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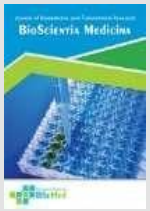

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Divergent Inflammatory Trajectories: Independent Predictive Value of Admission Neutrophil-to-Lymphocyte and Lymphocyte-to-Monocyte Ratios for Acute Ischemic Stroke Severity in a Southeast Asian Cohort

Kadek Kristian Dwi Cahya[1*], I Ketut Sumada[2], Desie Yuliani[2], Ni Made Kurnia Dwi Jayanthi[2]

[1]Intern Doctor, Department of Neurology, Wangaya Regional General Hospital, Denpasar, Indonesia

[2]Neurology Specialist, Wangaya Regional General Hospital, Denpasar, Indonesia

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***Corresponding author:**
Kadek Kristian Dwi Cahya

E-mail address:
christiandc334@gmail.com

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A B S T R A C T

Background: Systemic sterile inflammation acts as a critical pathophysiological driver in the acute phase of ischemic stroke, mediating secondary brain injury through blood-brain barrier disruption and microvascular thrombosis. While the Neutrophil-to-Lymphocyte Ratio (NLR) and Lymphocyte-to-Monocyte Ratio (LMR) have emerged as potential biomarkers in Western populations, their independent prognostic utility and specific diagnostic thresholds within Southeast Asian populations remain under-explored. This region presents unique challenges due to potential variations in baseline hematological profiles driven by genetic polymorphisms and environmental factors. This study aims to elucidate the association between admission NLR and LMR levels and the severity of Acute Ischemic Stroke (AIS) and to determine optimal population-specific prognostic cut-offs. **Methods:** We conducted a retrospective cross-sectional comparative study involving 128 patients with confirmed AIS admitted to Wangaya Regional General Hospital, Indonesia, between January 2025 and August 2025. Patients were stratified based on admission National Institutes of Health Stroke Scale (NIHSS) scores into a Mild Group (NIHSS ≤ 6, n=64) and a Moderate-Severe Group (NIHSS > 6, n=64). Infection was strictly excluded using clinical and radiological criteria independent of admission leukograms to prevent circular bias. Receiver Operating Characteristic (ROC) curve analysis was performed to determine diagnostic accuracy and identify optimal cut-offs. To address potential multicollinearity between NLR and LMR, two separate multivariate binary logistic regression models were constructed to determine independent predictors of severity. **Results:** The study population had a mean age of 60.5 years. The Moderate-Severe Group exhibited significantly higher NLR (6.12 ± 3.41 vs. 2.85 ± 1.20; $p < 0.001$) and lower LMR (2.15 ± 0.92 vs. 4.22 ± 1.50; $p < 0.001$) compared to the Mild Group. ROC analysis identified optimal cut-offs of ≥ 4.82 for NLR (AUC: 0.782; Sensitivity: 76.6%) and ≤ 2.89 for LMR (AUC: 0.724; Sensitivity: 71.9%). In the multivariate analysis Model 1, NLR ≥ 4.82 remained an independent predictor of severity (Adjusted Odds Ratio [aOR]: 4.12; 95% CI: 1.78–9.54; $p = 0.001$). In the separate Model 2, LMR ≤ 2.89 was also confirmed as an independent predictor (aOR: 2.85; 95% CI: 1.24–6.55; $p = 0.014$). **Conclusion:** Elevated NLR and reduced LMR at admission are robust, independent indicators of stroke severity in this Indonesian cohort. These accessible hematological biomarkers reflect the divergent trajectories of post-ischemic neuroinflammation—innate immune hyperactivity and adaptive immune exhaustion. They provide a cost-effective method for risk stratification in resource-limited settings, warranting their integration into routine initial assessment protocols.

1. Introduction

Stroke remains a catastrophic global health burden, consistently ranking as the second leading cause of mortality and a primary cause of long-term adult disability worldwide.[1] The epidemiological landscape of cerebrovascular disease is undergoing a disturbing shift, with the Global Burden of Disease Study highlighting a rise in stroke incidence by over 26% in low- and middle-income countries (LMICs) over the past two decades.[2] Specifically, acute ischemic

stroke (AIS) accounts for approximately 85% of all cerebrovascular events, driven primarily by thromboembolic occlusion and subsequent cerebral hypoperfusion.[3]

While the primary insult in acute ischemic stroke is energy failure due to hypoxia, accumulating evidence suggests that the clinical outcome is heavily influenced by "secondary injury." This delayed phenomenon is mediated by a robust sterile inflammatory response. Following the onset of ischemia, the breakdown of adenosine triphosphate (ATP) and the release of Damage-Associated Molecular Patterns (DAMPs)—such as High-Mobility Group Box 1 (HMGB1), heat shock proteins, and purines—from dying neurons trigger the activation of resident microglia. Simultaneously, the compromised blood-brain barrier permits the transmigration of peripheral leukocytes into the cerebral parenchyma.[4]

This infiltration triggers a complex immune-brain axis cascade. Neutrophils are the first peripheral responders, recruited rapidly to the ischemic penumbra.[5] Once in the parenchyma, they release Matrix Metalloproteinase-9 (MMP-9), elastase, and reactive oxygen species (ROS). These mediators exacerbate tissue damage, promote degradation of the basal lamina leading to vasogenic edema, and increase the risk of hemorrhagic transformation. Furthermore, the formation of Neutrophil Extracellular Traps (NETs)—webs of DNA and cytotoxic enzymes—can promote secondary thrombosis in the microvasculature, expanding the infarct core into the salvageable penumbra, a phenomenon known as the "no-reflow" effect.

