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Platelet-to-Lymphocyte Ratio as a Predictor of Disability Prognosis in Acute Ischemic Stroke Patients at Bethesda Hospital

Platelet-To-Lymphocyte Ratio sebagai Faktor Prediktor Prognosis Disabilitas Pasien Stroke Iskemik Akut di RS Bethesda

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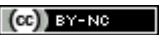
Abstract

Stroke precipitates a neuroinflammatory response. Platelet-to-lymphocyte ratio (PLR) is an inflammatory biomarker conveying plaque adhesion and infarct volume. A high level of PLR is associated with stroke patient's poor clinical outcomes. This study highlights PLR's potential as a predictive biomarker for post-stroke disability. This study aims to measure PLR at admission and to investigate its potential as a predictor for post-stroke disability. A retrospective cohort study was designed with 98 subjects from Bethesda Hospital Yogyakarta. ROC/AUC analyzed PLR to find the optimal cut-off value. Risk factors were analyzed to find the correlation and causality. From 98 patients, the optimal PLR cut-off is 146.86. A significant positive correlation was observed between PLR and modified Rankin Scale (mRS) scores ($p=0.017$), and National Institutes of Health Stroke Scale (NIHSS) scores ($p=0.043$). A significant mean difference in PLR values was also identified between mRS outcomes ($p=0.017$). PLR was a predictor for mRS ($OR=4.051$, $p=0.037$), although it did not predict NIHSS outcomes. The findings indicate that PLR is predictive of post-stroke disability in cases of ischemic stroke. An elevation in PLR suggests a disequilibrium between inflammatory mediators and neuroprotective factors. In conclusion, PLR has the potential as a predictor for post-stroke disability in ischemic stroke.

Keywords: acute ischemic stroke; platelet-to-lymphocyte ratio; stroke patients; stroke disability

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Abstrak

Stroke mengakibatkan respons neuroinflamasi. *Platelet-to-Lymphocyte Ratio* (PLR) adalah biomarker inflamasi yang menunjukkan adhesi plak dan volume infark. Angka PLR yang tinggi berhubungan dengan prognosis stroke iskemik akut yang buruk. Studi ini bertujuan menyoroti potensi PLR sebagai biomarker prediktif untuk disabilitas pasca stroke iskemik. Penelitian ini bertujuan untuk mengukur PLR saat masuk rumah sakit dan mengetahui potensinya sebagai faktor prediktor disabilitas pasca stroke iskemik. Desain dari studi ini adalah kohort retrospektif dengan 98 subjek dari RS Bethesda Yogyakarta. PLR dianalisis dengan ROC/AUC untuk mencari nilai *cut-off* yang optimal. Faktor risiko dianalisis untuk mencari korelasi dan kausalitas. Dari 98 pasien, *cut-off* PLR optimal adalah 146,86. Korelasi positif yang signifikan ditemukan antara PLR dan *modified rankin scale* (mRS) ($p=0,017$), serta dengan skor *National Institutes of Health Stroke Scale* (NIHSS) ($p=0,043$). Perbedaan rata-rata yang signifikan dalam nilai PLR diidentifikasi antara hasil mRS ($p=0,017$). PLR terbukti menjadi prediktor mRS (OR=4,051, $p=0,037$), meskipun tidak memprediksi hasil NIHSS. Temuan menunjukkan bahwa PLR dapat menjadi prediksi disabilitas pasca stroke iskemik. Peningkatan PLR menunjukkan ketidakseimbangan antara mediator inflamasi dan faktor neuroprotektif. Hasil ini berbeda dengan penelitian sebelumnya yang melaporkan adanya korelasi negatif antara PLR dan mRS. Kesimpulan, PLR berpotensi menjadi prediktor disabilitas pasca stroke pada pasien stroke iskemik

Kata kunci: disabilitas stroke; *platelet-to-lymphocyte ratio*; stroke iskemik akut; pasien stroke

