# NEUTROPHIL LYMPHOCYTE RATIO IN DIAGNOSIS OF STROKE TYPE IN MOHAMMAD HOESIN HOSPITAL PALEMBANG

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**Abstract**

Background and aims: Stroke is a disease of acute focal and global functional brain disorder due to blood flow occlusion to the brain. Disorder of blood brain barrier may trigger leukocyte infiltration and release of proinflammatory cytokines following an acute ischaemic stroke. CT-scan is the gold standard for diagnosing stroke which is not available yet in remote areas in Indonesia. This research aims to indentify the diagnostic value of neutrophil and lymphocyte ratio in order to determine stroke type (hemorrhagic and non hemmorrhagic).

Method: this diagnostic test research was conducted in the inpatients ward of Neurology Departement of Dr Mohammad Hoesin Hospital in Palembang from August 2017 to November 2017. The number of samples in this research that meet the inclusion criteria and exclusion criteria were 228 samples. The frequency and distribution of the data are explained through tables and figures and the cut point of N/L ratio are analyzed by ROC curve and the sensitivity and specificity value is obtained based on the N/L cut point. Analysis of the data was conductedusing SPSS22.0version.

Results: This research shows that there is no difference on the age range, sex, and onset of the disease in patients with stroke hemorrhagic and non hemorrhagic (p>0.05). Based on ROC analysis, cut point of N/L ratio is 3.14 with AUC value 0.764 (0.701-0,826). Based on the cutting point value to determine classification of hemorrhagic and non hemorrhagic stroke, the sensitvity value is 72.99%, specificity 75.82%, positive predictive value (PPV) 82%, and negativepredictivevalue(NPV)65.1%.

Conclusion: Ratio of N/L with cut point value 3.414 has sensitivity 72.99% and specificity 75.82%

Keywords: Hemorrhagic, Ischaemic, Sensitivity, Specificity, Cut Point, Diagnostic Test

## 1.Introduction

Stroke is a disease of acute focal and global functional brain disorder due to occlusion of blood flow to the brain. These impairment of brain function will lead to the symptoms of stroke.[1] Stroke is a manifestation of disturbances in the blood flowing to the brain usually called "cerebral arterial disease" or "cerebrovascular disease" and can potentially interrupt the blood supply to the brain.

Cytokines are chemical mediators of the immune and inflammatory processes that are small molecules of proteins with various biological activities and is active at even at small concentrations. Cytokines arise as a primary reaction to external stimulation and do not exist in normal hemostasis.[9] As a direct consequence of ion imbalance and free calcium accumulation arising from ischemic brain lesions, the

cytokines release free amino acids and other pro-inflammatory cells as result of fat metabolism. This is believed to increase, induce and release the proinflammatory cytokine cascade.

Impaired blood-brain barrier causes leukocyte infiltration and release of proinflammatory cytokines after the occurrence of acute non-hemorrhagic stroke. Recent studies have shown that peripheral leukocyte levels are elevated after brain ischemia. The number of early peripheral leukocytes after stroke can help predict the severity of stroke, disability rate, and final infarct volume. Some publications show that the number of leukocytes at admission can predict the likelihood of non-hemorrhagic stroke and the impact of neurological disability in daily living activities. Recent studies have shown that peripheral leukocyte cells and other inflammatory processes play an important role in the pathophysiology of acute non-hemorrhagic stroke. The neutrophil-to-lymphocyte (NLR) ratio is an easily accessible, economical, and readily available inflammatory parameter in small and Clinical Hospitals and has recently emerged as a prognostic marker useful for predicting the mortality and prognosis of some cardiovascular and neurologic diseases.

Researches conducted so far were only to compare the output based on lymphocyte neutrophil ratio between non hemorrhagic stroke patients and hemorrhagic stroke, but there is no research that assesses what is the cut point ratio of lymphocyte netrophil in non hemorrhagic and haemorrhagic stroke patients, besides Gold standard to diagnose stroke is an head CT Scan where this diagnostic tool is still difficult to find in remote areas of Indonesia. This encourages researchers to conduct research that aims to find out how sensitive and specific are neutrophil and lymphocyte counts whic is discouraged in the form of neutrophil and lymphocyte ratiom compared to the gold standard in determining stroke type.

