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Original Article

Neutrophil-to-lymphocyte ratio predicted cerebral infarction and poor discharge functional outcome in aneurysmal subarachnoid hemorrhage: A propensity score matching analysis

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ABSTRACT

Background: Neutrophil-lymphocyte-ratio (NLR) and platelet-lymphocyte-ratio (PLR) have emerged as potential biomarkers in predicting the outcomes of aneurysmal subarachnoid hemorrhage (aSAH). Since a study was never conducted on the Southeast Asian and Indonesian population, we designed the present study to evaluate the potential of NLR and PLR in predicting cerebral infarction and functional outcomes and find the optimal cutoff value.

Methods: We retrospectively reviewed patients admitted for aSAH in our hospital between 2017 and 2021. The diagnosis was made using a computed tomography (CT) scan or magnetic resonance imaging and CT angiography. Association between admission NLR and PLR and the outcomes were analyzed using a multivariable regression model. A receiver operating characteristic (ROC) analysis was done to identify the optimal cutoff value. A propensity score matching (PSM) was then carried out to reduce the imbalance between the two groups before comparison.

Results: Sixty-three patients were included in the study. NLR was independently associated with cerebral infarction (odds ratio, OR 1.197 [95% confidence interval, CI 1.027–1.395] per 1-point increment; $P = 0.021$) and poor discharge functional outcome (OR 1.175 [95% CI 1.036–1.334] per 1-point increment; $P = 0.012$). PLR did not significantly correlate with the outcomes. ROC analysis identified 7.09 as the cutoff for cerebral infarction and 7.50 for discharge functional outcome. Dichotomizing and performing PSM revealed that patients with NLR above the identified cutoff value significantly had more cerebral infarction and poor discharge functional outcome.

Conclusion: NLR demonstrated a good prognostic capability in Indonesian aSAH patients. More studies should be conducted to find the optimal cutoff value for each population.

Keywords: Biomarker, Cerebral infarction, Functional outcome, Neutrophil-lymphocyte-ratio, Subarachnoid hemorrhage

INTRODUCTION

Despite the significant advances in the management of aneurysmal subarachnoid hemorrhage (aSAH), its mortality remains as high as 20%.[7] The most significant contributor to mortality and morbidity in aSAH is cerebral infarction.[1,20] At present, nimodipine is approved for prophylaxis, but seeing that the mortality and morbidity rates remain high, this points to a significant knowledge gap in treatment. New treatment strategies are being developed, and recently, there has been an increased interest in new drugs to prevent infarction. These drugs, namely, clazosentan and heparin, have shown good potential.[9,18] Hopefully, in the future, the treatment of aSAH will focus on preventing infarction before it can occur and leave permanent damage to the patient's brain.

A good screening model is required to stratify those high-risk patients that would benefit from a preventive treatment while taking the risk of additional side effects. The widely used parameters, the Hunt and Hess scale, the World federation of neurosurgical societies (WFNS) scale, and the modified Fisher (mFisher) scale, only take into account the patient's clinical and radiographical characteristics. With the elucidation of the complex biological process behind infarction,[8] it is imperative to find a suitable biomarker to complement those two widely used scales. Inflammatory markers such as C-reactive protein, matrix metallopeptidase 9 (MMP9), and several interleukins have been studied.[15,22] They have shown they can predict infarction and outcome, but their expensive cost would hamper adoption and usage. To address this issue, researchers try to find a cheaper alternative. Neutrophil-lymphocyte-ratio (NLR) and platelet-lymphocyte-ratio (PLR), which could be calculated from a cheap laboratory examination, have recently garnered interest.[2,11,25,29-34] However, not all of those researches study cerebral infarction. The researches that did analyze the occurrence of cerebral infarction also did not use a stringent criterion for defining an infarction.[2,25,29,30] Moreover, current research mainly studies the Caucasian and East Asian populations. On the other hand, the Indonesian and Southeast Asian population have been heavily underrepresented, not just in NLR and PLR study but almost in all medical research field. Seeing that NLR could be affected by racial differences,[4] we designed the present study to analyze the association between NLR and PLR with cerebral infarction and functional outcome and find the optimal cutoff value for Indonesian aSAH patients. The low cost and availability of NLR and PLR would prove even more crucial in low-to-middle income settings such as Southeast Asian countries.

MATERIALS AND METHODS

Study population

We retrospectively collected the data for all aSAH patients admitted to our hospital between 2017 and 2021. Our hospital was one of the tertiary referral centers for neurosurgical patients in Indonesia. We excluded patients with non-aSAH, those aged <18 years old, those that had an infection on admission, and those that did not undergo either coiling/clipping procedure. Patients were diagnosed with a head computed tomography (CT) scan or magnetic resonance imaging (MRI) and supplemented by a CT angiographic study. This study was approved by the Local Ethics Committee at the Local Institutional Research Board. No informed consent was required due to the retrospective nature and exclusion of patients' identifier.