Introduction

The Centers for Disease Control and Prevention (CDC) defines stroke as a focal or generalized cerebral perfusion disturbance that causes an acute neurological deficit.¹ Stroke is the world's second-highest cause of death (DALYs). There has been a 70% increase in stroke incidents, 43% mortality, 102% in prevalence, and 143% DALYs caused by stroke from 1990 to 2019.² In total, Asia has a higher stroke incidence and mortality rates. The incidence of stroke in Asia ranges from 116 to 483 per 100,000 individuals annually.³ The higher rate of stroke in Asia is Centers theorized differences in lifestyle.

According to the 2018 Basic Health Research (RISKESDAS) data, (10,9%) of the Indonesian population suffered from a stroke. East Kalimantan had the highest prevalence at 14,7% followed by Yogyakarta at 14,6%. Stroke in Indonesia has a high prevalence among those aged >75 years (50,2%) and 65-74 years (45,3%). Indonesian men have a higher stroke prevalence (11%) compared to women (10,9%). Furthermore, Stroke causes the highest death rate in Indonesia, accounting for 21,2% of total deaths. In 2010, Indonesia had the highest mortality rate due to stroke at 193,3/100,000 individuals per year.⁴ Lastly, stroke causes DALYs to 3,382,2/100,000 individuals in Indonesia, higher compared to the number stated by the World Stroke Organization in 2022 which is 820,40/100,000 individuals.⁵

Currently, stroke survivors often experience post-stroke disability. According to the American Heart Association (AHA), 15-30% of stroke patients suffer from severe disability, and

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75% experience post-stroke dysfunction.⁶ Further statistics show that 22-40% of stroke survivors have disability at 6 months post-stroke, while 29-44% still experience disability 10 years later.⁷ Other sources state that post-stroke disability prevalence is decreasing from 63,8 to 46,7%.⁸ These inconsistencies highlight the need for further research regarding post-stroke disability. It is suggested that using predictive biomarkers such as Platelet-to-Lymphocyte Ratio (PLR) may offer a more comprehensive approach to managing post-stroke disability

The platelet-to-lymphocyte ratio (PLR) is a systemic inflammation biomarker that potentially is a predictor of acute ischemic stroke severity and clinical outcomes (prognosis) of stroke patients. Patients with National Institute of Health Stroke Scale (NIHSS) > 6 have a higher PLR value compared to patients with NIHSS <6.^{9,10} PLR is theorized to increase in acute ischemic stroke and associated with a poor functional prognosis as measured using the modified Rankin scale (mRS). Research indicates that lower PLR values are correlated with positive clinical outcomes three months post-therapy. Specifically, ischemic stroke patients with low PLR values exhibited mRS scores <2.¹¹ These results convey that increases in PLR values are related to stroke severity.¹² It has been found that PLR is more significant in predicting stroke clinical outcomes compared to NLR.¹³ Studies regarding the potential of PLR to predict post-stroke disability are limited. Thus, this study aims are to measure PLR at admission and to investigate its potential as predictor for post-stroke disability predictor in ischemic stroke.

Methods

This retrospective cohort study was carried out on 98 acute ischemic stroke populations from STROKE REGISTRY at Bethesda Hospital Yogyakarta. The subject's data was taken from 2021-2022. All risk factors data, including laboratory and clinical information, as well as co-mediations, were recorded upon the patient's admission to the hospital. PLR results were obtained at the same time. The severity of the stroke was measured using NIHSS, while post-stroke disability was measured using mRS 30 days after discharge. The Patients were followed up at 30 days post-stroke and the length of stay average were 4 days. The sampling method was conducted sequentially from medical records, subjects who met the criteria were enrolled as research participants.

The study inclusion criteria were: (1) diagnosed with acute ischemic stroke through head CT-Scan or MRI, (2) over 18 years of age, (3) admitted to the hospital within 24 hours of the onset of the stroke, with complete stroke registry and medical records including NIHSS results at the time of admission and MRS results at 30 days post-discharge, (4) complete stroke registry data and medical records, especially PLR examination results, and (5) not referred patients.