## 2.Research Purposes

### 2.1. General Purpose

To determine the diagnostic value of lymphocyte netrophil ratio in determining stroke type (haemorrhagic or non hemorrhagic).

### 2.2. Special Purpose

To know the cut-off point of neutrophil-lymphocyte ratio in determining stroke type (haemorrhagic or non hemorrhagic). Comparing diagnostic values (sensitivity and specificity)of neutrophil-lymphocyte ratio to the gold standard (Head Ct-scan) in determining stroke type (haemorrhagic or non hemorrhagic)

## 3.Research Methods

### 3.1. Research Design

This study is a diagnostic test comparing the neutrophil-lymphocyte ratio to the gold standard (Head Ct-Scan) in determining stroke type.

*3.2 Place and Time of Research*

   This research was conducted in Medical Record Departement RSUP dr Mohammad Hoesin Palembang. in August to October 2017.

*3.3. Population and Sample*

   The target population is all adult patients with stroke (stroke) who seek treatment at the clinic or hospitalized in the hospital. Affordable population are all stroke patients who come to the clinic and hospitalization of Neurology Department Dr.Muhammad Hoesin Palembang Hospital. The sample in this study was taken from medical record data of stroke patients who met the study criteria. The study included all patients who were diagnosed with stroke. Medical record data, laboratory results in the form of Leukocytes differential count to obtain data of neutrophil-lymphocyte ratio and the results the head CT-scan were noted. The data obtained are then classified by coding, entering the data into computer which then is processed using SPSS 22, and performed data cleaning to recheck the data that has been entered into the computer and fix it if there is error. Then the cut-off point off the neutrophil- lymphocyte ratio were made based on hemorrhagic or non haemorrhagic diagnosis. Then calculations were made to obtain sensitivity, specificity values of the the neutrophil-lymphocyte ratio calculation.

**4. Research Result**

   A diagnostic test research to determine the diagnostic value of neutrophil-lymphocyte ratio in determining stroke type (haemorrhagic or non hemorrhagic) has been done at the Hospital Department of Neurology Hospital Dr.Muhammad Hoesin Palembang, starting from January 2015 to December
2016. Research sample is 369 patients, and 228 patiens meets the inclusion criteria.

*4.1. General Characteristics of Research Subjects*

   In this study of 228 subjects, 91 patients (39.9%) were diagnosed with Hemorrhagic Stroke and 137 patients (60.1%) with non Hemorrhagic Stroke.

**Table 1**. Characteristics of Anatomical Pathology Classification

| STROKE | Frequency | |
|---|---|---|
| | N | % |
| Hemorrhagic | 91 | 39,9 |
| Non Hemorrhagic | 137 | 60,1 |
| Total | 228 | 100,0 |

   The general characteristics of the study subjects of adult patients with stroke are shown in Table 2. The mean age of stroke patients was $60.23 \pm 13.14$ years old with age range of 29-90 years where mean age of patients with non hemorrhagic stroke was $61.15 \pm 12.85$ years with age range of 33-90 years while patients with Hemorraghic stroke were $58.86 \pm 13.51$ years with an age range of 29-85 years. From the statistical analysis, there were no significant differences in age between the non hemorrhagic stroke group and the hemorrhagic stroke ($p = 0.273$; $p > 0.05$).

