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Neutrophil-Lymphocyte ratio as a predictor of haemorrhagic stroke outcomes

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ABSTRACT

Original Article

Background: Haemorrhagic stroke causes high disability and mortality. Moreover, the prevalence is increasing. There is evidence of the involvement of the inflammatory process in haemorrhagic strokes. The neutrophil-lymphocyte ratio (NLR) is a strong and easily assessed marker of inflammation.

Objective: This study aims to determine the NLR during hospital admission as a predictor of neurological deterioration in acute haemorrhagic strokes.

Methods: This study was a prospective cohort study. The subjects were acute haemorrhagic stroke patients treated at the Stroke Unit of the RSUP Dr. Sardjito between March and November 2018. The demographic and laboratory test data, including NLR and National Institutes of Health Stroke Scale (NIHSS) measurement upon admission, were investigated. Logistic regression was performed to identify independent risk factors of neurological deterioration.

Results: A total of 65 haemorrhagic stroke patients were included in this study. There were 21 subjects experiencing neurological deterioration, and 44 subjects did not. In bivariate analysis, there was a significant association between hyperglycaemia and neurological deterioration (RR=3.073; 95%CI=1.772-5.329; p=0.011). Glasgow Coma Scale (GCS) at admission was significantly associated with neurological deterioration (RR=2.732; 95%CI=1.455-5.131; p=0.006) as well as the NLR (RR=3.750; 95%CI=1.229-9.4441; p=0.005). The logistic regression results demonstrated that the variables that independently influenced neurological deterioration were NLR (RR= 4.424; 95%CI=1.196-16.369; p=0.026) and GCS (RR=7.461; 95%CI=1.711-32.526; p=0.007).

Conclusion: High NLR can predict deterioration in acute haemorrhagic stroke.

Latar Belakang: *Stroke perdarahan menyebabkan kecacatan dan kematian yang tinggi. Terlebih lagi, prevalensinya semakin meningkat. Terdapat bukti keterlibatan proses inflamasi pada stroke perdarahan. Rasio neutrofil-limfosit (NLR) merupakan penanda inflamasi yang kuat dan mudah dinilai.*

Tujuan: *Penelitian ini bertujuan untuk mengetahui NLR saat masuk rumah sakit sebagai prediktor perburukan neurologis pada stroke perdarahan akut.*

Metode: *Penelitian ini merupakan penelitian kohort prospektif. Subjek adalah pasien stroke perdarahan akut yang dirawat di Unit Stroke RSUP Dr. Sardjito pada bulan Maret sampai November 2018. Data demografi, hasil tes laboratorium termasuk NLR dan* National Institutes of Health Stroke Scale *(NIHSS) dievaluasi saat masuk. Faktor risiko independen perburukan neurologis ditentukan dengan analisis regresi logistik.*

Hasil: *Didapatkan 65 pasien stroke hemoragik yang terlibat dalam penelitian ini. Terdapat 21 subjek*

mengalami perburukan neurologis, sedangkan 44 subjek tidak. Pada analisis bivariat didapatkan hubungan signifikan antara hiperglikemia dengan perburukan neurologis (RR=3,073; 95%CI=1,772-5,329; p=0,011). Glasgow Coma Scale *(GCS) saat masuk secara signifikan terkait dengan kerusakan neurologis (RR=2.732; 95%CI=1.455-5.131; p=0.006) serta NLR (RR=3.750; 95%CI=1.229-9.4441; p =0,005). Hasil regresi logistik menunjukkan bahwa variabel yang secara independen mempengaruhi perburukan neurologis adalah NLR (RR=4,424; 95%CI=1,196-16,369; p=0,026) dan GCS (RR=7,461; 95%CI=1,711-32,526; p=0,007).*

Kesimpulan: *NLR yang tinggi dapat menjadi prediktor perburukan pada stroke perdarahan akut.*

INTRODUCTION

Intracerebral haemorrhage (ICH) is the second-largest stroke subtype that can cause disability and mortality. It is common in Asia, in old age, among men, and among low-middle-income countries. The mortality rate is high (40% in 1 month and 54% in 1 year), and only 12-39% of patients can live independently in the long term.[1]