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Patients were excluded from the study if they met any of the following criteria: (1) recurrent strokes, (2) altered mental consciousness, (3) active infections, or (4) history of hematological and autoimmune diseases. Based on the subject criteria, 70 patients were excluded from the study

The data were analyzed using IBM SPSS Statistics 26. An ROC/AUC test analysis was performed to determine the optimal PLR cut-off. Demographic characteristics were identified using univariate analysis. The Spearman bivariate analysis was carried out to evaluate correlation between dependent and independent variables, and Mann-Whitney was used to compare the mean PLR values in the good (≤ 2) and poor (> 2) mRS groups. Multivariate analysis, such as logistic regression and ordinal regression analysis were used to find the weight of dependent variables with significantly correlated independent variables in bi-variate analysis. This research was approved by the Hospital Health Research Ethics Committee Bethesda Yogyakarta with letter number No.71/KEPK-RESB/XI/23.

Results

The univariate analysis (Table 1) showed that patients over the age of 55 and males constituted the dominant age group within the population. A greater number of patients exhibited a low PLR value (< 146.86) rather than a high PLR value (≥ 146.8). The average PLR result for the population was 152.1. Moderate strokes (NIHSS 5-15) were found to be the most prevalent, followed by mild strokes (NIHSS 1-4). There were no patients with moderately severe strokes (NIHSS 15-20) or severe strokes (NIHSS 21-42). Lastly, the mRS results indicated that the patient population mainly had a good outcome (mRS ≤ 2), with only 12 patients exhibiting poor outcomes (mRS > 2).

The most prevalent comorbidities from the modifiable risk factors in the population were hypertension, diabetes mellitus, and cardiovascular disease. Out of the total population, most of the patients were found to be hypertensive. Despite this, the majority of patients did not have a history of diabetes mellitus or cardiovascular disease.

The CT-Scan results showed that subcortical infarct was the most common lesion location followed by cortical infarcts and mixed infarcts were the most common lesion locations. The majority of the patients did not experience atrophy. Moreover, it was found that patients generally suffered from a single lesion.

An ROC/AUC analysis was used to determine the optimal cutoff for PLR (Table 2). This analysis was based on mRS outcomes comprised of good (≤ 2) and poor (> 2) outcomes. The AUC, sensitivity, and specificity were obtained from the ROC/AUC. The optimal PLR cutoff value was 146.86, with a sensitivity of 66.7% and a specificity of 68.6%.

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The Spearman correlation analysis (Table 3) showed a weak correlation between PLR and mRS 30 days after a stroke. Additionally, a weak correlation was between PLR and NIHSS at the time of admission. Moreover, the mRS was moderately correlated to NIHSS. Cortical lesion was weakly correlated with NIHSS, and the number of lesions was weakly correlated with NIHSS. However, there was a negative correlation observed between cerebral atrophy and mRS, and other variables were not significantly correlated with mRS and NIHSS ($p>0,05$).

Table 1 Patient's Basic Characteristics

Variable	Frequency (n)	Percentage (%)
Age		
≥55 Years	78	79.6%
< 55 Years	20	20.4%
Gender		
Female	39	39.8%
Male	59	60.2%
Platelet-to-lymphocyte ratio (PLR), (mean)	152,1	
(High) ≥146.86	35	33.7%
(Low) <146.86	63	66.3%
Stroke Severity (NIHSS)		
Mild (1-4)	28	28.6%
Moderate (5-15)	70	71.4%
30 days post-stroke disability (mRS)		
Good (≤2)	86	87.8%
Poor (>2)	12	12.2%
Hypertension		
Yes	50	51.0%
No	48	49.0%
Diabetes Mellitus		
Yes	32	32.7%
No	66	67.3%
Cardiovascular disease		
Yes	17	17.3%
No	81	82.7%
Cortical infarct	23	23.4%
Sub-cortical infarct	56	57.0%
Mixed	19	19.6%
Atrophy	30	30.6%
Without Atrophy	68	69.4%
Single lesion	53	54.1%
Multiple lesion	45	45.9%