Data collection

We collected patients' admission baseline characteristics from the medical records. These included demographic data, emergency room findings (i.e., signs and symptoms, Glasgow coma scale [GCS], blood pressure, and WFNS scale), and laboratory parameters. The severity of aSAH was determined by the WFNS scale and was classified as severe (WFNS scale 3–5) and non-severe (WFNS scale 1–2). We only collected admission laboratory parameters. We used the full blood count differentials and platelet count to identify and calculate NLR and PLR. We also collected data on routine laboratory examinations such as hemoglobin, urea, and electrolytes. We did not plan to analyze other laboratory examinations such as random blood glucose, liver enzymes, lactate, or albumin because those examinations were not routinely performed in our center, so not all patients were examined for those parameters. We collected patients' radiological images from our electronic database and used the mFisher scale to evaluate the bleeding extent. We collected patients' discharge data from the medical records.

Imaging

The diagnosis of aSAH was established on admission using either a head CT scan or MRI. Non-aSAH was excluded using CT-angiography. We identified iatrogenic infarcts by radiologically examining patients 24–48 h after the procedure and differentiated them from infarcts that occurred afterward. During the patients' stay, an additional radiographic evaluation could be ordered according to the judgment of the treating neurosurgeon. A final radiographical evaluation was done on all patients before their discharge.

During the data collection process, a radiologist blinded to the patient's data performed another reading of the radiographic image to confirm the diagnosis of aSAH, grade them using the mFisher scale, and identify any intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH), or cerebral infarction. In our study, we followed the definition for cerebral infarction as proposed by Vergouwen *et al.*[28] We defined cerebral infarction as the presence of cerebral

infarction on CT or MRI of the brain during the hospital stay until a maximum of 6 weeks or on the latest CT or MRI study obtained before death within 6 weeks, and not attributable to other causes such as surgical clipping or endovascular treatment. We excluded neurological impairment from the definition as they may spontaneously resolve, while radiologically documented infarction demonstrated the true outcome of an ischemic event.

Clinical management

Patients diagnosed with aSAH underwent either a coiling or clipping procedure, according to the judgment of the treating neurosurgeon at the time. Standard supportive and symptomatic medical therapies were given to all patients along with prophylaxis nimodipine in the intensive care setting after the procedure. Patients were then transferred to the medical ward and discharged following stabilization and improvement of clinical condition.

Outcome evaluation

Cerebral infarction was the primary outcome of this study. In addition, we also evaluated patients' discharge functional outcome. We used the modified Rankin scale (mRS), and we classified poor outcome at discharge as an mRS score of 3–6, representing functional dependence.

Statistical analysis

Patients' baseline characteristics, clinical condition on admission, radiographic characteristics, and laboratory parameters were categorized according to the presence of cerebral infarction and discharge functional outcome. Categorical variables were compared using Chi-square or Fisher's exact test. Continuous variables were analyzed for their distribution and were compared using Student's *t*-test or Mann–Whitney U-test according to their distribution. Any variables showing statistical significance in the bivariate analysis were analyzed in a multivariate logistic regression model. We then performed a receiver operating characteristic (ROC) analysis to determine their respective cutoff value. All statistical significance was set at $P < 0.05$.

We then dichotomized the patient's data according to the identified cutoff value. To reduce confounding bias, we performed a propensity score matching (PSM) with a 1:1 match ratio and caliper 0.15. We included demographic data such as age and sex, clinical parameters such as GCS, WFNS scale, blood pressure, ICH, IVH, mFisher scale, treatment (clipping or coiling), and those variables that were statistically significant in the initial multivariate analysis as covariates. Balance diagnostic was performed using p-value and standardized difference according to the formula outlined by Austin.[3] Patients in the PS-matched cohort were then dichotomized according to the primary and secondary outcomes and analyzed.

RESULTS

Patient characteristics

We identified 73 aSAH patients who underwent coiling or clipping procedures in our center between 2017 and 2021. We excluded seven patients due to incomplete laboratory data, one patient due to incomplete discharge data, one patient that died before treatment, and one adolescent patient [Figure 1]. From this cohort, 40 (63.4%) patients had a severe WFNS scale, 22 (34.9%) patients had cerebral infarction, and 41 (65.1%) patients had poor discharge functional outcome. The baseline characteristics are shown in Table 1. Patients with cerebral infarction had worse GCS on admission (9 [6–12] vs. 15 [9–15]; $P = 0.022$), a higher urea level (29.9 ± 2.9 vs. 23.3 ± 2.3; $P = 0.030$), a higher rate of ICH (7 [31.8%] vs. 3 [7.3%]; $P = 0.011$), and a worse mFisher scale (grade 1: 1/21 [4.5%] vs. 11/42 [26.8%]; grade 2: 5/21 [22.7%] vs. 15/42 [36.6%]; 7/21 [31.8%] vs. 9/42 [22.0%]; grade 4: 9/21 [40.9%] vs. 6/42 [14.6%]; $P = 0.027$). Patients with discharge poor functional outcome had higher proportion of severe WFNS scale (30/41 [75.0%] vs. 10/22 [43.5%]; $P = 0.012$) and a higher urea level (28.1 ± 15.8 vs. 21.1 ± 10.5; $P = 0.022$). We also found that patients with cerebral infarction had a statistically significant higher NLR (13.8 ± 2.2 vs. 7.6 ± 1.0; $P = 0.002$) and PLR level (292.3 ± 49.6 vs. 223.5 ± 32.7; $P = 0.041$). On the other hand, patients with poor discharge functional outcome also had a higher NLR (12.1 ± 9.5 vs. 5.6 ± 3.7; $P = 0.001$) and PLR

