

Vol. 23, No. 3, July 2017

p-ISSN 0854-4263
e-ISSN 4277-4685

INDONESIAN JOURNAL OF
**Clinical Pathology and
Medical Laboratory**

Majalah Patologi Klinik Indonesia dan Laboratorium Medik

IJCP & ML (Maj. Pat. Klin. Indonesia & Lab. Med.)	Vol. 23	No. 3	Page 203-309	Surabaya July 2017	ISSN 0854-4263
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Published by Indonesian Association of Clinical Pathologists

Accredited No. 36a/E/KPT/2016, Tanggal 23 Mei 2016

INDONESIAN JOURNAL OF
**CLINICAL PATHOLOGY AND
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Website: <http://www.indonesianjournalofclinicalpathology.or.id>

Accredited No. 36a/E/KPT/2016, Tanggal 23 Mei 2016

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RESEARCH

NEUTROPHIL-LYMPHOCYTE RATIO AND HIGH SENSITIVITY C-REACTIVE PROTEIN AS ISCHEMIC STROKE OUTCOME PREDICTOR

(Rasio Neutrofil–Limfosit dan High Sensitivity C–Reactive Protein sebagai Peramal Hasil Strok Iskemik Akut)

Tissi Liskawini Putri¹, Ratna Akbari Ganie¹, Aldy S. Rambe²

ABSTRAK

Proses inflamasi merupakan perjalanan penyakit dari strok iskemik akut, yang melibatkan penumpukan mediator inflamasi dan infiltrasi leukosit. Nilai Rasio Neutrofil-Limfosit (RNL) di beberapa penelitian dapat digunakan untuk meramalkan strok akibat iskemik akut yang caranya mudah dilakukan. High sensitivity C Reactive Protein (hs-CRP) merupakan reaktan tahap akut yang kadarnya meningkat di strok iskemik. Oleh karena itu bermanfaat sebagai petanda peramal hal terkait. Penelitian ini bertujuan untuk mengetahui perbedaan nilai antara RNL dan hs-CRP dalam meramalkan hasil pasien strok iskemik akut. Metode penelitian analitik observasional dengan rancangan kohort prospektif. Hasil dinilai dengan modified Rankin Scale (mRS) (1–2=baik; 3–6=buruk) dan Barthel Index (BI) (0–20=ketergantungan jumlah keseluruhan, 21–60=berat; 1–90=sedang; 91–99=ringan dan 100=normal). Dari 43 sampel, didapatkan laki-laki 24 orang (55,8%) dan perempuan 19 orang (44,2%) dengan rerata usia $57,12 \pm 9,8$ tahun. hubungan positif didapatkan sedang dan bermakna antara RNL dengan hasil mRS dan BI pasien strok iskemik akut ($r=0,585$; $p=0,001$ dan $r=0,564$; $p=0,001$). Hubungan positif didapatkan kuat dan bermakna antara hs-CRP dan hasil mRS ($r=0,614$; $p=0,001$) serta didapatkan hubungan positif dengan kekuatan sangat kuat dan bermakna antara hs-CRP dan hasil BI pasien strok iskemik akut ($r=0,881$; $p=0,001$). Dengan membandingkan ketepatan kedua data didapatkan RNL 86% dan hs-CRP 88% ($p=0,6554$). Perbedaan tidak bermakna terdapat antara nilai RNL dan hs-CRP sebagai peramal hasil pasien strok iskemik akut.

Kata kunci: Rasio neutrofil-limfosit, hs-CRP, hasil, strok iskemik akut, inflamasi

ABSTRACT

Inflammation process is the pathogenesis of the acute ischemic stroke, which involves the accumulation of inflammatory mediators and leukocyte infiltration. The neutrophil-lymphocyte ratio (NLR) in some studies can be used to predict the outcome of an acute ischemic stroke and is easy to carry out. The high sensitivity C-reactive protein (hs-CRP) is an acute phase reactant which levels increase in existence of ischemic stroke, and therefore is useful as the predictor marker of the disease. The aim of this study is to know the difference value of RNL with hs-CRP in predicting the outcome of patients with acute ischemic stroke by determination. The analysis was carried observationally with cohort prospective design. The outcome was then measured by modified Rankin Scale (mRS) (1–2 = good; 3–6 = poor) and Barthel Index (BI) (0–20 = total dependence; 21–60 = severe; 61–90 = moderate; 91–99 = mild and 100 = normal). Of the 43 samples, there were 24 males (55.8%) and 19 females (44.2%) with the mean age about 57.12 ± 9.8 years. There was positive, moderate and significant correlation between RNL with mRS and BI outcome of the acute ischemic stroke patients ($r=0.585$; $p=0.001$ and $r=0.564$; $p=0.001$). There was positive, strong and significant correlation between hs-CRP with mRS outcome ($r=0.614$; $p=0.001$); and there was positive, very strong and significant correlation between hs-CRP with BI outcome of acute ischemic stroke patients ($r=0.881$; $p=0.001$). By comparing its accuracy, it was found that RNL is about 86% and 88% and hs-CRP ($p=0.6554$). There was no significant difference between the value of RNL with hs-CRP as the outcome predictor of acute ischemic stroke patients

