Neutrophils-To-Lymphocyte Ratio Associates With Clinical Outcome In Acute Ischemic Stroke

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Citation

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Abstract

Introduction: Ischemic stroke occurs as the arteries narrow or becomes blocked, leading to a severe reduction in blood flow or ischemia. Pathophysiology of ischemic stroke relates to the role of white blood cells. Previous studies have shown that lymphocytes may contribute as neuroprotective function and had a role in the neurological outcome in acute ischemic stroke, so decreasing lymphocyte count will worsen clinical outcomes. Neutrophil and lymphocyte count can convert into Neutrophil to Lymphocyte Ratio (NLR), which compares between the number of neutrophil and lymphocyte.

Objective: Here, we examined the relationship between NLR, neutrophil, lymphocyte and clinical outcome in acute ischemic stroke patients.

Methods: A retrospective study of 391 medical records of hospitalized ischemic stroke patients from January 2015 to December 2017. We calculated NLR and National Institute of Health Stroke Scale (NIHSS) for assessing clinical outcomes. Statistical significance calculated with Spearman rank test, ANOVA, and multiple logistic regression.

Result: After collecting 391 subjects, 213 were women (54.5%) and 178 were men (45.5%). Eighty-two percent of subjects had hypertension as a risk factor. The mean of neutrophils and lymphocytes was 76.78±11.95 uL and 27.69±10.78 uL. The mean of NIHSS was 7.53±3.86. Lymphocyte count and NIHSS had a strong negative significant correlation ($r=-0.88, p<0.001$), but had a solid positive considerable correlation between NLR and NIHSS ($r=0.91, p<0.001$). From logistic regression, we found that neutrophil was statistically significance correlate with NIHSS ($p < 0.05$). The coefficient if NLR is the highest (absolute value) among other independent variables. It shows that NLR and neutrophil has positive effect on clinical outcome using NIHSS tools in acute ischemic stroke patients.

Conclusion: NLR, neutrophil and lymphocyte count had a strong relationship with NIHSS. The higher NLR and neutrophil will provide higher NIHSS. NLR and neutrophil harms in acute ischemic stroke.

INTRODUCTION

Ischemic stroke is responsible for around eighty percent of strokes. It occurs as the arteries narrow or become blocked, leading to reduce blood flow or ischemia. It is a medical emergency, and time management is crucial to minimize neuronal damage and potential complications.1,2

Pathophysiology of ischemic stroke relates to the role of white blood cells. Various inflammatory mediators releases after ischemic occur, and it can induce endothelial and brain tissue damage. It makes the brain cannot function properly. Increasing the number of white blood cells, predominantly neutrophils in peripheral blood, are related to the severity of a stroke, tend to have worsened clinical outcome, and had a possibility for stroke recurrent.3

Previous studies have shown lymphocytes may contribute as neuroprotective function and have played a role in the neurological outcome in acute ischemic stroke, so decreasing of lymphocyte count will have to worsen clinical outcome.4 Neutrophil and lymphocyte count can convert into Neutrophil to Lymphocyte Ratio (NLR), which is a comparison between the number of neutrophil and lymphocyte.

METHODS

It was a retrospective study of medical records of

hospitalized stroke patients from 2015 until 2017. Inclusion criteria were stroke patients diagnosed based on CT scans and inpatients who had laboratory results on neutrophil counts and lymphocyte counts in their medical records. We calculated NLR and National Institute of Health Stroke Scale (NIHSS) for assessing clinical outcomes. Statistical significance calculated with Spearman rank test, ANOVA, and multiple logistic regression. We exclude a history of hematologic disease, immunosuppressant drug users, infection within two weeks, and recurrent stroke. Research Ethics Committee of Universitas Padjadjaran approved this study (no. 1123/UN6.KEP/EC/2018).

RESULTS

We included 391 research subjects in this study, and we found that women are more than men (table 1). Hypertension is the most frequent stroke risk factor.