Note: NIHSS = National Institutes of Health Stroke Scale; mRS= Modified Rankin Scale

Table 2 ROC Analysis Result

AUC	p-value	95% CI
0.676	0.049*	0.511 – 0.841

Note: *Significant ($p<0.05$) by AUC/ROC test; AUC = Area Under Curve

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The Mann-Whitney analysis was carried out to compare the mean PLR values between the good and poor mRS outcomes. The mean PLR value in the good mRS outcomes (≤ 2) was 148.49 ± 88.36 , while in the poor outcomes ($\text{mRS} > 2$) it was 178.18 ± 83.68 . A significant mean difference was found in the PLR numbers of the good ($\text{mRS} \leq 2$) and poor ($\text{mRS} > 2$) outcomes ($p=0.017$).

The multivariate regression analysis (Table 4 and Table 5) showed that PLR significantly affect the 30 days post-stroke disability (mRS). In the ordinal regression analysis with the NIHSS as outcomes, number of lesions had the most significant influence compared to PLR and cortical infarct.

Table 3 The Spearman Correlation Bivariate Analysis With mRS 30 Days Post Stroke and NIHSS On Admission As An Outcome

Variable	mRS 30 Days Post Stroke		NIHSS Admission	
	Rho (r)	p-value	Rho (r)	p-value
PLR	0.241**	0.017*	0.205**	0.043*
CT-Scan (Cortical Lesion)	0.054	0.558	0.288**	0.024*
CT-Scan (Number of Lesion)	0.093	0.362	0.275**	0.006*
N	98			

Note: *significant ($p<0.05$) by spearman correlation test **correlated; NIHSS= National Institute of Health Stroke Scale; mRS= Modified Rankin Scale; PLR= Platelet-to-Lymphocyte Ratio

Tabel 4 Logistic Regression with Outcome Of 30 Days Post-Stroke Disability (mRS)

Variable	Odds Ratio	95% CI	p-value
PLR	4.051	1.091-15.042	0.037*
Atrophy	0.284	0.079-1.022	0.054

Note: *significant ($p<0.05$) by Logistic Regression test; PLR= Platelet-to-Lymphocyte Ratio

Tabel 5 Ordinal Regression With Outcome Of Admission Stroke Severity (NIHSS)

Variable	95% CI	p value
PLR	-0.009-1.498	0.053
Number of Lesions	-1.540- -0.061	0.034*
Cortical Infarct	-1.468 – 0.000	0.050

Note: *significant ($p<0.05$) by Ordinal Regression test; PLR= Platelet-to-Lymphocyte Ratio

Discussion

The study findings suggest that PLR was predictive for post-stroke disability in acute ischemic stroke. The study observed that 63 patients (66.3%) had a low PLR value (<146.86), whereas 35 patients (33.7%) had a high PLR value (≥ 146.86). The study used a cut-off of 146.86 with a specificity of 68.6% and a sensitivity of 66.7%. The PLR value indicated the neuroinflammatory process in stroke. PLR biomarkers indicate the disequilibrium of

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inflammatory mediators and the regulation of neuroprotective factors in acute ischemic stroke. Elevated inflammatory activity can lead to the apoptosis of neuroprotective factors, such as lymphocytes.¹⁴ Lymphocyte apoptosis is attributed to the release of cortisol and changes in systemic blood pressure following a stroke.¹⁵ Platelet aggregation in stroke leads to plaque formation in the cerebrovascular system and the release of platelet granulation, including chemokines and pro-cytokines such as IL-1, IL-2, IL-6, TNF- α , and IFN- γ . The release of inflammatory mediators trigger leukocyte recruitment such as neutrophils. Migration of leukocytes in turn exacerbates neuroinflammation response. Resulting in an expansion of stroke volume and an escalation in the severity of neurological deficits and poor stroke clinical outcomes.¹⁶