Recently, evidence supports the mechanism of inflammation involved in brain damage after ICH.[2] There is an inflammatory response, such as peripheral leukocyte infiltration, microglia activation, and release of several cytokines reported in animal models of ICH.[3] Clinical studies demonstrated that inflammatory markers are associated with poor outcomes in ICH patients.[4] Leukocyte count is easily available compared to other inflammatory markers. Previous studies have demonstrated that increased leukocytes are associated with a large volume of haematoma and poor outcomes in ICH patients. Neutrophils and lymphocytes are leukocyte components. Recent studies suggested that the neutrophil-lymphocyte ratio (NLR) demonstrated a robust inflammatory marker compared to neutrophils or lymphocytes alone.[5,6]

NLR was associated with adverse clinical outcomes and mortality in patients with ischemic stroke, haemorrhagic stroke, and breast cancer.[6–9] NLR is assessed by calculating neutrophils count divided by lymphocyte count. Its increase can be a cheap marker of systemic inflammation.[10] This ratio shows a balance of immune response between natural immunity (neutrophil granulocytes) and adaptive immunity (lymphocytes). Thus, the presence of increased neutrophils and reduced lymphocytes shows physiological stress.[11] NLR was associated with recovery of ICH patients at 3 months, yet, the relationship with short-term outcomes is unknown.[12] This study aims to determine the role of the ratio of neutrophil lymphocytes at hospital admission as predictors of neurological deterioration in acute haemorrhagic strokes.

METHODS

This study is a prospective cohort study comparing two groups of at-risk and non-risk. All patients with haemorrhagic stroke treated at the Stroke Unit of Dr. Sardjito Hospital, Yogyakarta, from March to November 2018 were investigated prospectively. Inclusion criteria were: 1) haemorrhagic stroke patients based on head computerised tomography (CT) scan, 2) age ≥18 years, 3) onset ≥72 hours, and 4) willingness to participate in the study. Exclusion criteria were: 1) history of autoimmune disease, malignancy, infection, or haematological abnormalities, 2) using immunosuppressant drugs, and 3) subarachnoid haemorrhage.

Subjects who met the criteria carried out routine blood tests in the clinical pathology laboratory of RSUP Dr. Sardjito to get random blood glucose, neutrophils, lymphocyte, and leukocyte counts. The NLR was assessed by calculating the absolute number of neutrophils divided by the absolute number of lymphocytes.[11] The cut-of-point ratio of NLR was 4.58, as reported in a previous study.[13] Therefore, the NLR was considered to increase if the value exceeds 4.58 in this study.

The National Institutes of Health Stroke Scale (NIHSS) was assessed on admission and at the start of day 14. Furthermore, Glasgow Coma Scale (GCS), blood pressure, and non-contrast head CT scan were also performed. A CT scan was used to evaluate whether the bleeding site is infratentorial or supratentorial, haematoma volume, and ventricles bleeding.

The data were analysed using bivariate analysis of Chi-Square and Fisher's exact. Then proceed with multivariate logistic regression analysis to determine the independent risk factors. Neurological deterioration was defined as the NIHSS score on day 14 having increased at least 2 points, or the patient died. This study has received approval from the Ethics Committee for Research in humans, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University, with the number KE/FK/0617/EC/2018.

RESULTS

A total of 65 haemorrhagic stroke patients

Table 1. Demographic, clinical manifestation, and laboratory data of haemorrhagic stroke

Variable		Mean±SD	Min-Max	Total	Percentage (%)
Age	>65 years old	62.37±13.72	29-92	26	40
	≤65 years old			39	60
Sex	Male			46	70.8
	Female			19	29.2
Hypertension	Yes			46	70.8
	No			19	29.2
Diabetes mellitus	Yes			17	26.2
	No			48	73.8
History used antiplatelet and/or anticoagulant	Yes			6	9.2
	No			59	90.8
Glasgow Coma Scale	≤8	12.78±3.11		14	21.5
	>8			51	78.5
Volume of haematoma	≥30 cm^3			15	23.1
	<30 cm^3			50	76.9
Intraventricular haemorrhage	Yes			24	36.9
	No			41	63.1
Haematoma site	Infratentorial			12	18.5
	Supratentorial			53	81.5
Systolic blood pressure	≥140 mmHg	180.02±30.07	98-240	60	92.3
	<140 mmHg			5	7.7
Diastolic blood pressure	≥90 mmHg	99.60±19.45	55-139	48	73.8
	<90 mmHg			17	26.2
Random glucose	≥200	135.49±50.44	76-374	6	9.2
	<200			59	90.6
Leukocyte	>11.000	11.93±3.86	5-23	35	53.8
	≤11.000			30	46.2
Neutrophil	>70%	76.76±10.75	48-93	49	75.4
	≤70%			16	24.6
Lymphocyte	<22%	14.99±7.88	4-34	54	83.1
	≥22%			11	16.9
Neutrophil-lymphocyte ratio	>4.58	7.33±4.95	2-22	40	61.5
	≤4.58			25	38.5