**Table 2**. Characteristics of Research Subject

| Characeristic | Population | Stroke | | P-value |
|---|---|---|---|---|
| | | Non Hemorrhagic | Hemorrhagic | |
| Age (tahun), | | | | |
| Mean ± SD | 60,23 ± 13,14 | 61,15 ± 12,85 | 58,86 ± 13,51 | 0,273[a] |
| Median (min-max) | 60 (29-90) | 60 (33-90) | 59 (29-85) | |
| Jenis Kelamin, n(%) | | | | |
| Male | 119 (52,2) | 66 (48,2) | 53 (58,2) | 0,175[b] |
| Female | 109 (47,8) | 71 (51,8) | 38 (41,8) | |
| Onset, (hari) | | | | |
| mean ± SD | 1,71 ± 1,29 | 1,85 ± 1,44 | 1,48 ± 0,99 | 0,057[a] |
| Median (min-max) | 1 (1-7) | 1 (1-7) | 1 (1-6) | |

[a] *Mann-Whitney*, p =0,05

[b] *Chi square, Continuity correction*, p =0,05

From the total of 228 stroke patients 119 (52.2%) are males and 109 (47.8%) are females where in patients with non hemorrhagic Stroke, 66 (48.2 %) are male and 71 (51.8%) are female whereas in patients with Hemorrhagic Stroke, male patients were 53 people (58.2%) and 38 are women (41.8%). From the statistical analysis, there were no significant differences of sex between the non hemorrhagic stroke group and the hemorrhagic stroke (p = 0.175; p> 0.05).

The mean onset of stroke in this study was 1.71 ± 1.29 with an onset range of 1 to 7 where the mean onset of patients with non hemorrhagic stroke was 1.85 ± 1.44 with an onset range of 1-7 whereas patients with hemorrhagic stroke were 1 , 48 ± 0.99 with an onset range of 1-6. From the statistical analysis, there was no significant difference in onset between the non hemorrhagic stroke group and the hemorrhagic stroke (p = 0.057; p> 0.05).

## 4.2. *Characteristics of Research Subject Laboratory*

Laboratory characteristics of study subjects of adult patients with stroke are shown in table 3. The mean of neutrophil of stroke patient was 70,42 ± 12,41 with netrofil 47-96 where the mean of neutrophil of patient with non hemorrhagic stroke was 65,89 ± 12,44 with 47-93 netrophil range while the patient with hemorrhagic stroke was 77,24 ± 8.74 with a netrofil range of 60-96. From the statistical analysis, there were significant differences in the number of neutrophils between the non-hemorrhagic stroke group and the hemorrhagic stroke group in which the number of neutrophils of non hemorrhagic stroke patients was lower than the number of hemorrhagic stroke patients (p = 0,000; p <0.05).

**Tabel 3**. Laboratory characteristic of study subjects.

| Characteristic | Population | Stroke | | P-value |
| --- | --- | --- | --- | --- |
| | | Non Hemorrhaguc | Hemorraghic | |
| Neutrophil, (%) | | | | |
| Mean ± SD | 70,42 ± 12,41 | 65,89 ± 12,44 | 77,24 ± 8,74 | 0,000[a] |
| Median (min-max) | 70 (47-96) | 62 (47-93) | 78 (60-96) | |
| Lymphocytes, (%) | | | | |
| mean ± SD | 21,34 ± 10,61 | 24,57 ± 10,04 | 16,47 ± 9,57 | 0,000[a] |
| Median (min-max) | 21 (2-45) | 26 (3-42) | 16 (2-45) | |
| NLR,(%) | | | | |
| Mean ± SD | 5,59 ± 6,37 | 4,3 ± 5,23 | 7,55 ± 7,39 | 0,000[a] |
| Median (min-max) | 3,33 (1,12-48) | 2,45 (1,12-31) | 4,88 (1,64-48) | |

[a] *Mann-Whitney*, p =0,05

The mean lymphocyte of stroke patients was 21.34 ± 10.61 with the lymphocyte range 2-45 where the mean lymphocyte of patients with non hemorrhagic stroke was 24.57 ± 10.04 with the lymphocyte range of 3-42 whereas the patients with hemorrhagic stroke were 16.47 ± 9.57 with 2-45 lymphocyte range. From the statistical analysis, there were significant differences in the number of lymphocytes between the non-hemorrhagic stroke group and the hemorrhagic stroke where the number of non- hemorrhagic stroke lymphocytes was higher than the number of lymphocytes of Hemorrhagic Stroke patients (p = 0.000, p <0.05).