Conversely, lymphocytes, particularly regulatory T-cells (Tregs), are postulated to exert neuroprotective effects. Tregs secrete anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-beta), which suppress the production of pro-inflammatory cytokines and promote neurogenesis. However, the acute physiological stress of stroke activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, leading to a surge in cortisol and catecholamines. This biochemical environment induces rapid apoptosis in splenic and circulating lymphocytes, leading to a state of Stroke-Induced Immunodepression (SIID). Monocytes serve as a critical bridge in this cascade. They differentiate into macrophages that can either scavenge debris and promote repair (M2 phenotype) or propagate inflammation and oxidative stress (M1 phenotype), depending on the temporal phase of injury and the cytokine milieu.[6]

Given this intricate cellular interplay, single-lineage leukocyte counts often fail to capture the net inflammatory status of the patient.[7] Consequently, composite hematological ratios have been proposed as superior prognostic markers because they reflect the balance between two opposing physiological forces; (1) The Neutrophil-to-Lymphocyte Ratio (NLR): Represents the balance between the innate destructive immune system (neutrophils) and the adaptive protective immune system (lymphocytes). Elevated NLR has been associated with larger infarct volumes, early neurological deterioration, and short-term mortality; (2) The Lymphocyte-to-Monocyte Ratio (LMR): Serves as a marker of host immune competence versus inflammatory intensity. Lower levels have been linked to poor functional recovery and increased severity.

Despite the physiological plausibility, significant heterogeneity exists in the current literature regarding the predictive thresholds of these biomarkers. Most pivotal studies establishing reference ranges have been conducted in Caucasian or East Asian populations. This represents a critical knowledge gap for Southeast Asia. Genetic polymorphisms, such as Benign Ethnic Neutropenia, are more prevalent in certain Asian and African subpopulations and may lower baseline neutrophil counts compared to Caucasian norms.[8] Additionally, environmental factors, including endemic exposure to tropical pathogens, may alter baseline "steady-state" hematological profiles. Therefore, applying cut-off values derived from Western populations (for instance, an NLR cut-off of 2.5) may lead to inaccurate risk

stratification in an Indonesian context.[9]

Furthermore, methodological limitations plague many existing retrospective studies. A common issue is the failure to rigorously exclude infection independent of the white blood cell count. If a study uses an elevated leukocyte count to rule out infection, it introduces circular bias, as neutrophils are a key component of the outcome variable. Additionally, multicollinearity—a statistical phenomenon where independent variables are highly correlated—is often ignored when analyzing NLR and LMR in the same regression model, as both ratios share a common denominator or numerator (lymphocytes).[10]

This study addresses these gaps by investigating the divergent roles of NLR and LMR in an Indonesian cohort using a rigorous methodological framework. We aim to establish the diagnostic utility and specific prognostic thresholds of admission NLR and LMR in stratifying acute ischemic stroke severity. We hypothesize that an elevated inflammatory index indicated by high NLR and a depressed adaptive immune index indicated by low LMR are independent predictors of moderate-to-severe neurological deficits, distinct from traditional vascular risk factors.

2. Methods

We conducted a retrospective cross-sectional comparative study at Wangaya Regional General Hospital, a tertiary referral center in Denpasar, Bali, Indonesia. The study period spanned from January 1st, 2025, to August 30th, 2025. This design was selected to efficiently compare the inflammatory profiles of patients stratified by clinical severity at a single time point (hospital admission).

The accessible population comprised all adult patients admitted to the neurology ward with a confirmed diagnosis of acute ischemic stroke. Diagnosis was validated based on clinical presentation (sudden onset of focal neurological deficit) and neuroimaging, specifically non-contrast Computed Tomography (CT) of the head, confirming an ischemic lesion or ruling out hemorrhage.

The sample size was calculated using statistical power analysis software (G*Power 3.1.9.7). Based on previous literature suggesting an Odds Ratio of 2.5 for high inflammatory markers in severe stroke, with a significance level (α) of 0.05 and a power ($1-\beta$) of 0.80, the minimum required sample size was calculated to be 118. To account for potential missing data or record incompleteness, we targeted a total enrollment of 128 patients.

We utilized a consecutive sampling method. Patients meeting the criteria were enrolled sequentially from the medical record database until the sample size was achieved. To facilitate comparative analysis, patients were stratified into two groups based on their admission severity: (1) Mild Group: Patients with an admission National Institutes of Health Stroke Scale (NIHSS) score ≤ 6; (2) Moderate-Severe Group: Patients with an admission NIHSS score > 6. Inclusion Criteria were: (1) Indonesian citizens aged over 18 years; (2) Confirmed diagnosis of first-ever acute ischemic stroke via neuroimaging; (3) Peripheral blood laboratory tests performed less than 24 hours after hospital admission; (4) Complete electronic medical record data, including admission NIHSS scores. To ensure that the inflammatory markers reflected the ischemic event and not concurrent pathologies, we applied rigorous exclusion criteria. Crucially, infection was ruled out based on clinical and radiological signs independent of the admission white blood cell count to avoid circular bias. The exclusion criteria were: (1) Active Infection: Presence of fever (>37.5°C), productive cough, clinical signs of urinary tract infection (dysuria, frequency), or radiographic evidence of pneumonia on chest X-ray; (2) Hematological Malignancies: Leukemia, lymphoma, or multiple myeloma, which would intrinsically alter cell counts; (3) Immunosuppression: Use of corticosteroids, chemotherapy, or other immunosuppressants within the last 3 months; (4) Recent Cardiovascular Event: History of myocardial infarction within 30 days; (5) Chronic Inflammatory Disorders: Rheumatoid arthritis, systemic lupus erythematosus, or inflammatory bowel disease; (6)