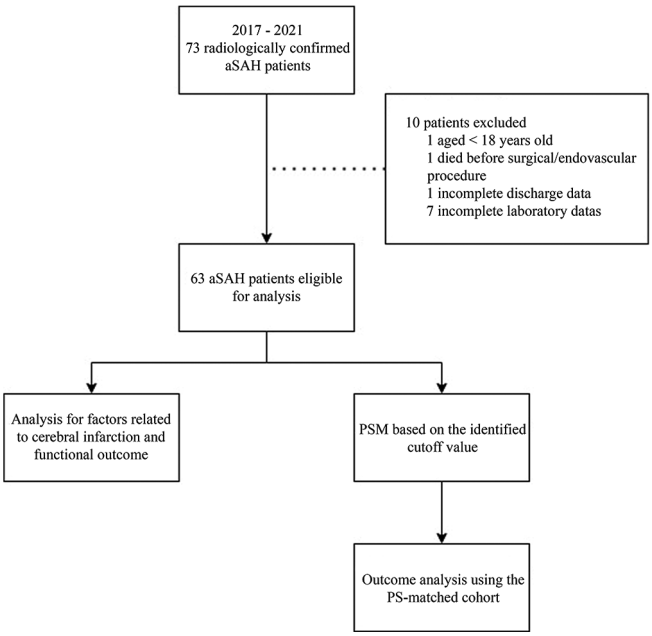

Figure 1: Study flow diagram. aSAH: Aneurysmal subarachnoid hemorrhage, PSM: Propensity score matching, PS: Propensity score.

Table 1: Baseline characteristics according to cerebral infarction and discharge functional outcome.

Variable	Cerebral infarction		*P*-value	Discharge functional outcome		*P*-value
	Yes (*n*=22)	No (*n*=41)		Poor (*n*=41)	Good (*n*=22)	
Demographic						
Age	56.3±12.6	52.8±12.6	0.290	56.3±12.9	50.0±11.3	0.053
Male	12 (54.5)	15 (36.6)	0.170	17 (42.5)	10 (43.5)	0.940
Symptoms on admission						
Cephalgia	12 (54.5)	32 (78.0)	0.053	25 (62.5)	19 (82.6)	0.094
Seizure	1 (4.5)	6 (14.6)	0.405	5 (12.5)	2 (8.7)	1.000
Motoric deficit	3 (13.6)	6 (14.6)	1.000	7 (17.5)	2 (8.7)	0.467
Nuchal rigiditiy	4 (18.2)	9 (22.0)	1.000	8 (20.0)	5 (21.7)	1.000
Comorbidities						
Hypertension	11 (50.0)	18 (43.9)	0.643	17 (42.5)	12 (52.2)	0.458
DM	1 (4.5)	2 (4.9)	1.000	2 (5.0)	1 (4.3)	1.000
CAD	0 (0)	2 (4.9)	0.538	1 (2.5)	1 (4.3)	1.000
CHF	1 (4.5)	1 (2.4)	1.000	1 (2.5)	1 (4.3)	1.000
Admission status						
GCS†	9 (6–12)	15 (9–15)	**0.022**	12 (8–15)	14 (9–15)	0.536
WFNS severe (3–5)	17 (77.3)	23 (56.1)	0.096	30 (75.0)	10 (43.5)	**0.012**
Systole >140/diastole >90	11 (50.0)	26 (63.4)	0.303	26 (65.0)	11 (47.8)	0.183
Laboratory values						
Hb, g/dL	12.7±0.5	12.3±0.3	0.596	12.4±2.3	12.6±2.0	0.622
NLR	13.8±2.2	7.6±1.0	**0.002**	12.1±9.5	5.6±3.7	**0.001**
PLR	292.3±49.6	223.5±32.7	**0.041**	288.4±261.3	176.4±72.4	0.087
Na, mmol/L	138.2±1.2	137.8±0.9	0.817	138.7±5.6	136.7±6.0	0.189
K, mmol/L	3.7±0.1	3.6±0.1	0.531	3.6±0.5	3.5±0.5	0.349
Ur, mg/dL	29.9±2.9	23.3±2.3	**0.030**	28.1±15.8	21.1±10.5	**0.022**
Radiological data						
ICH	7 (31.8)	3 (7.3)	**0.011**	8 (20.0)	2 (8.7)	0.302
Hydrocephalus	13 (59.1)	17 (41.5)	0.182	21 (52.5)	9 (39.1)	0.306
IVH	14 (63.6)	21 (51.2)	0.344	22 (55.0)	13 (56.5)	0.907
mFisher scale						
1	1 (4.5)	11 (26.8)	**0.027**	6 (15.0)	6 (26.1)	0.170
2	5 (22.7)	15 (36.6)		10 (25.0)	10 (43.5)	
3	7 (31.8)	9 (22.0)		12 (30.0)	4 (17.4)	
4	9 (40.9)	6 (14.6)		12 (30.0)	3 (13.0)	
Treatment						
Clipping	20 (90.9)	30 (73.2)	0.116	33 (82.5)	17 (73.9)	0.522
Ventilator	19 (86.4)	31 (75.6)	0.315	32 (80.0)	18 (78.3)	1.000
Shunt	9 (40.9)	11 (26.8)	0.252	13 (32.5)	7 (30.4)	0.865