The mean number of neutrophil counts in the study subjects was 76.78, and the mean lymphocyte count was 27.69. The mean NLR for all subjects is 3.04, and the mean NIHSS for all subjects is 7.52 (table 1). Lymphocyte and NIHSS had a strong negative significant correlation (r=-0.88;p<0.001) and had a strong positive significant correlation between NLR and NIHSS (r-0.91;p<0.001). We can see the complete data in table 2. The sum of squared errors was 26908.27 and total sum squared errors was 27833 (Table 3), so we found R-Square 0.9667. It mean 96% of total variation in clinical outcome (NIHSS) across 390 acute ischemic stroke patients (Table 4).

From logistic regression, we found that NLR and neutrophil were statistically significance correlate with NIHSS ($p < 0.05$). The coefficient if NLR is the highest (absolute value) among other independent variables (Table 5). It shows that NLR has positive effect on clinical outcome using NIHSS tools in acute ischemic stroke patients (Figure 1).

Table 1

Clinical characteristic research subjects

Variable	Total (n=391)
Gender	
Men (n,%)	179 (45.5)
Women (n,%)	213 (55.5)
Age (year), mean ± SD	57.14 ± 11.55
Risk factors*	
Hypertension	321(83.2)
Diabetes Mellitus	68 (17.4)
Smoking	60 (15.3)
Cardiac problem	102 (26.1)
Mean neutrophil, n(uL) ± SD	76.78 ± 11.95
Mean lymphocyte, n(uL) ± SD	27.69 ± 10.78
Mean NLR, n ± SD	3.04 ± 0.12
Mean NIHSS, n ± SD	7.52± 3.86

*Risk factors can be > 1

Table 2

Relationship between neutrophil, lymphocyte, NLR and NIHSS

Variable		Mean NIHSS n(uL) ± SD	r(p)
Mean neutrophil n(uL) ± SD	76.78 ± 11.95	7.52± 3.86	-0.57 (0.004*)
Mean lymphocyte n(uL) ± SD	27.69 ± 10.78	7.52± 3.86	-0.88 (0.001*)
Mean NLR n(uL) ± SD	3.04 ± 0.12	7.52± 3.86	0.91 (0.001*)

*Significance p<0.05

Table 3

Analysis of Varian

	df	*SS*	*MS*	*F*	*Significance F*
Regression	5	26908.27	5381.655	2240.597	1.5594E-281
Residual	385	924.7254	2.401884		
Total	390	27833			

Table 4

Regression statistic of independent variable

Regression Statistics	
Multiple R	0.983247646
R Square	0.966775934
Adjusted R Square	0.963833346
Standard Error	1.549801349
Observations	390

Table 5

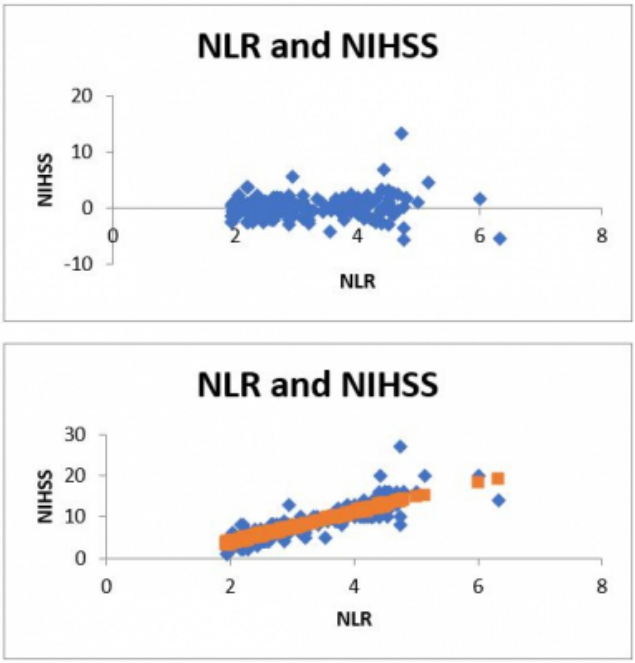
Confidence interval of neutrophil, NLR, lymphocyte, leucocyte, and age

