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DIAGNOSTIC VALUE OF NEUTROPHIL LYMPHOCYTE RATIO TO DIFFERENTIATE ISCHEMIC AND HEMORRHAGIC STROKE

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ABSTRACT

Stroke is a neurologic emergency disease and the main cause of high mortality. The inflammatory process in stroke due to cell and tissue damage causes an increase of leucocyte prominently neutrophil. Neutrophil Lymphocyte Ratio (NLR) is an easy-to-measure inflammatory marker. There is only a few data of NLR in Indonesia. This study aimed to know the difference in NLR values among ischemic and hemorrhagic stroke and to find out the diagnostic NLR to differentiate ischemic and hemorrhagic stroke patients. This study was a retrospective cross-sectional study using secondary data from Medical Record of Wahidin Sudirohusodo Hospital, Makassar. Leucocyte, neutrophil, and lymphocyte first data from adult stroke diagnosed patients were taken. Data statistically analyzed and diagnostic value of NLR was determined by Receiver Operating Curve (ROC) analysis. Total of 402 patients was enrolled, 214 (54.72%) with ischemic stroke and 182 (46.8) with hemorrhagic stroke. There was a significant NLR difference between ischemic stroke (median 7.23) and hemorrhagic stroke (median 3.65) (p<0.001). Using cut-off 5.18, ROC curve showed of (AUC) 0.730 which had a weak performance to differentiate ischemic and hemorrhagic stroke with sensitivity 67.8% and specificity 68.6%. The neutrophil-lymphocyte ratio in hemorrhagic stroke is higher than ischemic stroke. Further studies with larger and more evenly distributed samples and consideration of sampling time are a suggestion.

Key words: Stroke, ischemic, hemorrhagic, NLR

INTRODUCTION

Stroke is defined by the World Health Organization (WHO) as a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin. Stroke is a serious neurological emergency and ranked high among death causes. Stroke affects approximately 750,000 USA people every year and ranked third among mortality causes. In every 1000 people in Indonesia, there are eight suffer from a stroke in the population of 45-54 years old.² Three types of stroke are; hemorrhagic and ischemic stroke. Hemorrhagic strokes are the strokes that caused by the rupture of blood vessels in the brain which can inundate and suppress the brain tissues and causes damages in brain coordination function. The reduced blood flow to an area in brain tissues caused ischemic strokes. Reperfusion injury in ischemic stroke is a further dysfunction of the brain due to inflammation response to body reaction to returning the blood flow to the ischemic area in stroke. The inflammatory response begins with the production of proinflammatory cytokines in an ischemic area that will result in mobilization and upregulation of leukocytes, particularly the neutrophil.

According to several studies, the extent of damage in brain tissue correlates to the presence of leukocyte accumulation. A study by Grigorian suggests that neutrophil accumulation is first detected in the first six hours after the occurrence, and reaches a maximum at 24 hours and remains at a high level until nine days before it decreases. A study by Hamzah suggests that the higher stroke lesion volume will cause higher neutrophil number either in ischemic or hemorrhagic stroke.³

Neutrophil-Lymphocyte Ratio (NLR) is an inflammation marker which is currently being used in various studies due to its simple procedure and inexpensive cost compared to other markers such as C-Reactive Protein (CRP) and procalcitonin. At the beginning of its process, stroke induces the entrance of neutrophil into the brain but not lymphocyte, making the ratio increases. The neutrophilic reaction caused by the stroke is not significantly high, that the
average value of neutrophil is not highly significant compared to NLR. The physiological NLR is less than 5 (normal neutrophil value <75% and lymphocyte >15%). In a pathologic condition, for example by severe infection or systemic inflammation, the neutrophil-lymphocyte ratio increases to more than 6. A study by Gokhan et al. showed that NLR patients with hemorrhagic and ischemic stroke increased significantly that it could be used in establishing the diagnosis and as prognostic predictor in hemorrhagic or ischemic stroke. 

Data on NLR in stroke in Indonesia, as far as the authors know, is limited. Therefore we are interested in studying the NLR in ischemic and hemorrhagic stroke patients in the Dr. Wahidin Sudirohusodo Hospital, Makassar. This study is expected to help clinicians to differentiate ischemic and hemorrhagic stroke based on the neutrophil-lymphocyte ratio. This study aims to know the difference in NLR values among ischemic and hemorrhagic stroke and to find out the diagnostic NLR to differentiate ischemic and hemorrhagic stroke patients.

METHODS

This study was a cross-sectional retrospective study using secondary data obtained from the Medical Record Installation of Dr. Wahidin Sudirohusodo Hospital Makassar, from July 2015 to June 2016. From 1289 patients diagnosed with stroke, 402 patients were meeting the inclusion criteria. Inclusion criteria in this study were adult patient (above 18 years old) diagnosed with hemorrhagic or ischemic stroke by a clinician based on evaluation results and CT scan completed with routine blood test results taken during admission to the Dr. Wahidin Sudirohusodo Hospital, Makassar. The neutrophil-lymphocyte ratio was the results of absolute neutrophil value divided by absolute lymphocyte value and expressed as cell/µL. This data was obtained from routine blood results using K3EDTA blood sample and measured with flow cytometer Sysmex XT-2000i.

