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## Correlation between white blood cell count and clinical severity based on NIHSS in acute ischemic stroke patients



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### ABSTRACT

**Background:** Stroke is a major cause of mortality, with the Indonesian Stroke Registry reporting stroke prevalence nationwide was 8.2/1000 people and that, of 1087 stroke patients 67.1% were diagnosed with ischemic stroke. Preventing acute ischemic stroke by determining pathophysiology and prognostic indicators is important. Previous studies revealed white blood cells contributed to post-stroke inflammation and worsening clinical severity, with a positive independent correlation between white blood cell count and stroke severity existing. Therefore, the objective of this study was to analyze the correlation between white blood cell count and clinical severity based on the National Institutes of Health Stroke Scale in acute ischemic stroke patients.

**Methods:** This retrospective cross-sectional study using consecutive sampling involved 54 patients diagnosed with acute ischemic stroke at the Department of Neurology, Dr. Soetomo Hospital, between September and November 2015. Data were collected using medical records and analyzed using Fisher's Exact test with  $p < 0.05$ .

**Results:** There were no correlations between white blood cell count and clinical severity based on admission and discharge NIHSS scores.

**Conclusion:** There was no correlation between white blood cell count and clinical severity based on NIHSS. Further research is needed to define the importance of the amount and type of white blood cells as a prognostic indicator in acute ischemic stroke cases.

**Keywords:** white blood cell, NIHSS, acute ischemic stroke

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### BACKGROUND

Stroke is a problematic health concern that induces a dramatic change in the lives of not only individuals afflicted with the disease but also leaves a lasting impact on the family, caregivers, and other close members.<sup>1</sup> Since the publication of latest updates from the American Heart Association and American Stroke Association concerning stroke, stroke has now been classified by various subtypes: CNS infarction including ischemic stroke, stroke due to intracerebral hemorrhage, stroke due to subarachnoid hemorrhage, and stroke due to central venous thrombosis.<sup>2</sup>

Ischemic stroke is defined as a neurological dysfunction caused by focal occlusion in the brain, spine, or retina; hemorrhagic stroke is a neurological dysfunction caused by focal bleeding within the brain parenchyma or ventricular system or into the subarachnoid space; and stroke by central venous thrombosis is defined as a neurological dysfunction caused by thrombosis of the central venous structure.<sup>2</sup>

Among people of all ages, more than 85% of global deaths from stroke occur in developing countries, where approximately 85% of the world's total population resides.<sup>3</sup> Due to the epidemiological transition that most developing countries

are going through, the rate of stroke mortality is expected to increase even faster in these countries compared to the situation in developed countries.<sup>4</sup> Therefore, the need to focus on countries such as Indonesia is clear.

In Indonesia, stroke is reported as the primary cause of death in individuals over the age of five.<sup>5</sup> The Indonesian Stroke Registry reported that stroke prevalence nationwide was 8.2/1000 people and that, of the 1087 stroke patients studied, 67.1% were diagnosed with ischemic stroke.<sup>6</sup>

Unfortunately, the annual prevalence of ischemic stroke, related deaths, and loss of disability-adjusted life years (DALY) are still increasing.<sup>7</sup> Therefore, it is important to prevent acute ischemic stroke by determining the pathophysiology and prognostic indicators to initiate earlier and effective reperfusion.

Previous studies have shown that white blood cells play an important role in post-stroke inflammation, contributing to further vascular injury and worsening clinical outcome in patients by releasing pro-inflammatory mediators and promoting eventual apoptosis.<sup>8</sup> Several studies have reported white blood cell count (WBC) as an indicator for inflammation, showing a positive

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and independent correlation between WBC count and severity of stroke.<sup>9</sup>

It is well known that the prediction of outcome after ischemic stroke is important in clinical settings.<sup>8,9</sup> However, identification of an independent prognostic marker in patients with stroke is still a matter of controversy. In Indonesia, however, there exists sparse evidence regarding the link between WBC count and the severity of stroke based on assessing clinical manifestations measure by the National Institutes of Health Stroke Scale (NIHSS).

A previous study conducted in Malang by Husna et al. (2015) compared between different NIHSS scores of patients with leukocytosis and those with normal WBC counts, concluding that patients who have normal WBC count upon admission were likely to have NIHSS scores similar to patients who showed leukocytosis; but they tended to have lower NIHSS scores upon discharge and also showed better improvement than patients with leukocytosis.<sup>10</sup> However, similar studies are yet to be conducted in Surabaya. Therefore, the aim of this research was to investigate the relationship between WBC values assessed on admission in predicting the clinical severity based on NIHSS in acute ischemic stroke patients.