Key words: Neutrophil-lymphocyte ratio, hs-CRP, outcome, acute ischemic stroke, inflammatory

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INTRODUCTION

The stroke cases in Indonesia tend to elevate in terms of death, incident, or disability. The mortality rate caused by stroke is high, namely 15.9% for the age between 45–55 years, 26.8% for the age between 55–64 years and 23.5% for the age of 65 years. The incidence of stroke is also high, 51.6/100,000. Stroke, moreover, can trigger disability, namely 1.6% for unchanged disability and 4.3% for continuously severe disability. Males are also known to have higher risk of stroke than females. The age profiles of stroke patients are 11.8% for under 45 years, 54.2% for between 45–64 years and 33.5% for above or equal to 65 years. In other words, stroke can attack people at both productive age and old age, which potentially leading to new problems in the national health development in the future.¹

Furthermore, many factors have been evaluated for predicting the infarct size, prognosis and mortality in acute ischemic stroke, such as acute-phase reactants (C-reactive protein) and blood cell components (leukocytes and neutrophil). The pathophysiologic of acute ischemic stroke is the inflammatory process, involving endothelial activation, blood-brain barrier disorder, inflammatory mediator accumulation and leukocyte and platelet infiltration.²

The accumulation of neutrophils in the brain region begins within six (6) hours of ischemic onset, ending up to six (6) days. In some researches, the degree of infiltration is related to the severity of its neurological injury. It is known that there is a strong correlation between stroke severity and the Lymphocyte Neutrophil Ratio (NLR).³ It is also known that there is a significant positive correlation between NLR and National Institute of Health Stroke Scale (NIHSS) in acute ischemic stroke cases ($r=0.64$; $p=0.001$).² The Neutrophil Lymphocyte Ratio (NLR) score is significantly higher in the dying group than in the acute stroke patients.³

In addition, cerebral ischemia may also trigger the acute response, monitored by a significant increase in high-sensitivity CRP (hs-CRP) in acute ischemic stroke, especially during the first week. High hs-CRP value indicates a strong risk factor for death in acute ischemic stroke.⁴ High hs-CRP value in stroke (ischemic and hemorrhagic) also indicates an inflammatory response to acute stroke. Besides, the elevated value of hs-CRP can be associated with extensive infarct and bleeding, severe neurological deficits and poor outcomes.⁵ In other words, the high sensitivity C Reactive Protein is an acute phase of reactant that increases in stroke (ischemic and hemorrhagic). As a result, hs-CRP may be useful as the predictor and diagnostic markers in stroke.⁶

Stroke outcomes are functional status using scores/parameters.⁷ For convenience and outcome measurement uniformity, there are several scoring assessments that have been widely used in the world, including modified Rankin Scale and Barthel Index.⁸ Follow-up evaluation (outcome review), therefore, is required to perform at the hospital on the first day and on the following day the patient is going home.⁷

METHODS

This research was an analytic observational research with cohort prospective design. This research was conducted at the Department of Clinical Pathology in collaboration with the Department of Neurology of H. Adam Malik Hospital Medan from December 2015 to March 2016. The number of samples consist of 43 people. The exclusion criteria determined were patients with: recurrent ischemic stroke, those with acute coronary syndrome, inflammation and infection, neoplasm and immunosuppressant drug users, those with hematological disorders, as well as impaired hepatic and kidney function. This research has already obtained Ethical Clearance approved by the Research Committee of Medical Division of Medical Faculty in University of Sumatera Utara (FK USU) No. 126/KOMET/FKUSU/2016. The research was then performed with the following steps:

First, Modified Rankin Scale, known as mRS (1–2=good; 3–6=bad), as well as Barthel Index, called as BI (0–20=total dependence, 21–60=weight; 1–90=moderate; 91–99=mild and 100=normal) of those acute ischemic stroke patients (onset <7 days) were measured by the same person at the time they were admitted to the hospital or on the day as stated in their medical records;