were included in this study. Only 21 patients experienced neurological deterioration. The mean age was 62.37 ± 13.72, with a range of 29-92 years. The mean leukocytes were 11.93 ± 3.86, neutrophils were 76.76 ± 10.75, and lymphocytes were 14.99 ± 7.88. It was found that 40 patients had higher NLR compared to the rest of the patients. The results of subject characteristics are shown in Table 1.

Subject characteristics based on NLR are presented in Table 2. Most of the variables did not differ significantly in the NLR. The

Table 2. Characteristic subjects with NLR ≤4.58 and >4.58

Variable		Neutrophil-Lymphocyte Ratio				p
		>4.58		≤4.58		
		n	%	n	%	
Age*	>65 years old	16	40.0	24	60.0	1.000
	≤65 years old	10	40.0	15	60.0	
Sex*	Male	26	65.0	14	35.0	0.196
	Female	20	80.0	5	20.0	
Hypertension*	Yes	29	72.5	11	27.5	0.914
	No	17	68.0	8	32.0	
Diabetes mellitus*	Yes	11	27.5	29	72.5	0.982
	No	6	24.0	19	76.0	
History used antiplatelet and/or anticoagulant**	Yes	2	5.00	38	95.0	0.294
	No	4	16.0	21	84.0	
Systolic blood pressure**	≥140	37	92.5	3	7.5	1.000
	<140	23	92.0	2	8.0	
Diastolic blood pressure*	≥90	29	72.5	11	27.5	0.982
	<90	19	76.0	6	24.0	
Glasgow Coma Scale *	≤8	12	30.0	28	70.0	0.074
	>8	2	8.0	23	92.0	
Random glucose**	≥200	6	15.0	34	85.0	0.111
	<200	0	0.00	25	100.0	
Leukocyte*	>11.000	29	72.5	11	27.5	<0.001***
	≤11.000	6	24.0	19	76.0	
Neutrophil*	>70%	40	100.0	0	0.00	<0.001***
	≤70%	9	36.0	16	64.0	
Lymphocyte**	<22%	40	100.0	0	0.00	<0.001***
	≥22%	14	56.0	11	16.9	
Volume haematoma*	≥30 cm^3	15	37.5	25	62.5	0.001***
	<30 cm^3	0	0.00	25	100.0	
Intraventricular haemorrhage*	Yes	22	55.0	18	45.0	<0.001***
	No	2	8.0	23	92.0	
Haematoma site**	Infratentorial	8	20.0	32	80.0	0.341
	Supratentorial	2	8.0	23	92.0	

*Chi-Square, **Fisher's exact, ***Statistically significant (p<0.05).

variables leukocytes, lymphocytes, neutrophils, haematoma volume, and IVH involvement demonstrated significant differences and could be confounding factors.

The results of the bivariate analysis are presented in Table 3. The NLR, GCS, and random glucose were significantly associated with neurological deterioration. In multivariate

Table 3. Bivariate analysis of NLR and other factors concerning neurological deterioration