All values are presented as number of patients (%) and mean±SD, unless indicated. Boldface type indicates statistical significance. †Median (IQR).
n: Number of patients, DM: Diabetes mellitus, CAD: Coronary artery disease, CHF: Congestive heart failure, GCS: Glasgow coma scale, WFNS: World federation of neurosurgical societies, Hb: Hemoglobin, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, Na: Sodium, K: Kalium, Ur: Urea, ICH: Intracerebral hemorrhage, IVH: Intraventricular hemorrhage, mFisher: modified Fisher

level (288.4 ± 261.3 vs. 176.4 ± 72.4; $P = 0.087$), but only the difference in NLR reached statistical significance.

Association of NLR and PLR with outcomes

In the multivariate logistic regression [Table 2], we included variables that showed statistical significance in the bivariate analysis. We included NLR, PLR, GCS score, mFisher scale, urea level, and ICH in the model for cerebral infarction. We found that NLR was independently associated with cerebral infarction (odds ratio, OR 1.197 [95% confidence interval, CI 1.027–1.395] per 1-point increment; $P = 0.021$). We also found that mFisher grade (OR 2.982 [95% CI 1.322–6.724] per 1-point increment; $P = 0.008$) and GCS score (OR 0.794 [95% CI 0.642–0.893] per 1-point increment; $P = 0.034$) were independently associated with cerebral infarction.

We included NLR, severe WFNS score, and urea level in the model for poor discharge functional outcomes. We found that NLR was independently associated with discharge poor functional outcome (OR 1.175 [95% CI 1.036–1.334] per

Table 2: Multivariate analysis of parameters associated with cerebral infarction and poor discharge functional outcome.

Parameter	Odds ratio	95% Confidence interval	*P*-value
Cerebral infarction			
NLR per 1-point increment	1.197	1.027–1.395	0.021
mFisher per 1-point increment	2.982	1.322–6.724	0.008
GCS per 1-point increment	0.794	0.642–0.983	0.034
PLR per 1-point increment	0.999	0.995–1.003	0.640
Ur per 1-point increment	0.998	0.953–1.044	0.921
ICH	6.047	0.976–37.485	0.053
Poor discharge functional outcome			
NLR per 1-point increment	1.175	1.036–1.334	0.012
WFNS severe	3.830	1.107–13.247	0.034
Ur per 1-point increment	1.033	0.974–1.096	0.282

Boldface type indicates statistical significance. GCS: Glasgow coma scale, WFNS: World federation of neurosurgical societies, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, Ur: Urea, ICH: Intracerebral hemorrhage, mFisher: modified Fisher

1-point increment; $P = 0.012$). Severe WNFS scale was also independently associated with discharge poor functional outcome (OR 3.830 [95% CI 1.107–13.247]; $P = 0.034$).

ROC analysis

We performed an ROC analysis for NLR and PLR [Figure 2]. For predicting cerebral infarction, the best NLR cutoff value was 7.09 (Youden's index 0.452; AUC 0.737 [95% CI 0.610–0.864]; $P = 0.002$). It had 81.8% sensitivity, 63.4% specificity, 54.5% positive predictive value (PPV), and 86.7% negative predictive value (NPV). For predicting poor discharge functional outcome, we identified 7.50 as the best NLR cutoff value (Youden's index 0.433; AUC 0.743 [95% CI 0.621–0.866]; $P = 0.001$). It had 65.0% sensitivity, 78.3% specificity, 84.8% PPV, and 54.5% NPV.