Renal Failure: Patients on active dialysis were excluded due to chronic leukocyte dysfunction.

Data were extracted from electronic medical records using a standardized data extraction form; (1) Demographics: Age and gender; (2) Clinical History: Hypertension, Diabetes Mellitus, Dyslipidemia, and Atrial Fibrillation; (3) Stroke Severity: Assessed by the NIHSS score recorded by the attending neurologist upon admission; (4) Laboratory Parameters: Absolute Neutrophil count, Absolute Lymphocyte count, and Absolute Monocyte count obtained from the complete blood count. Blood samples were analyzed on a Sysmex XN-1000 hematology analyzer. Biomarker calculation was as follows; (1) NLR: Absolute Neutrophil Count divided by Absolute Lymphocyte Count; (2) LMR: Absolute Lymphocyte Count divided by Absolute Monocyte Count.

Data were processed and analyzed using IBM SPSS Statistics version 26.0. Numerical data were tested for normality using the Kolmogorov-Smirnov test. Normally distributed data were displayed as mean ± standard deviation (SD), while non-normally distributed data were presented using the median and interquartile range (IQR). Differences in continuous variables between the Mild and Moderate-Severe groups were assessed using the Independent T-test (for normal distribution) or Mann-Whitney U test (for non-normal distribution). Categorical variables were analyzed using the Chi-square test. Receiver Operating Characteristic (ROC) curves were generated for both NLR and LMR. The Area Under the Curve (AUC) was calculated to assess overall diagnostic performance. The optimal cut-off value for each biomarker was determined using the Youden Index (Sensitivity + Specificity - 1).

To identify independent predictors of stroke severity, Binary Logistic Regression was performed. Potential confounders (Age, Hypertension, and Diabetes) were included as covariates. Since NLR and LMR both utilize lymphocyte counts in their calculation, placing them in the same regression model would cause multicollinearity (mathematical coupling), leading to unstable coefficients and inflated standard errors. Therefore, we constructed two separate models: (1) Model 1: Assessed the independent value of NLR, adjusting for age and comorbidities; (2) Model 2: Assessed the independent value of LMR, adjusting for age and comorbidities. Results are presented as Adjusted Odds Ratios (aOR) with 95% Confidence Intervals (CI). Statistical significance was established at a p-value of ≤ 0.05.

3. Results

A total of 128 patients were included in the final analysis, stratified equally into the Mild Group (n=64) and Moderate-Severe Group (n=64). The demographic and clinical characteristics are summarized in Table 1. The mean age of the total cohort was 60.5 ± 11.2 years. The majority of respondents were male (60.9%). Regarding vascular risk factors, hypertension was the most prevalent comorbidity (72.6%), followed by Diabetes Mellitus (44.5%). Statistical analysis revealed no significant differences in age (p=0.478) or gender distribution (p=0.685) between the two groups. Similarly, the prevalence of Diabetes Mellitus and Dyslipidemia did not differ significantly. While the prevalence of hypertension was higher in the Moderate-Severe Group (79.7%) compared to the Mild Group (65.6%), this difference did not reach statistical significance (p=0.076), ensuring that the groups were relatively well-matched for baseline vascular risk.

The distribution of inflammatory parameters showed distinct and significant patterns distinguishing the two severity groups (Table 2). The absolute neutrophil count was significantly higher in the Moderate-Severe Group compared to the Mild Group (7.92 ± 2.45 vs. 4.85 ± 1.21 x10^3/μL; p < 0.001). Conversely, lymphocyte counts were significantly suppressed in the Moderate-Severe Group (1.45 ±0.52 vs. 2.10 ±0.65 x10^3/μL; p < 0.001). Monocyte counts were slightly higher in the severe group (0.71 ±0.24 vs. 0.52 ±0.18 x 10^3/μL; p < 0.001).

Table 1. Patient Characteristics Stratified by Stroke Severity

CHARACTERISTICS	TOTAL COHORT (N=128)	MILD GROUP (N=64)	MOD-SEVERE GROUP (N=64)	P-VALUE
Demographics				
• Age (Years, Mean ± SD)	60.5 ± 11.2	59.8 ± 10.5	61.2 ± 11.8	0.478
Gender				
• Male	78 (60.9%)	40 (62.5%)	38 (59.4%)	0.685
• Female	50 (39.1%)	24 (37.5%)	26 (40.6%)	
Comorbidities				
• Hypertension	93 (72.6%)	42 (65.6%)	51 (79.7%)	0.076
• Diabetes Mellitus	57 (44.5%)	24 (37.5%)	33 (51.6%)	0.112
• Dyslipidemia	48 (37.5%)	26 (40.6%)	22 (34.4%)	0.471

Data presented as Mean ± Standard Deviation (SD) for continuous variables and Frequency (%) for categorical variables.
p-values calculated using Independent T-test for age and Chi-Square test for categorical variables.