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Neutrophil	-0.04706778	0.023005462	-2.04594	**0.041441**	-0.092299846	-0.00183571	-0.0922998	-0.0018357
NLR	-0.00755804	0.034347108	-0.22005	**0.025951**	-0.075089428	0.059973346	-0.0750894	0.0599733
Lymphocyte	3.550158517	0.265168894	13.38829	7.93E-34	3.028798071	4.071518963	3.02879807	4.0715189
Leucocyte	2.47695E-06	6.59417E-06	0.375628	0.707401	-1.04881E-05	1.54421E-05	-1.0488E-05	1.54421E-05
Age	0.00889371	0.006823667	1.303362	0.19323	-0.004522608	0.022310028	-0.0045226	0.0223100

Bold signifies p<0.05

Figure 1

Correlation NLR and NIHSS



DISCUSSION

This study found that women were more than men on research subjects, and the mean age was 57.14 years. It was suitable with another study results that the mean age of the subjects was 58.76 years.3

Hypertension is still the most stroke risk factor compared with diabetes mellitus, smoking, or cardiac abnormalities, and we found the same results from another sudy.3

Brain ischemia results in an inflammatory reaction that begins within hours, days and can last several months. Interleukins, a functional subclass of cytokines, mediate an inflammatory response. Pro-inflammatory interleukins such as IL-6 can affect the function and synthesis of 22 other cytokines through a complex cytokine network. Various cell types, such as microglial cells, astrocytes, leukocytes, directly modulate the processes of apoptosis, differentiation, and proliferation of the central nervous system.5,6 Transcription factors such as nuclear factor-kappa-light chain-enhancer of activated B cells (NFkB), Activator Protein-1 (AP-1), hypoxia-inducible factor-1 (HIF-1), and interferon regulatory factor-1 are activated and induces the production of inflammatory mediators including adhesion molecules, proteolytic enzymes, and cytokines (IL-6). 6,10 Inflammation as an initial response to ischemic stroke, neutrophils extravasate to the brain parenchyma involving the transfer, activation, and transmigration of P and E-selectins followed later by increased levels of ICAM and VCAM and increased leukocyte migration to the brain parenchyma.10

IL-6 will inhibit the process of neutrophil diapedesis. In the final phase of this response, IL-6 creates a transition between the innate and adaptive immune responses by recruiting monocytes and T-cells as an advanced immune response. The inflammatory response in early stroke triggers microglia and astrocytes to produce the inflammatory mediator cytokine IL-6 and proteolytic enzymes (MCP-1, MIP-1, MMP) after stroke events. Termination of this inflammatory process also triggers the ability to remodeling of damaged brain tissue.8,11,14

The leukocytes involved are polymorphonuclear cells, monocytes, macrophages, and natural killer cells. Adaptive immunity responds specifically to an antigen and involves a longer lag time from exposure to an antigen until it elicits a response. The hallmark of adaptive immunity is the memory capacity which allows for a more rapid and efficient rise of antibodies as an immune response after exposure to an antigen. The leukocytes involved are T lymphocytes and B lymphocytes. Various immune cells, mainly T lymphocytes, B lymphocytes, neutrophils, monocytes, and macrophages, produce cytokines. Il-6 increases the expression of ICAM-1 and selectin on endothelial cells and astrocytes, facilitating infiltration and increasing leukocyte activation.5-7 Bonding occurs between adhesion molecules on the surface of neutrophils/leukocytes and their receptors on the endothelium of blood vessels during the release of cytokines.8,13,15 Neutrophils/leukocytes damage the endothelium resulting in increased permeability, exacerbating tissue inflammation and edema, and nerve cell death. Increased expression of IL-6 in acute ischemic stroke not only affects the size of the infarct but also the magnitude of the neurological deficit and predicts the outcome of stroke patients.9,11,12

This study found a strong negative significant correlation ($r=-0.9603; p<0.001$) between lymphocyte and NIHSS. It means that a lower lymphocyte count will provide higher NIHSS, and there was a strong positive correlation between NLR and NIHSS ($r=0.91; p<0.001$). It shows that NLR harms clinical outcomes using NIHSS tools in acute ischemic stroke patients.The coefficient if NLR is the highest (absolute value) among other independent variables. It shows that NLR has positive effect on clinical outcome using NIHSS tools in acute ischemic stroke patients.

CONCLUSION

NLR, neutrophil and lymphocyte count were associated with the severity and clinical outcome of acute ischemic stroke. The higher NLR and neutrophil will provide higher NIHSS. NLR and neutrophil harms in acute ischemic stroke.

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