The mean NLR of stroke patients was 5.59 ± 6.37 with NLR range 1.12-48 where the mean NLR of patients with non hemorrhagic stroke was 4.3 ± 5.23 with NLR range of 1.12-31 whereas patients with hemorrhagic stroke were 7.55 ± 7.39 with NLR range 1.64-48. From the statistical analysis, there were significant differences in the number of NLR between non-hemorrhagic stroke group and Hemorrhagic Stroke where the number of NLR of non hemorrhagic Stroke patients was lower than the number of NLR of Hemorrhagic Stroke patients (p = 0,000; p <0.05).

*4.3. Diagnostic Value of Netrophil Lymphocytes Ratio (NLR) in Determining the Stroke type (Hemorrhagic or Non Hemorrhagic)*

To find out the diagnostic value of Netrophil Lymphocyte ratio in determining stroke type (haemorrhagic or non hemorrhagic) we need to get NLR sensitivity and specificity by analyzing it using receiver operating curve (ROC) to find NLR cut off point. Figure 1 is the ROC curve of NLR stroke patients. The curve has an area value under the curve (AUC, area under curve) 0.764 (IK 0.701-0.826) which means that the NLR ROC curve AUC value has quite good discrimination Netrophil Lymphocyte ratio.
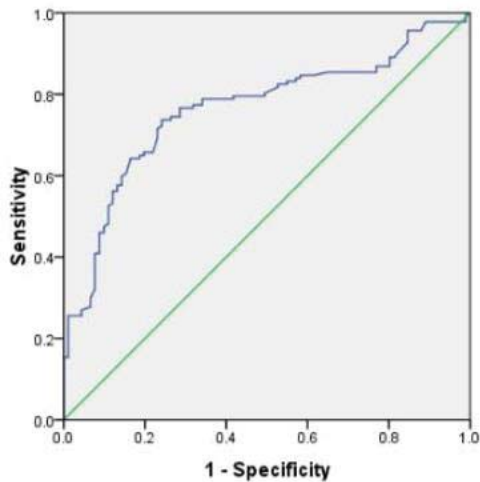
**Figure 1**. The ROC curve of NLR stroke patients.Determination of NLR cutting points, done by making a curve between sensitivity, specificity and NLR.
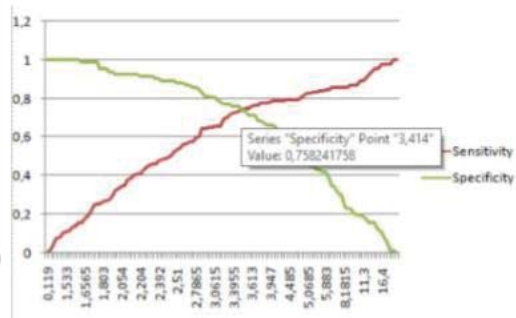
**Figure 2.** Intersection of sensitivity curve and specificity curve of, NLR in stroke patients.

The sensitivity and specifity curve intersects in the number 3,414 as shown in figure 2. This means that NLR value smaller or equal to 3,414 or greater than 3,414 is best to determine stroke type.

**Tabel 4.** Diagnostic test table.

| | | Diagnose | | Total |
|---|---|---|---|---|
| | | non Hemorrharic Stroke | Hemorrhagic Stroke | |
| Ratio | ≤ 3.414 | 100a | 22b | 122 |
| N/L | >3.414 | 37c | 69d | 106 |
| Total | | 137 | 91 | 228 |

Based on Table 4, diagnosing stroke based on NLR has a sensitivity of 72.99%, 75.82% specificity, 82% positive predictive value (PPV) and negative predictive value (NPV) of 65.1%.