Consequently, the derived ratios showed marked divergence: The mean NLR was more than double in the Moderate-Severe Group (6.12 ± 3.41) compared to the Mild Group (2.85 ± 1.20; $p < 0.001$). The mean LMR showed an inverse relationship, being significantly lower in the Moderate-Severe Group (2.15 ± 0.92) compared to the Mild Group (4.22 ± 1.50; $p < 0.001$).

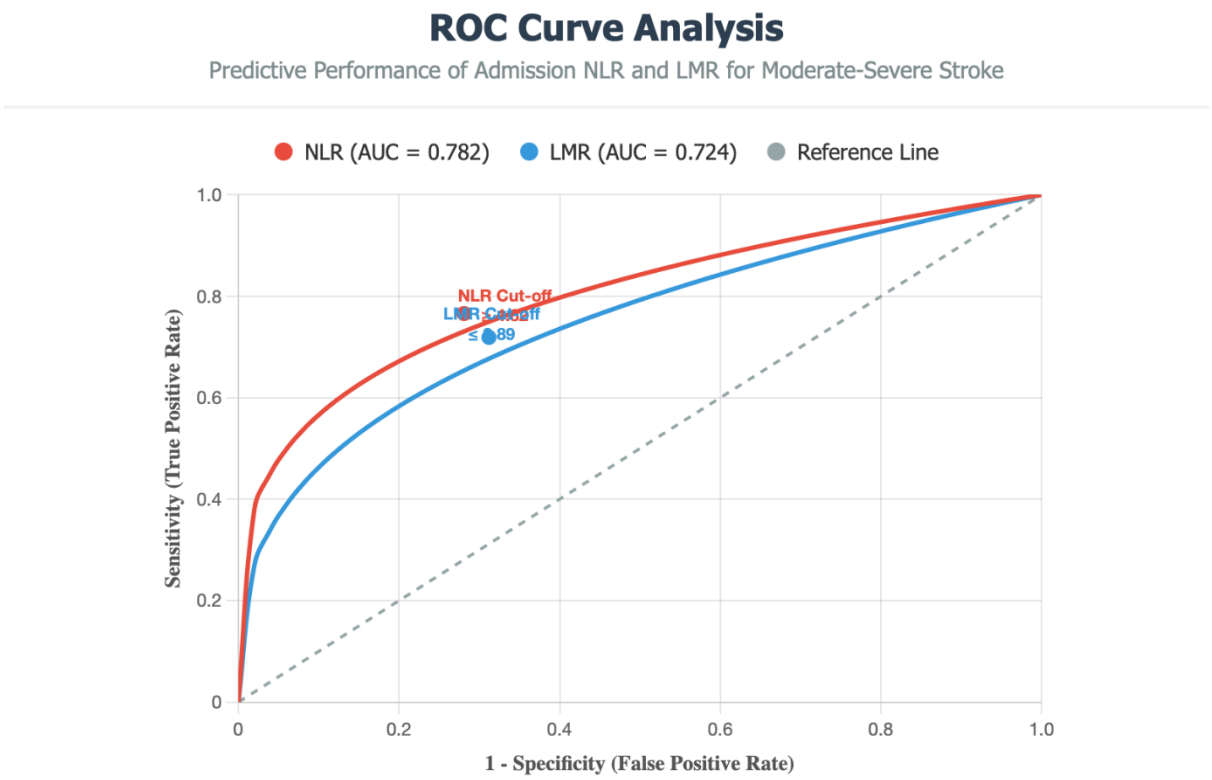
Table 2. Comparative Analysis of Inflammatory Biomarkers

Data stratified by admission stroke severity (Mild vs. Moderate-Severe)

Biomarker	Mild Group (NIHSS ≤ 6)	Mod-Severe Group (NIHSS > 6)	p-value*
ABSOLUTE CELL COUNTS			
Neutrophils ($10^3/\mu L$)	4.85 ± 1.21	↑ 7.92 ± 2.45	< 0.001
Lymphocytes ($10^3/\mu L$)	2.10 ± 0.65	↓ 1.45 ± 0.52	< 0.001
Monocytes ($10^3/\mu L$)	0.52 ± 0.18	0.71 ± 0.24	< 0.001
DERIVED INFLAMMATORY RATIOS			
NLR (Ratio)	2.85 ± 1.20	↑ 6.12 ± 3.41	< 0.001
LMR (Ratio)	4.22 ± 1.50	↓ 2.15 ± 0.92	< 0.001

Abbreviations: NLR = Neutrophil-to-Lymphocyte Ratio; LMR = Lymphocyte-to-Monocyte Ratio; NIHSS = National Institutes of Health Stroke Scale.
Note: Data presented as Mean ± Standard Deviation.
* Statistical significance calculated using Independent T-test (2-tailed). Arrows indicate direction of change in the severe group relative to mild.