For PLR, the best cutoff value for predicting delayed cerebral ischemia (DCI) was 213.5 (Youden's index 0.319; AUC 0.657 [95% CI 0.518–0.796]; $P = 0.041$). It had 63.6% sensitivity, 68.3% specificity, 51.9% PPV, and 77.8% NPV. For predicting poor discharge functional outcome, the best PLR cutoff value was 252.0 (Youden's index 0.363; AUC 0.630 [95% CI 0.494–0.767]; $P = 0.087$). It had 45.0% sensitivity, 91.3% specificity, 90.1% PPV, and 47.1% NPV. However, the ROC analysis of PLR and poor discharge functional outcome did not reach statistical significance.

Outcomes in the PS-matched cohort

The balance diagnostic of the created PS-matched cohort are shown in Tables 3 and 4. After PS-matching, the cohort was more evenly balanced. In this PS-matched cohort, there was a higher proportion of cerebral infarction in patients with NLR ≥ 7.09 (12/16 [75.0%] vs. 10/28 [35.7%]; $P = 0.012$). Patients with NLR ≥ 7.50 also had a higher proportion of poor discharge functional outcome (20/29 [69.0%] vs. 4/19 [21.1%]; $P = 0.001$]. Patients with PLR ≥ 213.5 and 252.0 had a higher proportion of cerebral infarction (13/26 [50.0%] vs. 8/18 [44.4%]; $P = 0.158$) and poor discharge functional outcome (12/19 [63.2%] vs. 8/19 [42.1%]; $P = 1.00$). However, only the NLR-dichotomized cohort produced statistically significant differences [Figure 3].

DISCUSSION

Based on the results of our literature search and several systematic reviews,[12,17,24] our study was the first to evaluate the association of NLR and PLR with aSAH in a Southeast Asian population. We demonstrated the association between admission NLR with cerebral infarction. NLR measures the proportion of neutrophils to lymphocytes. In a damaged brain, neutrophils are recruited early and reach a peak within 1 day.[13] Neutrophils release proinflammatory cytokines and reactive oxygen species and induce the expression and release of MMP9.[6,14] MMP9 can break down the tight junction of blood–brain barrier (BBB), opening the way for more inflammatory cells and molecules to enter the brain.[26] MMP-9 also breaks down varieties of protein, and their end products, called the remnant epitopes, are proinflammatory.[27] These processes promote inflammation in the brain. On the other side, lymphocyte has been correlated with the protective mechanism in the brain after an injury. Regulatory T-cells reduce inflammation by blocking the activation of the Toll-like receptor/nuclear factor-kappa B, hence reducing the effect that MMP-9 has on the BBB. Although a different subset of T cells, namely, T-helper17, promotes the inflammatory response in the brain, the net effect of lymphocyte in the brain remains protective.[6] In the case of aSAH, the decrease in lymphocyte mainly happens to the protective regulatory T-cells.[16] Therefore, a high NLR value captures the imbalance between factors that promote and inhibit inflammation in the brain. Neuroinflammation has been found to be one of the main mechanisms of cerebral infarction,[8] providing the potential link between NLR and cerebral infarction. We suggested future studies to confirm the relationship between NLR and neuroinflammation by correlating NLR with cerebrospinal fluid (CSF) analysis of proinflammatory cytokines such as interleukin (IL)-6, IL-8, IL-1β, tumor necrosis factor-alpha, and monocyte chemoattractant protein-1.

Platelet has also been implicated in the development of cerebral infarction through the formation of microthrombi and increased inflammation level.[8] Interestingly, our study did not find any correlation between PLR and cerebral