Second, the blood material of the research subjects was taken using a vein puncture needle from the median cubital vein. The vein puncture had to be cleaned first with 70% alcohol and then dried. Next, the blood is placed in vacutainer K2EDTA tube as much as 3 mL by using venoject, while the blood in the vacutainer gel clot activator tube was taken as much as 5 mL. The content of the vacutainer K2EDTA tube was then homogenized slowly eight (8) times. Afterwards, an examination was completed within one hour after the sampling. Next, the blood in the vacutainer gel clot activator tubes was frozen for 20 minutes at room temperature and centrifuged at 3000 rpm for 20 minutes. The serum then was separated and inserted into a 1 mL aliquot;

Third, the measurement of hs-CRP values was performed after it is stored in a freezer -20°C until a predetermined check time (maximum of 6 months).⁹ Measurement of hs-CRP values was simultaneously conducted after a number of the ingredients were collected. An examination then was conducted using Cobas C 501 analyzer tool. First of all, the frozen material was melted at room temperature and then homogenized with a vortex. Next, the control solution was also equated with room temperature (20–25°C). Finally, the examination was performed with particle-enhanced turbidimetric immunoassay technique. In general, the principle of the examination is that the material is added with the R1 (buffer) reagent and R2 (latex Anti-CRP Antibodies) and then anti-CRP antibody binding to the latex microparticle will react with the antigen in the sample to form the Ag-Ab complex. Agglutination of this Ag-Ab complex is measured turbidimetrically.¹⁰ A hs-CRP value of <1 is considered as low risk, while a hs-CRP value of 1–3 is considered to be moderate and a hs-CRP value of >3 is considered to be high risk of poor outcome;

Fourth, analysis was performed using automatic cell counting Sysmex XT-4000i to obtain NLR value by examining Complete Blood Count (CBC) using flowcytometry method. The ratio of lymphocyte neutrophil was obtained by dividing absolute neutrophil value with absolute lymphocyte value.¹⁰ Neutrophil-lymphocyte ratio with a value of ≤5 can be considered to have low risk, while NLR with a value of >5 can be considered to have high risk.

Fifth, on the 14th day before the patients going home, outcome examination on the entire research subjects was conducted (BI and mRS replication) by the same person; And the last step, the data analysis was performed using SPSS. A correlation test with contingency and gamma coefficients was conducted. The sensitivity, specificity, accuracy values as well as Z value for meaning were also examined. For all the statistical tests were performed, a p value of <0.05 was considered to be significant.

RESULTS AND DISCUSSION

The number of the research subjects in this research was 43 (forty-three) patients who suffer acute stroke, consisted of 24 (twenty-four) males (55.8%) and 19 (nineteen) females (44.2%). The mean age of those research subjects was 57.12±9.8 years old with the age range of 33 to 75 years. The highest number of those research subjects was found in the age group of 47–60 years, about 20 (twenty) patients (46.6%). Meanwhile, the lowest number of those research subjects was found in the age group between 33–46 years, about five people (11.6%).

The correlation of NLR with modified Rankin Scale (mRS) of acute ischemic stroke outcomes was then assessed by performing a correlation test with contingency coefficient. The results of the correlation test indicated a linier correlation with moderate and significant strength (r=0.585; p=0.001) as seen in Table 1.

Table 1. The correlation of NLR with mRS of acute ischemic stroke outcome

		Outcome (mRS)		Total	r	P
		Bad	Good			
NLR values	>5 (High risk)	18	3	21	0.585	0.001
	≤5 (Low risk)	3	19	22		
Total		21	22	43		

Contingency Coefficient Test

Table 2. The correlation of NLR with BI of acute ischemic stroke patients

NLR values	Outcome (BI)					Total	r	p
	Dependency:							
	Total	Severe	Moderate	Mild	Normal			
>5 (High risk)	9	9	3	0	0	21	0.585	0.001
≤5 (Low risk)	1	3	18	0	0	22		
Total	10	12	21	0	0	43		

Contingency Coefficient Test

Next, the correlation of NLR with Barthel Index (BI) of acute ischemic stroke outcomes was also assessed by conducting a correlation test with contingency coefficient. Results of the correlation test showed a linier correlation with moderate and significant correlation strength ($r=0.564$; $p=0.001$) as seen in Table 2.

Afterwards, the correlation of hs-CRP with mRS of acute ischemic stroke outcomes was assessed by performing a correlation test with contingency coefficient. The results of the correlation test indicated the linier correlation with a strong and significant correlation strength ($r=0.614$; $p=0.001$) as seen in Table 3.