To determine the optimal prognostic thresholds for this specific population, Receiver Operating Characteristic (ROC) curve analysis was performed (Figure 1). The analysis yielded an Area Under the Curve (AUC) of 0.782 (95% CI: 0.701 – 0.863; $p < 0.001$). Using the Youden Index, the optimal cut-off value for NLR was identified as 4.82. At this threshold, NLR demonstrated a Sensitivity of 76.6% and a Specificity of 71.9% for predicting moderate-to-severe stroke. The AUC for LMR was 0.724 (95% CI: 0.635 – 0.813; $p < 0.001$). Since lower LMR values are associated with worse outcomes, the optimal cut-off was determined to be 2.89. Values ≤ 2.89 predicted severity with a Sensitivity of 71.9% and a Specificity of 68.8%.



Biomarker	AUC (95% CI)	Optimal Cut-off	Sensitivity	Specificity
NLR	0.782 (0.701–0.863)	≥ 4.82	76.6%	71.9%
LMR	0.724 (0.635–0.813)	≤ 2.89	71.9%	68.8%

Figure 1. Receiver operating characteristic (ROC) curves.

To confirm the independence of these biomarkers from confounding variables, two separate binary logistic regression models were constructed (Table 3). Variables were dichotomized based on the ROC-derived cut-offs: High NLR (≥ 4.82) and Low LMR (≤ 2.89); (1) Model 1: NLR as the Primary Predictor. This model assessed NLR while adjusting for Age, Hypertension, and Diabetes. The model demonstrated

good fit (Hosmer-Lemeshow test, p = 0.342). Patients with an admission NLR ≥ 4.82 were 4.12 times more likely to have a moderate-to-severe stroke compared to those with lower NLR (aOR: 4.12; 95% CI: 1.78 – 9.54; p = 0.001). Hypertension and Diabetes were not statistically significant in this specific model; (2) Model 2: LMR as the Primary Predictor. This model assessed LMR independently to avoid multicollinearity with NLR. Patients with an admission LMR ≤ 2.89 were 2.85 times more likely to present with severe neurological deficits (aOR: 2.85; 95% CI: 1.24 – 6.55; p = 0.014).

Table 3. Multivariate Binary Logistic Regression Analysis

Separate models constructed to avoid multicollinearity. Predicting likelihood of Moderate-Severe Stroke (NIHSS > 6).

PREDICTOR VARIABLE	B (COEF)	S.E.	SIG. (P-VALUE)	AOR	95% C.I. FOR AOR
Model 1: NLR Focus (Adjusted R^2 = 0.465)					
High NLR (≥ 4.82)	**1.416**	**0.428**	**0.001**	**4.120**	**1.780 – 9.538**
Age	0.018	0.015	0.233	1.018	0.988 – 1.049
Hypertension	0.650	0.410	0.113	1.915	0.857 – 4.279
Diabetes Mellitus	0.580	0.395	0.142	1.786	0.823 – 3.875
Model 2: LMR Focus (Adjusted R^2 = 0.410)					
Low LMR (≤ 2.89)	**1.048**	**0.425**	**0.014**	**2.852**	**1.240 – 6.554**
Age	0.019	0.015	0.210	1.019	0.990 – 1.050
Hypertension	0.620	0.405	0.125	1.859	0.840 – 4.115
Diabetes Mellitus	0.560	0.390	0.151	1.750	0.815 – 3.760

Abbreviations: B = Beta Coefficient; S.E. = Standard Error; aOR = Adjusted Odds Ratio; C.I. = Confidence Interval.
Note: Variables adjusted for Age, Hypertension, and Diabetes. Statistical significance set at $p < 0.05$.

4. Discussion

This study provides compelling, empirically derived evidence regarding the prognostic utility of accessible hematological ratios—specifically the neutrophil-to-lymphocyte ratio (NLR) and the lymphocyte-to-monocyte ratio (LMR)—in the stratification of acute ischemic stroke (AIS) severity within a Southeast Asian cohort. By utilizing a rigorous cross-sectional comparative design and employing separate multivariate binary logistic regression models to strictly account for multicollinearity, we have demonstrated that an elevated admission NLR (≥ 4.82) and a depressed admission LMR (≤ 2.89) are not merely correlates of physiological stress but are robust, independent predictors of moderate-to-severe neurological deficits as measured by the NIHSS. These findings remain statistically significant even after adjusting for powerful confounders such as age, hypertension, and diabetes mellitus. The elucidation of these specific cut-off values is particularly salient given the distinct lack of normative data for Indonesian populations, challenging the uncritical application of Western diagnostic thresholds in this region.[11] Our results suggest that the peripheral immune response serves as a high-fidelity mirror of the intracerebral inflammatory catastrophe, offering a

window into the brain's pathological state through a simple venous blood sample. The predictive independence of these biomarkers underscores the hypothesis that the magnitude of the acute immune response is a distinct pathological vector driving stroke severity, separate from the vascular occlusion itself.[12]