This study proved the correlation between PLR and stroke clinical outcomes ($r=0.241$, $p=0.017$) and stroke severity ($r=0.205$, $p=0.043$). These results align with a previous study that states a high PLR value has been associated with early neurologic deterioration (END), as shown by an increase of NIHSS >4 .¹⁷ It is shown in this study that the population with poor stroke clinical outcomes ($mRS > 2$) had a significantly higher PLR value. The mean PLR value in the good outcomes ($mRS \leq 2$) was (148.49 ± 88.36), while in the poor outcomes ($mRS > 2$) was (178.18 ± 83.68). The mean difference suggests that poor outcomes had a significantly higher PLR value due to the inflammation.

This study showed a significant association between high PLR value and post-stroke disability, as evidenced by $mRS (>2)$ ($OR=4.051$, $p=0.037$). It showed that PLR is a predictive factor for post-stroke disability in acute ischemic stroke. These results align with prior research, which suggests that an increase in PLR value is correlated with poor clinical outcomes, as demonstrated by $mRS (>2)$ ($OR=2.220$, $p=0.007$) and mortality ($OR=2.2825$, $p=0.040$).¹⁸ Other studies highlighted the association of PLR values with poor clinical outcomes through mRS results >2 ($OR=1.003$, $p=0.014$).¹⁹ The PLR shows benefits as a potential tool for post-stroke disability prognostic predictors. Furthermore, a positive correlation between PLR and poor clinical outcomes using the mRS instrument has been suggested. Changes in PLR values during ischemic stroke progression may serve as a predictive biomarker for neuronal damage attributable to neuroinflammation.²⁰ It is postulated that more severe inflammation exacerbates neurolysis, leading to worsened post-stroke clinical outcomes, ultimately resulting in post-stroke disability.²¹

The result of this study is different from previous research, which suggested a negative correlation between PLR and stroke severity at hospital admission as measured by NIHSS or functional outcomes 90 days post-stroke as measured by mRS . It is stated that the timing of PLR measurement appears to impact its predictive capability for post-stroke clinical outcomes. Factors

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such as hyperglycemia or infarct volume may influence NIHSS results.²² Unfortunately, these variables were not examined in this study. Previous research has also suggested higher PLR levels in hemorrhagic stroke were observed compared to acute ischemic stroke.²³

Due to the limited study, the precise pathophysiological relationship between PLR and post-stroke is not well understood. Nonetheless, this study supports the alternative hypothesis that PLR is a predictor factor for post-stroke disability in acute ischemic stroke. Our findings highlight a significant difference in PLR levels between patients with good (mRS ≤ 2) and poor (mRS >2) outcomes, as well as a positive relationship between PLR, mRS, and NIHSS. Despite that PLR did not affect NIHSS, it did affect mRS, suggesting that PLR can serve as a predictor for post-stroke disability.

The limitations of this study are retrospective cohort research method, utilizing secondary data, lack of data diversity, as evidenced by the presence of only mild and moderate-severe strokes in the NIHSS data. Furthermore, due to the limited prior research on the correlation between PLR and NIHSS and mRS, the pathobiological theory isn't well understood. It is important to note that unexplored confounding variables, such as blood sugar, infarct volume and infarct area, could potentially impact the results. Additionally, the absence of sub-classification of acute ischemic stroke into embolic and thrombotic categories may also have influenced the outcomes. We suggest further research regarding the potential use of PLR as a prognostic biomarker in cerebrovascular disease

Conclusion

Platelet-to-Lymphocyte Ratio (PLR) has proved as a predictor for post-stroke disability in acute ischemic stroke.

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