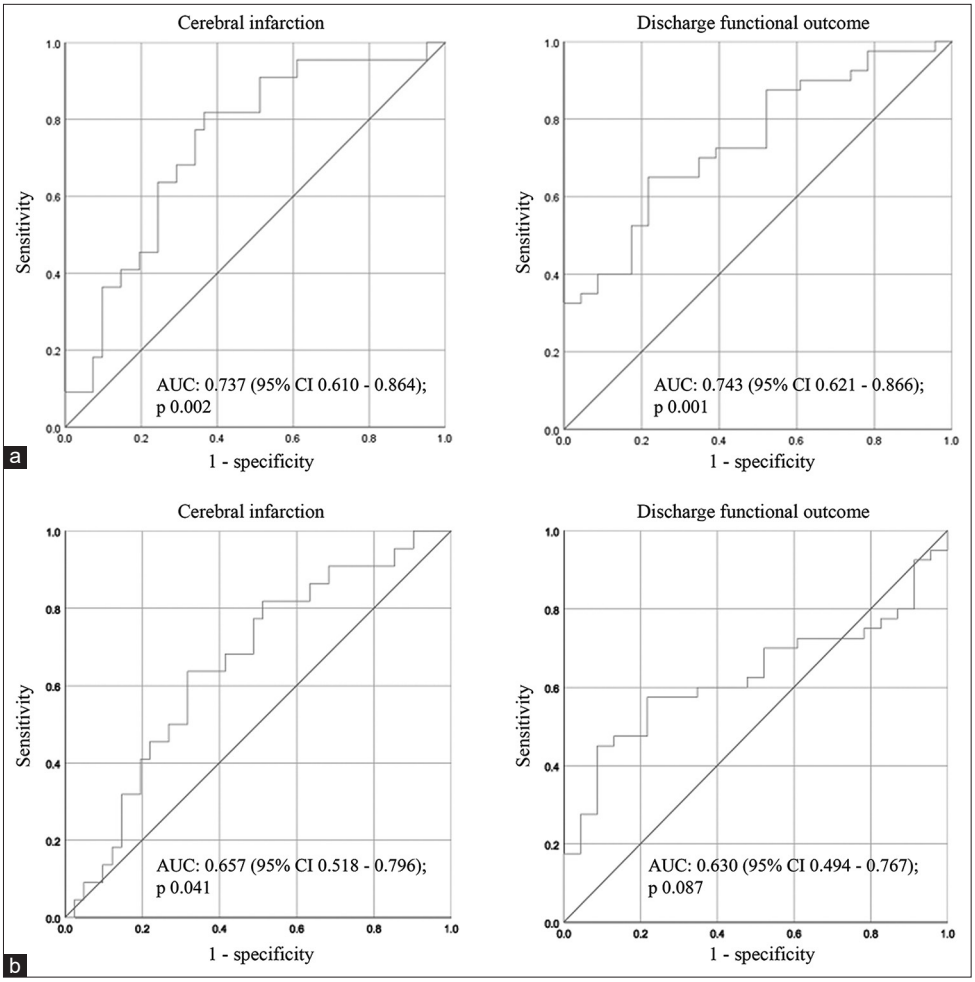

Figure 2: Receiver operating characteristic analysis for neutrophil-lymphocyte-ratio (a) and platelet-lymphocyte-ratio (b). AUC: Area under the curve, CI: Confidence interval.

Table 3: Balance diagnostic for NLR of the PS-matched cohort.

Variable	NLR on admission		*P*-value	d	NLR on admission		*P*-value	d
	≥7.09 (*n*=22)	<7.09 (*n*=22)			≥7.50 (*n*=24)	<7.50 (*n*=24)		
Age	56.0±14.5	54.4±11.1	0.677	0.12	54.9±15.4	54.3±10.6	0.888	0.05
Male	9 (40.9)	9 (40.9)	1.000	0	9 (37.5)	9 (37.5)	1.000	0
GCS†	11 (7–15)	12 (9–15)	0.763	0.16	10 (6–14)	12 (9–15)	0.773	0.22
WFNS severe (3–5)	15 (68.2)	14 (63.6)	0.75	0.08	17 (70.8)	14 (58.3)	0.365	0.27
Systole >140/diastole >90	13 (59.1)	11 (50.0)	0.303	0.18	13 (59.1)	11 (50.0)	0.303	0.18
ICH	3 (13.6)	3 (13.6)	1.000	0.0	4 (16.7)	3 (12.5)	1.000	0.11
IVH	12 (54.5)	12 (54.5)	1.000	0.0	12 (54.5)	12 (54.5)	1.000	0.18
mFisher scale								
1	4 (18.2)	3 (13.6)	1.000	0.11	3 (12.5)	4 (16.7)	0.810	0.11
2	8 (36.4)	7 (31.8)		0.08	8 (33.3)	9 (37.5)		0.10
3	6 (27.3)	7 (31.8)		0.11	6 (25.0)	7 (29.2)		0.09
4	4 (18.2)	5 (22.7)		0.12	7 (29.2)	4 (16.7)		0.29
Clipping	18 (81.8)	19 (86.4)	0.680	0.11	21 (87.5)	20 (83.3)	1.000	0.14

All values are presented as number of patients (%) and mean±SD, unless indicated. †Median (IQR). *n*: Number of patients, d: Standardized difference, GCS: Glasgow coma scale, WFNS: World federation of neurosurgical societies, NLR: Neutrophil-to-lymphocyte ratio, ICH: Intracerebral hemorrhage, IVH: Intraventricular hemorrhage, mFisher: modified Fisher, PS: Propensity score

Table 4: Balance diagnostic for PLR of the PS-matched cohort.