The obtained results were analyzed statistically with SPSS software. The data were analyzed using the Kolmogorov-Smirnov test to determine the distribution, and Mann-Whitney to compare NLR values in ischemic and hemorrhagic stroke with not normally distributed data, and the establishment of cut-off value using ROC curve. The results were presented in the form of tables.

RESULTS AND DISCUSSION

The total number of the samples was 402 with average age 60.40±12.01, with more dominant male subject (229 [54.7%]) and ischemic stroke as the most common stroke (214, [53.2%]). The mean value of leukocyte was 12.06±4.72, mean neutrophil 74.40±11.94, mean lymphocyte 16.39±8.72 and mean NLR 6.87±5.6 (Table 1).

Data were analyzed by the Mann–Whitney test for age, leukocyte, neutrophil, lymphocyte, and neutrophil because the sample distribution was not normal. A significant difference was found in age (p<0.001), leukocyte (p<0.001), neutrophil (p<0.0001), lymphocyte (p<0.001), and NLR (p<0.01) between ischemic stroke and hemorrhagic stroke, as shown in Table 2.

Analysis of NLR Receiver Operating Characteristics (ROC) of study subjects with hemorrhagic and ischemic stroke with CT scan results, the AUC-value was 0.730 with cutting point 5.181; sensitivity 67.8%; specificity 68.6% (Figure 1).

This study showed that the number of male subjects was higher than female subjects and the mean age was 60.4±12.01. This finding indicated that stroke was more frequently found in older patients. following the study of Alexander that stroke

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
<th>Mean ±SD</th>
<th>Median</th>
<th>Min-Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.40±12.01</td>
<td>60</td>
<td>28-95</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>220 (54.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>182 (45.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>214 (53.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>188 (46.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocyte value (10³/µL)</td>
<td>12.06±4.72</td>
<td>11.2</td>
<td>4.0-31.5</td>
<td></td>
</tr>
<tr>
<td>Neutrophil value (%)</td>
<td>74.40±11.94</td>
<td>76.25</td>
<td>33.70-94.0</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte value (%)</td>
<td>16.39±8.72</td>
<td>15.1</td>
<td>1.0-48.70</td>
<td></td>
</tr>
<tr>
<td>NLR</td>
<td>6.87±5.6</td>
<td>5.07</td>
<td>0.69-37.33</td>
<td></td>
</tr>
</tbody>
</table>
incidence rate and possible damages resulted from various risk factors will increase more than two-fold after the age of 55 years old.\textsuperscript{15}

This study also showed that 214 (53.2\%) patients referred to the Dr. Wahidin Sudirohusodo Hospital Makassar with ischemic stroke diagnosis, outnumbering the hemorrhagic stroke (188; [46.8\%]). The result was in accordance with O’Donnel et al. study. In a multi-center study, they found higher ischemic stroke incidence (78\%) compared to hemorrhagic stroke.\textsuperscript{14}

The median of leukocyte value in study subjects with hemorrhagic stroke (12.8x10^3/\mu L) was higher compared to ischemic stroke (9.8x10^3/\mu L). This result was following Hatta et al. study that found higher leukocyte increase in hemorrhagic stroke compared to ischemic stroke. Leukocytes in ischemic stroke, after the cell death, are released in the circulation and tissues for only 3-6 hours, and the highest leukocyte migration occurs at 24-72 hours after ischemic onset and then decreases up to the seventh day.\textsuperscript{15-17}

Median neutrophil in hemorrhagic stroke (81\%) was lower compared to ischemic stroke (69.5\%). Conversely, median lymphocyte in hemorrhagic stroke (11.35\%) was lower compared to ischemic stroke (19.2\%). The type of leukocytes mobilized due to acute inflammation is neutrophil.\textsuperscript{18} Proinflammatory cytokines, particularly interleukin-8, play a role in recruiting neutrophil as an inflammatory response. Reperfusion injury occurs due to neutrophil buildup and its inflammation in ischemic stroke lesion area.\textsuperscript{6}

Proinflammatory blood cells in hemorrhagic stroke including neutrophils are released directly in brain tissues within less than 48 hours. The released thrombin due to hemolysis is the potential stimuli for the inflammation to occur in hemorrhagic stroke. Reperfusion injury is not observed in hemorrhagic stroke.\textsuperscript{19} Decreased lymphocyte level is more due to lymphocyte activities, lymphocyte adhesion to endothelial cells increases during inflammation followed by lymphocyte migration to tissues having inflammation.\textsuperscript{17,18}

Study findings indicated a significant difference in NLR values in ischemic and hemorrhagic stroke. The diagnostic test for NLR showed the cutting point at 5.181. Receiver operating characteristics analysis revealed AUC = 0.73, indicating weak AUC-value, with a sensitivity of 67.8\% and specificity 68.6\%. When the NLR in routine blood is higher than cut-off value, it can be concluded as hemorrhagic stroke, and conversely, when the NLR value is lower than cut-off value, it is an ischemic stroke.

The limitations of this study included the retrospective method from secondary data, medical record data. Other causes of infection or inflammation could not be ruled out entirely. Another limitation was the different onset of checked routine blood after a stroke attack.

CONCLUSIONS AND SUGGESTION

Study results indicate that NLR value in hemorrhagic stroke is higher than ischemic stroke.
Further studies are suggested with cohort method and larger samples and normally distributed by considering the underlying diseases that can result in bias and considering the time of routine blood collection which represent the peak time for the neutrophil to enter circulation.

REFERENCES