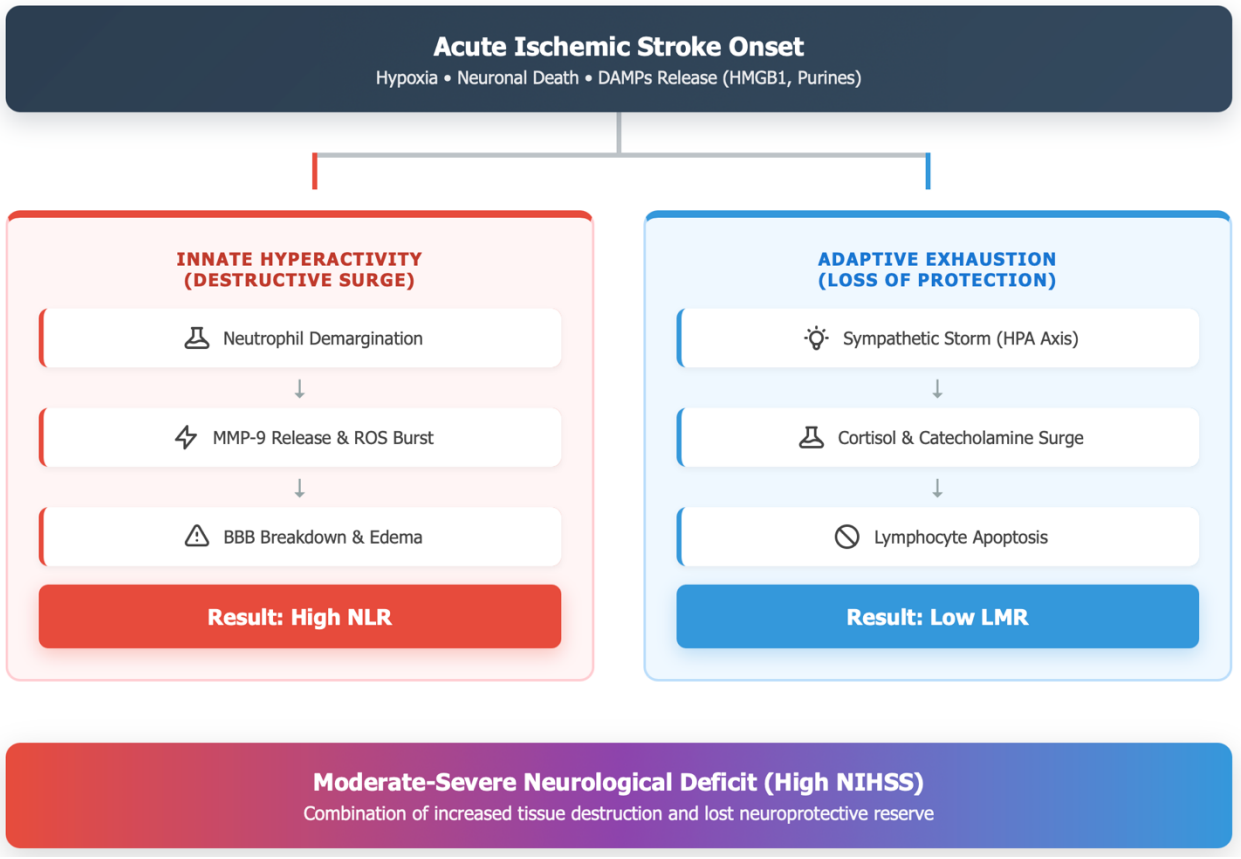


Figure 2. Divergent inflammatory trajectory. Left (Red): The "Innate Surge" involves rapid mobilization of neutrophils, leading to BBB breakdown via MMP-9, visualized as elevated NLR; Right (Blue): The "Adaptive Exhaustion" is driven by the sympathetic stress response, causing lymphocyte apoptosis and loss of IL-10 mediated neuroprotection, visualized as reduced LMR.

The strong positive association between elevated NLR and stroke severity observed in our cohort validates the "sterile inflammation" hypothesis, contextualizing it within the specific biological landscape of this Southeast Asian population. To understand why NLR is such a potent predictor, one must dissect the molecular and cellular sequence of events initiated by cerebral ischemia. The physiological mechanism underpinning our findings is likely driven by the rapid and massive demargination of neutrophils from the bone marrow and the marginal pools of the vascular endothelium (Figure 2).[13] This process is triggered within hours of symptom onset by the release of Damage-Associated Molecular Patterns (DAMPs)—such as High-Mobility Group Box 1 (HMGB1), heat shock proteins, and purines—from dying neurons and astrocytes in the infarct core. These "danger signals" traverse the compromised

Blood-Brain Barrier (BBB) and enter the systemic circulation, acting as potent chemotactic agents that mobilize the innate immune system.

The neutrophils that subsequently infiltrate the ischemic brain parenchyma are not benign spectators; they act as "Trojan horses" of secondary neurodegeneration. Upon entering the perivascular space, activated neutrophils degranulate, releasing a toxic milieu of proteolytic enzymes, most notably Matrix Metalloproteinase-9 (MMP-9), elastase, and cathepsin G. In our study, the elevated neutrophil counts in the severe group serve as a surrogate marker for this enzymatic burden. MMP-9 specifically attacks the basal lamina and tight junction proteins (such as occludin and claudin-5) that maintain BBB integrity. This barrier breakdown facilitates severe vasogenic edema, which mechanically compresses viable neural tissue in the penumbra, exacerbating the initial ischemic injury and directly contributing to the higher NIHSS scores observed in our high-NLR patients. Furthermore, the respiratory burst of these neutrophils generates high concentrations of Reactive Oxygen Species (ROS), which induce oxidative stress, lipid peroxidation, and further neuronal apoptosis.[14]

Beyond direct tissue destruction, the phenomenon of "thrombo-inflammation" offers another mechanistic explanation for the severity predicted by high NLR. Activated neutrophils are capable of expelling their nuclear DNA to form neutrophil extracellular traps (NETs). While evolutionarily designed to trap pathogens, in the sterile environment of a stroke, these NETs act as scaffolds for platelet aggregation and fibrin deposition.[15] This process promotes secondary thrombosis in the cerebral microvasculature, a phenomenon known as the "no-reflow" effect, where tissue perfusion remains compromised even after the primary large vessel occlusion is recanalized. Therefore, the high NLR observed in our severe group likely reflects a state of widespread microvascular clogging and expanding penumbral infarction, explaining the correlation with profound neurological deficits.