Variable	PLR on admission		*P*-value	d	PLR on admission		*P*-value	d
	≥213.5 (*n*=26)	<213.5 (*n*=26)			≥252.0 (*n*=19)	<252.0 (*n*=19)		
Age	54.5±11.7	54.3±13.1	0.947	0.02	50.2±12.5	52.3±13.3	0.618	0.16
Male	11 (38.5)	10 (42.3)	0.777	0.08	10 (52.6)	6 (31.6)	0.189	0.43
GCS†	11 (8–15)	10 (8–15)	1.000	0.09	11 (8–15)	10 (8–14)	0.514	0.04
WFNS severe (3–5)	19 (73.1)	18 (69.2)	0.760	0.08	12 (63.2)	13 (68.4)	0.732	0.11
Systole >140/diastole >90	17 (65.4)	13 (50.0)	0.262	0.18	10 (52.6)	12 (63.2)	0.511	0.22
ICH	5 (19.2)	5 (19.2)	1.000	0.00	4 (21.1)	3 (15.8)	1.000	0.14
IVH	16 (61.5)	16 (61.5)	1.000	0.00	11 (57.9)	10 (52.6)	0.744	0.11
mFisher scale								
1	4 (15.4)	4 (15.4)	1.000	0.00	3 (15.8)	3 (15.8)	1.000	0.00
2	10 (38.5)	9 (34.6)		0.08	7 (36.8)	7 (36.8)		0.00
3	6 (23.1)	6 (23.1)		0.00	5 (26.3)	6 (31.6)		0.12
4	6 (23.1)	7 (26.9)		0.09	4 (21.1)	3 (15.8)		0.14
Clipping	22 (84.6)	21 (80.8)	0.714	0.10	18 (50.0)	18 (50.0)	1.000	0.00

All values are presented as number of patients (%) and mean±SD, unless indicated. †Median (IQR). *n*: Number of patients, d: standardized difference, GCS: Glasgow coma scale, WFNS: World federation of neurosurgical societies, PLR: Platelet-to-lymphocyte ratio, ICH: Intracerebral hemorrhage, IVH: Intraventricular hemorrhage, mFisher: modified Fisher, PS: Propensity score

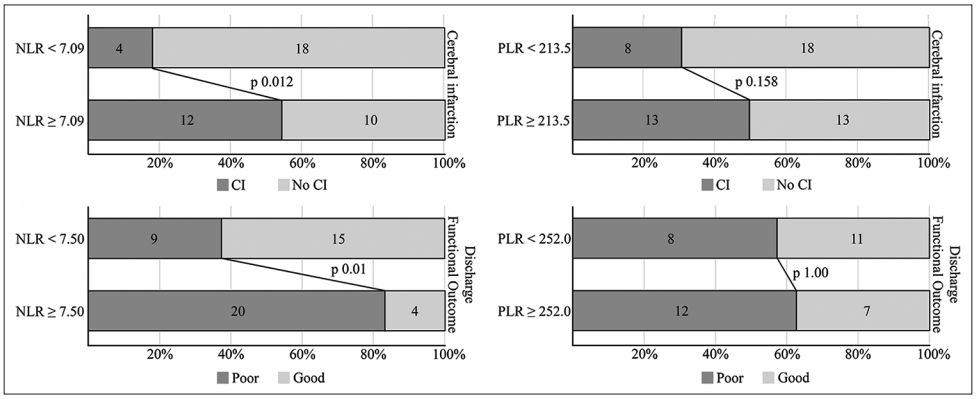

Figure 3: Cerebral infarction and discharge functional outcomes of the patients dichotomized according to the identified cutoff value after propensity score matching. NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CI: Cerebral infarction.

infarction. In the literature, PLR has fewer studies than NLR and relatively had more inconsistencies in the results. Bolton *et al.*[5] and Tao *et al.*[25] demonstrated an independent association between PLR and DCI, while Yun *et al.*[32] and Zhang *et al.*[34] found conflicting results. One possible explanation is the difference in the aSAH severity of their study populations. Tao *et al.* reported that their population had a median mFisher scale of 3,[25] while 91.8% of the study population in the study by Bolton *et al.* were patients with thick aSAH (mFisher grade 3–4),[5] much higher compared to the one in the study by Yun *et al.* (32.7%)[32] and Zhang *et al.* (29.8%).[34] One interesting study by Raatikainen *et al.* found that patients with a severe aSAH (Fisher grade 3–4) had significantly lower platelet count in the first 2 days post-ictus.[23] Although more studies are required to confirm this finding, there is a possibility that platelet and, therefore, PLR are affected by the mFisher scale. In our study, almost half of our patients had a thick aSAH. Our study also found that PLR lost its statistical significance after being controlled with the mFisher scale in the multivariate analysis. This issue should be addressed in future studies with an extra precaution on the effect of the mFisher scale on PLR value. As of now, we supported the use of NLR instead of PLR in predicting the outcome of aSAH.

We also found that a higher NLR value was independently associated with poor discharge functional outcome. Although we could only evaluate functional outcome on discharge, this result was in-line with other studies that evaluated outcome over a more extended period.[5,11,25,29] Cerebral infarction is one of the main contributors to neurological deficits and dependencies. As infarction usually occurs between 4 and 10 days post-ictus,[8] any deficits would have manifested on hospital discharge. Prediction of a poor functional outcome

on discharge could be helpful in alerting clinicians to the need for rehabilitation care as soon as possible after the patient's discharge.