Table 3. The correlation of hs-CRP with mRS of acute ischemic stroke outcome

hs-CRP values	Outcome (mRS)		Total	r	P
	Bad	Good			
>3 (High risk)	17	3	20	0.614	0.001
1-3 (Moderate risk)	3	1	4		
<1 (Low risk)	1	18	19		
Total	21	22	43		

Correlation test with contingency coefficient

Similarly, the correlation of hs-CRP with Barthel Index (BI) of acute ischemic stroke outcomes then was assessed by conducting the gamma correlation test. Results of the correlation test which showed a linier correlation with a very strong and significant correlation strength ($r=0.881$; $p=0.001$) as seen in Table 4.

Next, the differences between NL Rand hs-CRP values as predictors of an acute ischemic stroke outcome was assessed by comparing the accuracy,

Table 4. The correlation of hs-CRP with BI of acute ischemic stroke patients

hs-CRP values	Outcome (BI)					Total	R	p
	Dependency:							
	Total	Severe	Moderate	Mild	Normal			
High risk	9	8	3	0	0	20	0.881	0.001
Moderate risk	1	2	1	0	0	4		
Low risk	0	2	17	0	0	19		
Total	10	12	21	0	0	43		

Gamma correlation test

Table 5. The correlation of NLR values with mRS of acute ischemic stroke outcome

		Outcome (mRS)		Total
		Bad	Good	
NLR values	High risk	18	3	21
	Low risk	3	19	22
	Total	21	22	43

sensitivity and specificity of the two tests and then calculating the Z value to obtain significance. The results revealed that there was no significant difference in the accuracy between NLR and hs-CRP values as predictors of acute ischemic stroke outcome ($p=0.6554$) as seen in Table 5 and Table 6.

Table 6. The correlation of hs-CRP values with mRS of acute ischemic stroke outcome

		Outcome (mRS)		Total
		Bad	Good	
hs-CRP values	Moderate-high risk	20	4	24
	Low risk	1	18	19
	Total	21	22	43

NLR values used to predict bad outcome were derived from Table 5 as follow:

Accuracy = $a+d/N=18+19/43=37/43=0.86=86\%$;

Sensitivity = $a/a+c=18/18+3=18/21=0.85=85\%$; and

Specificity = $d/b+d=19/3+19=19/22=0.86=86\%$

Hs-CRP values used to predict bad outcome buruk were derived from Table 6 as follow:

Accuracy = $a+d/N=20+18/43=38/43=0.88=88\%$;

Sensitivity = $a/a+c=20/20+1=20/21=0.95=95\%$; and

Specificity = $d/b+d=18/4+18=18/22=0.81=81\%$.

$$Z = \frac{p - P}{\sqrt{P \cdot Q / N}}$$

$$= \frac{0.88 - 0.86}{\sqrt{(0.86 \times 0.14) / 43}} = 0.02 / 0.05 = 0.4$$

To assess the differences in accuracy between RNL values (86%) and hs-CRP values (88%), it is then necessary to find p value. But, Z value had to be analyzed first:

p value then could be derived from Z value =0.6554 (p<0.05=significant)

Note:

Z = accuracy

p = accuracy of hs-CRP (0.88)

P = accuracy of RNL (0.86)

Q = 1-P=1-0.86=0.14

N = Number of sample = 43

The correlation of NLR with mRS of an acute ischemic stroke outcome in this research was in linier with the moderate and significant correlation strength (r=0.585; p=0.001). Similarly, the correlation of NLR with Barthel Index (BI) of acute ischemic stroke outcome in this research was also in linier with the moderate and significant correlation strength (r=0.564; p=0.001). Like the results of the research conducted by Tokgoz *et al.*² in 2013 which examining the NLR values as a predictor of acute ischemic stroke also revealed the linier correlation with strong and significant correlation strength (r=0.64, p=0.001) using the National Institute Health of Stroke Scale (NIHSS).² Similarly, the research performed by Gokhan *et al.*³ in 2013 assessing NLR on ischemic and acute hemorrhagic strokes as well as on the transient ischemic attack showed that NLR values in the dead group were significantly higher (p=0.001), while NLR values in transient ischemic stroke patients were significantly lower than in the acute hemorrhagic stroke patients (p=0.001). In the research is also found that NLR values in the acute ischemic stroke group were significantly higher than in the ischemic stroke with large arterial atherosclerosis subtype (p=0.001).³

The pathogenesis of cerebral infarction, moreover, is an inflammatory process causing liquefaction necrosis. As a result, there existence of leukocyte migration to the infarction area were also increases. These inflammatory cells then exacerbate the damage by worsening the penumbral area as well as damaging the core area of the infarct. On the other hand, neutrophil migration to the damaged areas is considered as an early response to the brain ischemia. The migration

occurs within six (6) to 24 hours of the ischemic onset. Proteolytic enzymes, such as phosphatase acids and reactive oxygen species, will be released to the infarcted area via neutrophil accumulation in the ischemic area or in the reperfusion ones. Consequently, the number of neutrophils is related to the severity of brain tissue damage and poor neurological outcome.²