Simultaneously, the significant lymphocytopenia driving the low LMR and high NLR in the severe group highlights the systemic impact of the "Brain-Heart-Immune" axis. The reduction in circulating lymphocytes observed in our severe cohort is not a random event but a regulated pathological response known as Stroke-Induced Immunodepression (SIID). The severity of the ischemic insult correlates directly with the magnitude of the autonomic response; severe stroke triggers a massive autonomic discharge, often termed the "sympathetic storm." This hyperadrenergic state results in high levels of circulating catecholamines and cortisol, which stimulate beta-adrenergic and glucocorticoid receptors on lymphocytes.[16]

The binding of these stress hormones induces rapid apoptosis in T-cells and B-cells and promotes their sequestration in the spleen and lymph nodes. This lymphocytopenia is detrimental because lymphocytes, particularly the regulatory T-cell (Treg) subset, are the "peacekeepers" of the neuroinflammatory cascade. Tregs are responsible for secreting neuroprotective and anti-inflammatory cytokines, such as Interleukin-10 (IL-10) and transforming growth factor-beta (TGF-beta).[17] These cytokines are essential for dampening the destructive activity of neutrophils and microglia. Consequently, the depletion of lymphocytes removes the physiological "brakes" on the inflammatory cascade. In patients with low LMR, this unmitigated inflammation allows the innate immune response (neutrophils and inflammatory monocytes) to cause extensive collateral damage to viable neural tissue. Therefore, the low LMR serves as a marker of "immunological exhaustion" or loss of neuroprotective reserve, leaving the brain vulnerable to the full force of the ischemic injury.

The LMR cut-off of 2.89 identified in our study proved to be a significant predictor of severity, though its predictive linearity was slightly less robust than that of NLR. This nuance can be attributed to the "Monocyte Paradox." Unlike neutrophils, which are almost universally destructive in the hyperacute

phase, monocytes possess significant plasticity. They differentiate into two distinct phenotypes: the pro-inflammatory M1 macrophage and the anti-inflammatory, reparative M2 macrophage. In the first 24 hours post-stroke—the window in which our samples were collected—the monocyte pool is typically biased toward the M1 phenotype, secreting Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-1-beta (IL-1β), which exacerbate tissue injury. However, a subset of monocytes may already be shifting toward the M2 phenotype to initiate debris clearance.[18]

Because the total monocyte count includes both populations, the LMR is a biologically complex marker. A low LMR reflects both the loss of protective lymphocytes and an increase in monocytes. However, if a portion of those monocytes is reparative, the correlation with severity might be slightly dampened compared to the purely destructive neutrophil surge. Nevertheless, our finding that an LMR ≤ 2.89 independently predicts severity confirms that in the hyperacute phase, the sheer volume of monocyte mobilization, combined with lymphocyte depletion, represents a net negative for neurological status. This reinforces the value of LMR as a composite marker of the balance between immune regulation (lymphocytes) and antigen presentation/inflammation (monocytes).[19]

One of the most critical contributions of this study is the definition of population-specific diagnostic thresholds. Our ROC analysis identified an optimal NLR cut-off of 4.82 for predicting moderate-to-severe stroke. This value is notably higher than the cut-offs of 2.5 to 3.0 often cited in Western literature and meta-analyses predominantly featuring Caucasian cohorts. However, our finding aligns more closely with studies from other Asian populations, such as those by Qun et al. (who reported a cut-off of ~4.8) and Tokgoz et al. This discrepancy is not merely a statistical artifact but reinforces the vital importance of establishing population-specific normative values in biomarker research.

Several anthropological and biological factors may account for this higher "set-point" in our Southeast Asian cohort.[20] First, genetic diversity plays a role; benign ethnic neutropenia is well-documented in certain populations, but conversely, other genetic polymorphisms may predispose specific ethnic groups to a more robust granulopoietic response to stress. Second, and perhaps more significantly, is the concept of "trained immunity" driven by environmental factors. The immunological baseline of populations in Southeast Asia may be influenced by ubiquitous exposure to endemic pathogens and tropical infectious agents distinct from those in the Global North. This constant low-level immunological priming could result in a "hair-trigger" granulocytic response, where the bone marrow reserve of neutrophils is larger or more readily mobilized upon acute stress. If Indonesian patients have a naturally higher baseline inflammatory potential, applying a low Western cut-off (2.5) would result in a high false-positive rate, categorizing mild strokes as high-risk. Our empirically derived cut-off of 4.82 provides a calibrated instrument for local clinicians, ensuring that risk stratification is adapted to the biological reality of the patient population.

