute ischemic stroke
VEGF: Vascular Endothelial Growth Factor
NLR: Neutrophil-to-lymphocyte ratio
PLR: Platelet-to-lymphocyte ratio
LMR: Lymphocyte-to-monocyte ratio
BBB: Blood-brain barrier
MMP-9: Matrix metalloproteinase-9
IL-1β: Interleukin-1β
TNF-α: Tumor necrosis factor-α
CT: Computed tomography
NIHSS: National Institutes of Health Stroke Scale
HUMRC: Hasanuddin University Medical Research Center
ELISA: Enzyme-linked immunosorbent assay
HIF-1α: Hypoxia-inducible factor 1α

References

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 2021;20(10):795-820. doi:10.1016/S1474-4422(21)00252-0
2. Barthels D, Das H. Current advances in ischemic stroke research and therapies. Biochim Biophys Acta Mol Basis Dis. 2020;1866(4):165260. doi:10.1016/j.bbadis.2018.09.012
3. Coupland AP, Thapar A, Qureshi MI, Jenkins H, Davies AH. The definition of stroke. J R Soc Med. 2017;110(1):9-12. doi:10.1177/0141076816680121
4. Rehman S, Nadeem A, Akram U, et al. Molecular Mechanisms of Ischemic Stroke: A Review Integrating Clinical Imaging and Therapeutic Perspectives. Biomedicines. 2024;12(4):812. Published 2024 Apr 7. doi:10.3390/biomedicines12040812
5. Bernhardt J, Hayward KS, Kwakkel G, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce. Int J Stroke. 2017;12(5):444-50. doi:10.1177/1747493017711816
6. Rust R. Insights into the dual role of angiogenesis following stroke. J Cereb Blood Flow Metab. 2020;40(6):1167-1171. doi:10.1177/0271678X20906815
7. Bates DO. Vascular endothelial growth factors and vascular permeability. Cardiovasc Res. 2010;87(2):262-71. doi:10.1093/cvr/cvq105
8. Li W, Hou M, Ding Z, Liu X, Shao Y, Li X. Prognostic Value of Neutrophil-to-Lymphocyte Ratio in Stroke: A Systematic Review and Meta-Analysis. Front Neurol. 2021;12:686983. Published 2021 Sep 24. doi:10.3389/fneur.2021.686983
9. Lee SH, Jang MU, Kim Y, et al. The Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios Predict Reperfusion and Prognosis after Endovascular Treatment of Acute Ischemic Stroke. J Pers Med. 2021;11(8):696. Published 2021 Jul 22. doi:10.3390/jpm11080696
10. Ren H, Han L, Liu H, Wang L, Liu X, Gao Y. Decreased Lymphocyte-to-Monocyte Ratio Predicts Poor Prognosis of Acute Ischemic Stroke Treated with Thrombolysis. Med Sci Monit. 2017;23:5826-33. Published 2017 Dec 8. doi:10.12659/msm.907919
11. Hu X, De Silva TM, Chen J, Faraci FM. Cerebral Vascular Disease and Neurovascular Injury in Ischemic Stroke. Circ Res. 2017;120(3):449-71. doi:10.1161/CIRCRESAHA.116.308427
12. Jiang M, Ma C, Li H, et al. Sex Dimorphisms in Ischemic Stroke: From Experimental Studies to Clinic. Front Neurol. 2020;11:504. Published 2020 Jun 19. doi:10.3389/fneur.2020.00504
13. Wnuk M, Drabik L, Derbisz J, Słowik A. Prognostic significance of age in patients with acute ischaemic stroke treated with intravenous thrombolysis. Neurol Neurochir Pol. 2022;56(1):81-8. doi:10.5603/PJNNS.a2022.0010
14. Matsuo R, Ago T, Kiyuna F, et al. Smoking Status and Functional Outcomes After Acute Ischemic Stroke. Stroke. 2020;51(3):846-52. doi:10.1161/STROKEAHA.119.027230
15. GBD 2021 Stroke Risk Factor Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Neurol. 2024;23(10):973-1003. doi:10.1016/S1474-4422(24)00369-7
16. Mosenzon O, Cheng AY, Rabinstein AA, Sacco S. Diabetes and Stroke: What Are the Connections?. J Stroke. 2023;25(1):26-38. doi:10.5853/jos.2022.02306
17. Kim MS, Heo MY, Joo HJ, et al. Neutrophil-to-Lymphocyte Ratio as a Predictor of Short-Term Functional

Outcomes in Acute Ischemic Stroke Patients. Int J Environ Res Public Health. 2023;20(2):898. Published 2023 Jan 4. doi:10.3390/ijerph20020898

18. Escudero C, Acurio J, López E, et al. Vascular endothelial growth factor and poor prognosis after ischaemic stroke. Eur J Neurol. 2021;28(5):1759-64. doi:10.1111/ene.14641
19. Bhasin A, Srivastava MVP, Vivekanandhan S, et al. Vascular Endothelial Growth Factor as Predictive Biomarker for Stroke Severity and Outcome; An Evaluation of a New Clinical Module in Acute Ischemic Stroke. Neurol India. 2019;67(5):1280-85. doi:10.4103/0028-3886.271241

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Received: 3 September 2025
Accepted: 3 October 2025
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