Variable		Δ NIHSS				RR (95%CI)	p
		≥2		<2			
		n	%	n	%		
Age*	>65 years old	8	30.8	18	69.2	0.923 (0.446-1.911)	0.829
	≤65 years old	13	33.3	26	66.7		
Sex*	Male	16	34.8	30	65.2	1.322 (0.565-3.093)	0.503
	Female	5	26.3	14	73.7		
Hypertension*	Yes	14	30.4	32	69.6	0.826 (0.397-1.720)	0.615
	No	7	36.8	12	63.2		
Diabetes mellitus*	Yes	8	47.1	9	52.9	1.738 (0.876-3.448)	0.130
	No	13	27.1	35	72.9		
History used antiplatelet and/or anticoagulant**	Yes	3	50.0	3	50.0	1.639 (0.674-3.983)	0.293
	No	18	30.5	41	69.5		
Systolic blood pressure on admission**	≥140	19	31.7	41	68.3	0.792 (0.254-2.466)	0.523
	<140	2	40.0	3	60.0		
Diastolic blood pressure on admission*	≥90	17	35.4	31	64.6	1.505 (0.589-3.847)	0.279
	<90	4	23.5	13	76.5		
Glasgow Coma Scale *	≤8	9	64.3	5	35.7	2.732 (1.455-5.131)	0.006***
	>8	12	23.5	39	76.5		
Random glucose**	≥200	5	83.3	1	16.7	3.073 (1.772-5.329)	0.011***
	<200	16	27.1	43	76.9		
Leukocyte*	>11.000	14	40.0	21	60.0	1.714 (0.798-3.684)	0.152
	≤11.000	7	23.3	23	76.7		
Neutrophil*	>70%	19	38.8	30	61.2	3.102 (0.810-11.886)	0.051
	≤70%	2	12.5	14	87.5		
Lymphocyte**	<22%	20	37.0	34	63.0	4.074 (0.609-27.262)	0.067
	≥22%	1	9.1	10	90.9		
Volume haematoma*	≥30 cm^3	18	45.0	22	55.0	3.750 (1.229-11.441)	0.005***
	<30 cm^3	3	12.0	22	88.0		
NLR*	>4.58	7	46.7	8	53.3	1.667 (0.827-3.357)	0.149
	≤4.58	14	28.0	36	72.0		
Intraventricular haemorrhage*	Yes	11	45.8	13	54.2	1.879 (0.940-3.756)	0.074
	No	10	24.4	31	75.6		
Haematoma site**	Infratentorial	2	20.0	8	80.0	0.579 (0.159-2.107)	0.305
	Supratentorial	19	34.5	44	67.7		

*Chi-Square, **Fisher's exact, ***Statistically significant ($p<0.05$).

analysis (Table 4), the variables that independently affected neurological deterioration up to 2 weeks were NLR (RR=4.424; 95% CI=1.196-16.369; p=0.026) and GCS (RR=7.461; 95% CI=1.711-32.526; p=0.007). These results indicate that subjects with NLR >4.58 were associated with neurological damage at 2 weeks, which is 4 times more likely than subjects with NLR ≤4.58.

Table 4. Multivariate analysis of factors influencing poor neurological deterioration*

Variable		RR	95%CI		p
			min	max	
Diabetes mellitus	Yes	2.183	0.568	8.472	0.259
	No				
Glasgow Coma Scale	≤8	7.461	1.711	32.526	0.007**
	>8				
Blood Glucose	≥200	4.672	0.437	4.990	0.202
	<200				
Leukocyte	>11.000	1.330	0.329	5.377	0.689
	≤11.000				
Neutrophil	>70%	0.286	0.017	4.838	0.386
	≤70%				
Lymphocyte	<22%	1.167	0.078	17.442	0.911
	≥22%				
Neutrophil-lymphocyte ratio	>4.58	4.424	1.196	16.369	0.026**
	≤4.58				
Volume of haematoma	≥30 cm^3	1.771	0.355	8.845	0.486
	<30 cm^3				
Intraventricular haemorrhage	Yes	0.743	0.134	4.115	0.734
	No				

*Logistic regression test, **Statistically significant (p<0.05).

DISCUSSION

In this study, males were more frequent than females. It is consistent with previous studies that reported a higher incidence of ICH in males than females.[5,14,15] Regarding GCS, the mean score was 12.78 ± 3.11 with a greater number of GCS >8 subjects compared to GCS ≤8. In line with Wang et al., which reported a mean GCS of 12.64 ± 3.49 and Gusdon et al. for subjects with GCS <9 was 35 (22.9%).[15,16]

A bivariate analysis of age for worsening neurological deficits demonstrated no difference in neurological deterioration between subjects aged >65 and ≤65. Other studies also concluded that age does not affect mortality nor short- and long-term poor outcomes of ICH patients.[17,18] However, our study's results differ from Radholm et al., which reported that increasing age is related to mortality and dependence.[19] This finding may be due to differences in age grouping, the outcome parameters, and the follow-up period.