## 5. Discussion

Stroke is a manifestation of disturbances in the blood flowing to the brain usually called "cerebral arterial disease" or "cerebrovascular disease" and is a lethal potential interruption of blood supply to the brain.[2][3]

Based on the anatomical pathology of stroke, it can be grouped into Hemorrhagic Stroke and Non Hemorrhagic Stroke.[1] Of the samples obtained from medical records totaling 369 patients diagnosed as Stroke in 2015-2016, from reports of stroke patients in the neurology section there are 600 cases of stroke in 2017, the number of patients in the medical record is less because the program in the medical record is

being repaired, so many have not been recorded. In this study of 228 subjects that met the inclusion criteria, 39,9% of patients were diagnosed with Hemorrhagic Stroke and as many as 60.1% with non Hemoragic Stroke. Percentage of Non Hemorrhagic Stroke were more than Hemorrhagic Stroke. The results of this study are not much different from the research conducted by Mutmainna in 2013 where the percentage of hemorrhagic stroke is 23.9% while the percentage of non hemorrhagic stroke is 76.1% .[38] Similarly, research conducted by Taruli and Krisnawati in 2012 showed that the percentage of hemorrhagic stroke was 10.4%, the figure was smaller than non-hemorrhagic Stroke percentage of 89.6% .[39]

From the above research, it can be concluded that the percentage of non hemorrhagic Stroke incidence is greater than Hemorrhagic Stroke. In the United States Stroke is ranked the 3rd cause of death after heart disease and cancer. Every year 500,000 Americans have stroke, 400,000 of the people are affected by non-hemorrhagic stroke and 100,000 suffer hemorrhagic stroke (including intracerebral and subarachnoid hemorrhage) with 175,000 deaths.[4]

The percentage of sex in stroke patients is almost equal (5: 4) where male is more dominant than female but the difference is not too large and not statistically significant. These results were supported by research by Rio Christanto et al in the year in which sex percentages were almost equal with male slightly more than female (5: 4) . Similarly, research conducted by Lannywati et al in 2016 showed that the percentage of male and female in stroke patients is almost equal but the percentage of male  is less than female (4: 5) .[20]

In this study, the average age of stroke patients are approximately 60 years with age range 29-90 years. The results are similar with the research conducted by Taruli and Krisnawati in 2012 where the average age of stroke patients is found in approximately 60 years with age range 14-91 years.[39] Data in Indonesia showed more male patients than women with the age below 45 years 11.8%, age 45-64 years 54.2%, and age above 65 years by 33.5% .[5],[6],[7],[8] In Lampung the prevalence of stroke increases with age where the prevalence of stroke is similar to male and female.[5]

In this study the results obtained were; there is no difference in age, sex and onset of disease between patients with hemorrhagic and non hemorrhagic stroke. So it can be concluded that Stroke patients in this study were not influenced by sex and disease onset.

Neutrophils are a type of granulocytes with a typical solid core consisting of two to five lobes and a pale cytoplasm with irregular borders containing many pink-blue (azurophilic) or gray-blue granules, a normal amount of 55-70% of total number of leukocytes deployed in acute inflammation is neutrophils. In this study, the number of neutrophils in Hemorrhagic Stroke patients was higher than the number of neutrophils of non hemorrhagic Stroke patients and was statistically significant. In the acute phase (minutes to hours), the proinflammatory mediator is released by the ischemic brain tissue thus stimulating the expression of adhesive molecules on vascular endothelials and leukocytes.  This process leads to the adhesion of leukocytes to the endothelium, followed by the process of migrating leukocytes out of the blood vessels. In the subacute phase (hour-day), the leukocytes release cytokines and chemokines that strengthen the inflammatory reaction and cause disturbances in blood brain barrier, edema, and neuron death. In Hemorrhagic Stroke the proinflammatory mediator causes a strong

adhesion that so the more neutrophils converge in the damaged and broken vascular endothelium which is an inflammatory response.[31]

Lymphocytes are agranular leukocyte that is an important component of the immune response and is derived from hemopoietic stem cells, a normal amount is of 20-40%. [32] Lymphocytes in this study tended to be more numerous in non-hemorrhagic Stroke patients than Hemorrhagic Stroke with statistically significant differences.