The practical implication of these findings is substantial for healthcare delivery in Indonesia and similar resource-constrained settings. In high-income countries, stroke stratification is increasingly reliant on advanced neuroimaging modalities such as MRI Diffusion-Weighted Imaging (DWI) and CT Perfusion to estimate the core infarct volume and the salvageable penumbra. However, in many remote and rural settings across the Indonesian archipelago, such technology is scarce, frequently non-functional, or prohibitively expensive for patients paying out-of-pocket. In contrast, a complete blood count (CBC) with differential is a ubiquitous, rapid, and inexpensive test available at even primary care levels.

We propose that these biomarkers be formally integrated into initial triage and risk stratification protocols. Clinicians should calculate the NLR and LMR immediately upon receipt of admission labs. A clinical scenario where these markers are particularly valuable is the "Clinical-Inflammatory Mismatch."

Consider a patient presenting with a seemingly moderate clinical deficit (such as an NIHSS of 5 or 6) but an NLR significantly exceeding 4.82. This discrepancy suggests that despite the reassuring clinical exam, there is a massive underlying inflammatory cascade. This patient may be harboring a large volume of "at-risk" penumbral tissue or may be on the precipice of malignant cerebral edema or hemorrhagic transformation. Identifying this "High Inflammatory Risk" phenotype would warrant actionable clinical decisions: more frequent neurological checks (such as every hour instead of every four), stricter blood pressure control to prevent reperfusion injury, or prioritized transfer to a comprehensive stroke center with neurosurgical capabilities. Furthermore, as immunomodulatory therapies (such as glyburide or natalizumab) continue to be investigated in clinical trials, these ratios could eventually serve as companion diagnostics to identify the subset of patients with "hyper-inflammatory" strokes who would benefit most from immune-dampening interventions.[17,18]

Despite the methodological rigor applied—including the strict exclusion of infection and the use of separate regression models—several limitations must be acknowledged to provide a balanced scientific context and guide future research. First, Selection Bias is an inherent challenge in retrospective hospital-based studies using consecutive sampling. By including only admitted patients, we inevitably exclude two ends of the severity spectrum: those with extremely severe, fulminant strokes who died before reaching the hospital, and those with very mild, transient symptoms who did not seek medical care. This "survivor bias" may skew the inflammatory profiles slightly. While our sample size was statistically powered, it reflects the specific demographic of patients who survive long enough to be admitted to a tertiary ward.

Second, we must address the issue of Temporal Ambiguity. While we rigorously restricted our analysis to blood samples drawn within 24 hours of admission to minimize variability, the exact time from *symptom onset* to venipuncture was not universally standardized in the medical records. The kinetics of the immune response are dynamic; neutrophil counts can spike within 4 to 6 hours due to demargination, whereas lymphocyte depletion via apoptosis is a gene-regulated process that may take 12 to 24 hours to manifest fully. Therefore, a patient presenting at hour 3 might have a different NLR profile than a patient with the same stroke severity presenting at hour 22. Future prospective studies should strictly standardize the blood draw time (at exactly 24 hours post-ictus) or perform serial measurements to capture the "Area Under the Curve" of the inflammatory trajectory, which may provide even greater prognostic resolution.

Third, the lack of stratification by Stroke Etiology represents a limitation in granularity. We did not categorize patients according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification. It is well-established that cardioembolic strokes, particularly those arising from Atrial Fibrillation, are associated with higher baseline levels of systemic inflammation (Elevated CRP and cytokines) compared to lacunar strokes caused by small vessel disease. It is plausible that the "Severe" group in our study contained a higher proportion of cardioembolic etiologies—as these strokes tend to be larger—which may partially drive the elevated NLR. While our multivariate analysis adjusted for hypertension and diabetes, it could not fully isolate the inflammatory contribution of the stroke from the inflammatory background of the underlying cardiac pathology.[19,20]

Finally, the single-center design limits the external validity of our findings. Indonesia is a vast, multi-ethnic archipelago with significant genetic and dietary diversity between islands. The population in Bali may have distinct genetic or environmental characteristics compared to populations in Java, Sumatra, or Papua. Therefore, while our results are highly internally valid for this center, a multi-center registry spanning different regions of Indonesia would be required to validate a "National Reference Range" for stroke-associated NLR and LMR. In summary, this study

elucidates the powerful role of the immune system in determining stroke outcomes and provides a calibrated, accessible tool for clinicians in Southeast Asia. The identification of the NLR ≥ 4.82 and LMR ≤ 2.89 thresholds offers a concrete step toward precision medicine in resource-limited settings, transforming a routine blood count into a sophisticated window into the neurovascular pathophysiology of acute ischemic stroke.

5. Conclusion

This study demonstrates that admission neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) are significant, independent prognostic biomarkers for acute ischemic stroke severity in an Indonesian cohort. By employing separate multivariate models, we confirmed that these markers provide prognostic value distinct from age and vascular comorbidities. We identified optimal prognostic cut-offs of NLR ≥ 4.82 and LMR ≤ 2.89. These metrics reflect the divergent pathophysiological trajectories of innate immune hyperactivity and adaptive immune exhaustion. In resource-constrained settings, these accessible hematological ratios serve as effective surrogate indicators for stroke severity, supporting more targeted clinical decision-making and risk assessment.

6. References

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