We identified 7.09 and 7.50 as the optimal cutoff value for cerebral infarction and discharge functional outcome, respectively. Dichotomizing patients according to this cutoff value in the PS-matched cohort also showed a significantly higher proportion of patients in the NLR value group having the observed outcomes. The reported cutoff value from other studies ranged from 4.0 to 14.0, either for infarction or functional outcome.[2,11,25,29-32,34] Racial difference could be one of the explanations for this disparity, as Azab *et al*. reported that the NLR value of non-Hispanic African American, Hispanic, and non-Hispanic Caucasian.[4] Giede-Jeppe *et al*. reported a cutoff value of 7.05 for predicting poor 3-month functional outcome, the closest to our reported cutoff value.[12] Although they did not specifically describe the racial characteristics of their study population, it could be deduced from their study location in Germany that they were mainly Caucasian.[11] Nevertheless, it is too early to conclude that the Southeast Asian people's NLR value is comparable to those of the Caucasian's. Instead, our finding reinforced the notion that different population could have different NLR cutoff value. As our study was the first to report the optimal cutoff value for NLR in the Southeast Asian population, we hoped that our result could represent the Southeast Asian population in the literature about NLR.

The difference between our cutoff value for cerebral infarction with those aforementioned studies could also be attributed to the difference in outcome criteria. Three studies used the term DCI, which focused more on focal neurological impairment and unexplainable decrease in consciousness,[2,25,30] while the other one did not specify their criteria.[33] DCI itself is often regarded as cerebral infarction and the terms have been used interchangeably. However, Vergouwen *et al*. argued that the neurological impairment of DCI may resolve spontaneously or after treatment while documented infarction on CT-scan or MRI demonstrated the true outcome of any ischemic event.[28] One large cohort study also found that DCI only correlated with mortality and functional outcome after CT scan results were included in its definition.[10] Moreover, excluding other causes for the focal impairment could be difficult and subjective. Therefore, Vergouwen *et al*. suggested to use the term cerebral infarction which strictly refers to the presence of cerebral infarction on CT-scan or MRI not attributable to surgical or endovascular procedure within 6 weeks post-ictus or earlier before death.[28] One strength of our study was we strictly used radiographically confirmed cerebral infarction and this could result in the difference of the reported cutoff value.

Our result supported the prognostic importance of NLR as a biomarker for cerebral infarction and poor functional outcomes. However, rather than replacing the widely used WFNS and mFisher scale, we suggested using NLR in combination with those two scales. As mentioned above, clazosentan and heparin have been studied for preventing cerebral vasospasm and infarction. Several clinical trials for clazosentan have produced conflicting results. The Clazosentan to Overcome Neurological Ischemia and Infarct Occurring After Subarachnoid Hemorrhage (CONSCIOUS)-3 trials demonstrated that clazosentan reduced vasospasm-related morbidity and all-cause mortality but did not affect the long-term functional outcome.[19] In the post hoc analysis of the CONSCIOUS-2 and CONSCIOUS-3 trials, it was found that the effect of clazosentan was affected by the patients' WFNS scale and clot size.[21] On the other hand, the phase III study by Endo *et al*. found a beneficial effect of 10 mg/h of clazosentan in reducing vasospasm-related morbidity, all-cause mortality, and long-term functional outcome.[9] Their subgroup analysis according to the WFNS scale and clot size also produced a statistically significant beneficial effect. However, they only included patients with WFNS scale I–IV, less severe than the CONSCIOUS trials, which also included patients with a WFNS scale of V. Seeing the available results, we hypothesized that the benefits of clazosentan are affected by aSAH severity. Regarding heparin, we are still waiting for the aSAH Trial RandOmizing Heparin trial (registration no. NCT02501434). Having demonstrated the prognostic value of NLR, we proposed future clinical studies to incorporate NLR alongside the WFNS and mFisher scale to classify the patient's condition better. The obtained results could then be tailored to select patients that would benefit the most from prophylactic treatment.

Our study has several limitations. The retrospective and single-center nature of our study could have introduced confounding bias. We tried to minimize this by performing multivariate analysis and PSM and still found an independent association between NLR and cerebral infarction and functional outcome. However, unknown confounding bias could still have emerged and affected our findings. Another limitation is that we did not have our patients' follow-up data after discharge, so we cannot analyze functional outcome over a longer period. Finally, since our hospital mainly served privately insured patients, this led to the small number of samples in our study, which could reduce the confidence in our result. Conducting a large-scale study in Indonesia is difficult as, currently, there is no national cohort on aSAH. However, building on our result, we hope that larger studies in Indonesia and other developing countries could be conducted in the future.

CONCLUSION

NLR is independently associated with cerebral infarction and poor discharge functional outcome. There is a significant

disparity between studies regarding the reported cutoff value. As there is a possibility that NLR is affected by racial differences, we suggest that more research be conducted, especially in the developing countries. NLR's low cost and ease would serve as an especially important prognostic marker in those countries. In addition, since prophylaxis treatment is possibly affected by patients' severity, we suggest future research to incorporate NLR with WFNS and mFisher scale to classify aSAH patients' severity better.

Declaration of patient consent

The Institutional Review Board (IRB) permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

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