The lymphocytes also play a role in the inflammatory response. The lymphocytes begin to increase on the first day after the onset of stroke and its peak after seven (7) days. T lymphocytes are also thought to play the role in repairing of inflamed tissues. The improvement which caused by lymphocytes is associated with the release of cytokines and growth factors activating microglials. In addition, the lymphocytes have a negative correlation with the mortality in ischemic stroke.² Similarly, the recent researches also reveal that high NLR values also have the same predictive character values on the prognosis, severity and the mortality in atherosclerosis (ischemic stroke).³

The correlation of hs-CRP with mRS of the acute ischemic stroke outcomes in this research was in linier with a strong and significant correlation strength (r=0.614; p=0.001). Similarly, the correlation of hs-CRP with BI of the acute ischemic stroke outcomes in this research was linier with a very strong and significant correlation strength (r=0.881; p=0.001). Like these study results, the research conducted by Mishra *et al.*⁵ in 2010 showed that hs-CRP values in the stroke group were significantly higher than the control one (p=0.001). The hs-CRP values in the hemorrhagic stroke group were also significantly higher than in the ischemic group (14.8±6.2 vs 10.7±5.4) with a value of p=0.001. Thus, it can be concluded that a significant increase in hs-CRP values in stroke suggests an inflammatory response to the acute stroke and then enhancing further of the hs-CRP values which can be associated with the extensive infarct and bleeding, severe neurological deficits and poor outcomes.⁵ Similarly, a research conducted by Huang *et al.*¹¹ on hs-CRP as a strong risk factor for death in acute ischemic stroke in the Chinese population in 2012 revealed that high Hs-CRP as well as in the same condition of NIHSS on the day of admission (HR 2.35; p=0.003) was considered as an independent risk factor for the mortality (HR 6.48, 0=0.002).¹¹

Acute stroke can also trigger an inflammatory response, resulting in an increase in CRP. CRP is a glycoprotein produced by the hepatic. CRP is normally absent in the blood. The presence of acute inflammation with tissue damage can stimulate CRP production.¹² An increase in hs-CRP levels occurs

between 12–24 hours after stroke onset.⁵ A research shows CRP contributes to secondary brain damage after the onset of the related ischemic, this happened possibly through complement activation, leading to the tissue damage.¹²

Next, the difference between NLR values and hs-CRP values as the predictors of acute ischemic stroke outcome was assessed by comparing: the accuracy, sensitivity and specificity of the two tests and then followed by calculating the Z value to obtain the significance value. The results of the NLR examination in the predicting outcomes of acute ischemic stroke patients found an accuracy of 86%, a sensitivity of 85% and a specificity of 86%. On the other hand, the results of the hs-CRP examination in predicting the outcomes of the acute ischemic stroke patients showed an accuracy of 88%, a sensitivity of 95% and a specificity of 81%. The calculation of Z value indicated that p value was not significant (0.6554). Consequently, it can be concluded that there was no significant difference in the accuracy between NLR and hs-CRP values as the predictors of an acute ischemic stroke outcomes.

A previous research performed by Kim *et al.*¹³ in 2016 on NLR in predicting short-term functional outcomes of an acute ischemic stroke patients showed a sensitivity of 86.4% and a specificity of 53.3%.¹³ Another previous research conducted by Ghabaee *et al.*¹² in 2013 on the use of hs-CRP in predicting the mortality and poor outcomes at an acute ischemic stroke found a sensitivity of 81% and a specificity of 80%.¹² Similarly, a previous research conducted by Shoaeb *et al.*¹⁴ in 2014 on the use of hs-CRP in predicting poor outcomes (with mRS assessment) found a sensitivity of 75% and a specificity of 82%. Unfortunately, there still have not been any researches comparing the accuracy of NLR and hs-CRP values in predicting outcomes of acute ischemic stroke patients.¹²

CONCLUSION AND SUGGESTION

In conclusion, based on this research there is no significant difference between NLR and hs-CRP values as an acute ischemic stroke outcome predictors ($p=0.6554$). Consequently, the clinicians working in the areas where there is no hs-CRP examination facility may use NLR score to predict the outcomes of the acute ischemic stroke patients. Neutrophil-lymphocyte ratio scores can be obtained from a complete blood

examination that can be conducted in almost of all laboratory facilities with affordable cost.

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