Research conducted by Kowianski P et al states that a bleeding stroke is a natural injury that triggers an inflammatory response or inflammatory process. Kowianski further explains that the inflammatory process is a protective reaction of the organism from injury and is an integrated adaptive mechanism aimed at maximizing recovery and restoring the integrity and function of the damaged tissue. Inflammation is characterized by a double response that involves stress and adaptation and is controlled from the local and systemic levels with the aim of eliminating and replacing necrotic tissue and damaged tissue with connective tissue. The process of inflammation is a continuous cycle in increasing the pro-inflammatory mediators themselves, one of which is the leukocyte component.

Based on research conducted by Muhibbi (2004) it is explained that, the large extent of damage to brain tissue is associated with the accumulation of leukocytes. Leukocyte accumulation in non hemorrhagic stroke patients is more common in the ischemic center. However, leukocyte accumulation was not shown in patients with small infarct size in the head CT and head MRI. Whereas in hemorrhagic stroke patients, leukocyte accumulation was obtained in all patients. In stroke, the leukocytes are activated and caused inflammation. This activation increases the adhesion of leukocytes to the endothelium and the migration of leukocytes into the brain parenchyma.

The neutrophil-to-lymphocyte (NLR) ratio is an easily accessible, economical, and widely available inflammatory parameter and has recently emerged as a prognostic marker useful for predicting mortality and the prognosis of several cardiovascular and neurologic diseases.[11] In this study, NLR of non Hemorrhagic stroke patients is lower than the number of NLR in Hemorrhagic Stroke patients. The results of this study is different from some research, among others, research conducted Oh et al. (2009) in which the ratio of lymphocyte neutophyl (NLR) increased in non hemorrhagic stroke patients compared to normal people, especially in the type of vascular atherosclerosis and cardioembolic.[13] In addition, research conducted by Suh et al in 2017 states that an increase in NLR can be an independent risk factor of non-hemorrhagic stroke occurrence that may be used as a clinical indicator for non-hemorrhagic stroke.[14] The difference was probably due to previous studies being comparable to normal patients whereas in studies comparing NLR between non hemorrhagic and hemorrhagic Stroke patients does not exist.

In this study, NLR cutting point was 3.414 where patients with NLR less than or equal to 3.414 were more likely to suffer non hemorrhagic Stroke than Hemorrhagic Stroke or in other words NLR smaller or equal to 3,414 or more than 3,414 can determine stroke type, Sensitivity and the specificity value of NLR in determining stroke type was 72.99% and 75.82%, meaning NLR's ability to determine that stroke type suffered by the patient was non hemorrhagic stroke is 72.99% while NLR's ability to determine that the stroke type of patients is hemorrhagic stroke is 75.82%.

In this study, we also get the positive predictive value (PPV) 82% and negative predictive value (NPV) 65,1%, this means the ability of NLR value ≤ 3,414 in diagnosing non hemorrhagic stroke is 82% while the ability of NLR value >3,414 in diagnosing stroke hemorrhagic was 65.1%.

From the above data the sensitivity and specificity is less than 80% so the NLR value can not be used in diagnosing the stroke type. Head CT-scan is still need to make a definite diagnose of stroke.

The weakness of this study is the variation of onset at the time of data collection, so we do not know the best time of NLR for diagnosing Hemorrhagic Stroke or non Hemorrhagic Stroke and a comparison of other stroke predictors with NLR in strengthening the diagnosis of stroke is not done.

## 6. Conclusion

The cutoff ratio of NLR in determining stroke type was 3.414. Where the NLR of less than or equal to 3,414 was found in non Hemorrhagic Stroke and NLR value above 3,414 was found in Hemorrhagic Stroke. The NLR has a sensitivity of 72.99%, specificity of 75.82%. Which means the ability of NLR to determine that the type of stroke suffered by the patient is non hemorrhagic stroke is 72.99% while the ability NLR to determine that the type of stroke suffered by patients is hemorrhagic stroke is 75.82%.

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