There was no difference between male and female gender for worsening neurological deficits. Previous studies also suggested that gender is not associated with mortality or poor outcomes in ICH patients.[18,20] However, this result differ from Ganti et al., which demonstrated that females are still an independent predictor of short-term mortality.[21] A study by Zhou et al.

also found a significant relationship between females and mortality or dependence at month 3 but not significantly at month 6 and month 12.[22] This difference could be due to the various sample sizes, the different measuring instruments used in assessing the outcome, and the different timing of the assessment. The pathophysiology of sex differences in outcomes among patients with ICH remains unclear. Although recent preclinical data support the role of gonadal hormones affecting haemostasis and post-ICH neuroinflammatory regulation, their effects on human recovery are still unknown.[23]

Hypertension was not associated with neurological deterioration. The current study result is consistent with previous studies that reported hypertension is not associated with mortality nor poor outcomes.[13,24–29] The pathophysiology underlying the acute hypertensive response to stroke is still not clearly understood. However, a theory has been proposed, namely, the existence of autoregulation that is useful in improving cerebral perfusion in patients with increased intracranial pressure.[30]

There was no association between diabetes mellitus and neurological deterioration in our study. In agreement with several previous studies that diabetes mellitus is not associated with deathnor poor outcomes.[28,29,31-34]

In bivariate analysis, there was a significant association between hyperglycaemia on admission and neurological deterioration. This result is in line with a previous study that high glucose at admission to the hospital is associated with poor long-term outcomes and mortality.[34,35] The increase in blood glucose during acute ICH is probably a response to the stress and severity of ICH, which will last up to 72 hours. In the acute phase of ICH, a non-specific, programmed, and adaptive response activates the hypothalamic-pituitary-adrenal axis and finally releases hormones that cause hyperglycaemia. This condition plays a vital role in worsening lesions in the brain through increasing oxidative stress and cytokines, inducing excitotoxicity (stimulating NMDA receptors), increasing the influx of calcium into cells, and changing brain metabolism and perfusion.[36]

We observed no significant association between the location and volume of haematoma and neurological deterioration nor expansion into the ventricles. This finding is in line with a study by Jones et al. that reported no association between the location of supratentorial and infratentorial haematomas and 30-day mortality.[32] Additionally, according to Wang et al., intraventricular haematoma growth is not substantially related to mortality within 30 days.[15]

Leukocyte accumulation is not significantly associated with the neurological decline in bivariate analysis. This finding is in line with Yu et al.[37], which found that a rise in leukocyte count upon hospital admission was not a reliable indicator of a favourable clinical outcome within 90 days as measured by mRS and mortality. High leukocytes upon admission to the hospital are not associated with neurological deterioration, possibly because increased leukocytes are associated with a reduced risk of haematoma expansion.[38]

High NLR and GCS could be predictors of neurological deterioration. This study's mean of NLR (7.33 ± 4.95) is similar to Wang et al. (6.34 ± 5.85).[12] Recent studies demonstrated that NLR is an independent predictor of mortality and disability in 90 days.[12–15] While Wang et al. reported that the NLR at admission is not associated with mortality within 30 days (p=0.353), the relationship became significant in the NLR the next morning (p=0.044).[16] The NLR is a potential predictor of in-hospital mortality in patients with ICH.[17–19] The risk of in-hospital mortality increased 2.34-fold for each increase in NLR in haemorrhagic stroke.[18] Besides, a high NLR is independently predictive of early haematoma growth.[20]

Neutrophils infiltrate into and around the haematoma in less than 1 day after haemorrhage and reach a peak of 2-3 days in experimental animals.[21] Neutrophils actively

secrete and release various proteolytic enzymes and pro-inflammatory proteases, which can damage brain tissue directly. The high count of neutrophils and low count of lymphocytes at admission independently can predict neurological deterioration during the initial weeks of ICH onset. The NLR illustrates a reliable predictor of biomarkers.[5]

NLR is associated with poor outcomes, especially mortality in ICH, which is still unclear but possibly explained by several arguments. The NLR is a combination index that reflects pro-inflammatory and immunosuppressive status. Inflammatory cells, mediators, and cytokines are directly related to endothelial damage, neuronal death, and white matter damage that contribute to secondary brain damage.[12] In addition to NLR contributing to secondary brain damage, its high levels are also independently associated with perihematomal oedema growth.[12,22] This likely explains the high NLR associated with neurological deterioration in ICH patients.

GCS can be a predictor of neurological deterioration in haemorrhagic stroke patients. This scale can predict death within 30 days of ICH, and early awakening in patients who present in a coma after ICH.[23-25] Low GCS scores is independent poor prognosis marker for in-hospital mortality of haemodialysis patients with spontaneous ICH.[26] The limitations of this study, such as in the homogeneity analysis, several variables are not homogeneous; therefore, it could be a confounding factor.

CONCLUSION

The high NLR can predict worsening in acute haemorrhagic stroke patients.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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