## RESEARCH DESIGN AND METHODS

This research design used a retrospective cross-sectional study with consecutive sampling. By using consecutive sampling, patients were included in the study based on the inclusion and exclusion criteria. The inclusion criteria included patients diagnosed with acute ischemic stroke, above 18 years of age, and registered at Dr. Soetomo Hospital. The exclusion criteria included patients with incomplete medical records, who passed away during the period of research, diagnosed with other types of stroke, had leukocytosis due to infection or sepsis, diagnosed with diabetes mellitus, had a history of blood disorders, diagnosed with atherosclerosis, or diagnosed with vasculitis or lupus. This research was conducted between August 2016 and January 2017 and examined secondary data in the form of medical records of patients admitted to the Department of Neurology, Dr. Soetomo Hospital, during September–November 2015. The independent variable examined was WBC count. The dependent variable examined was clinical severity based on the NIHSS score on admission as well as the NIHSS score on discharge. Confounding variables included gender and age. Data taken from the medical records in the

Department of Neurology, Dr. Soetomo Hospital, were in the form of name registration, registration date, age, sex, medical history of stroke, including other medical conditions, and NIHSS score on admission and discharge, as well as the WBC count determined by laboratory examination. The collected data were analyzed and grouped based on the inclusion and exclusion criteria before taking the data into consideration for the purpose of our research. Thus, the data considered valid and reliable for our research were fed into our computer systems for data tabulation and statistical analyses using the SPSS software (version 17.0). Baseline data were analyzed using descriptive statistics tests where variables were expressed as either frequency and percentage or mean with standard deviation. Both independent and dependent variables used a nominal measurement scale. The correlation between WBC count and clinical severity based on NIHSS was analyzed using Fisher's Exact test. Statistical significance was defined if  $p < 0.05$ .

## RESULTS

Based on the data collected, we found that there was a total of 181 patients who were diagnosed with acute ischemic stroke and admitted to the Department of Neurology, Dr. Soetomo Hospital, during September–November 2015. After receiving ethical clearance from the hospital, these 181 patients had their medical records assessed for WBC count as well as NIHSS score upon admission and discharge. Out of the initial batch of 181 patients, 127 were excluded based on the exclusion criteria; 107 were excluded due to diagnosis of diabetes mellitus, 3 due to history of blood disorders, 3 due to diagnosis of infection, 3 due to diagnosis of sepsis, 4 due to acute ischemic stroke not being the primary diagnosis, and the medical records of 7 patients could not be found; thus, a total of 54 patients were included in the study.

Data presented in [Table 1](#) show that 68.5% of the patients were male ( $N = 37$ ). The average age of patients was  $55.57 \pm 11.71$  years. In terms of hospital stay, majority of patients were hospitalized for  $11 \pm 5$  days. As for hypertension, 74.1% of the patients had a history of the medical conditions ( $N = 40$ ). As much as 77.8% of patients had a normal WBC count ( $N = 42$ ) averaging at 7.87/ml. The average NIHSS score at the time of admission was 7 (moderate stroke) and at the time of discharge was 5 (moderate stroke).

According to [Tables 2](#) and [3](#), the Fisher's Exact tests revealed on admission that 71.4% of patients ( $N = 30$ ) had normal WBC count and 75% of

patients ( $N = 9$ ) with leukocytosis were diagnosed with moderate stroke, whereas on discharge 50% of patients ( $N = 21$ ) had normal WBC count and 66.7% of patients ( $N = 8$ ) with leukocytosis were also diagnosed with moderate stroke. The findings from both tables revealed that there was no correlation between WBC count and clinical severity based on NIHSS scores ( $p = 1.000$  on admission,  $p = 0.0568$  on discharge).

## DISCUSSION

This study, along with several others, has evaluated the efficacy of using WBC count as a prognostic marker among patients with acute ischemic stroke. Statistical analysis, however, revealed there was no correlation between WBC count and clinical severity based on NIHSS scores. Some studies confirm these research findings; for instance, a prospective study conducted by Sahan et al. (2013) on 115 patients with acute stroke in 2013 showed that there did not exist a correlation between WBC count and clinical severity based on NIHSS.<sup>11</sup> In another study conducted in Bakhshayesh-Eghbali in 2016 in Iran, a total of 102 patients with acute ischemic stroke were included and results also showed that WBC on admission in acute ischemic stroke patients was not associated with poor outcome.<sup>12</sup>

Despite similar studies confirming these findings, these studies are in contrast to other studies that have shown that WBC count is a significant predictor of clinical severity. For example, the Copenhagen Stroke Study conducted by Kammergaard et al. (1999) showed that increased WBC count on admission was significantly associated with initial stroke severity.<sup>13</sup> Audebert et al. (2004) also showed a significant correlation between stroke severity and the increase of WBC in the peripheral blood for the first 3 days.<sup>14</sup> Furthermore, a study conducted in Italy by Nardi et al. (2012) reported that elevated WBC count in acute ischemic stroke is a significant independent predictor of poor initial stroke severity, poor clinical outcome after 72 hours, and discharge disability.<sup>15</sup> Another study conducted in Canada by

**Table 1** Baseline Characteristics of Acute Ischemic Stroke Patients

Characteristics	Frequency ( $N = 54$ ) (%)	Mean $\pm$ SD
<b>Demographic and risk factors</b>		
<b>Gender</b>		
Male	37 (68.5)	
Female	17 (31.5)	
Age (years)		55.57 $\pm$ (11.71)
Length of stay (days)		11 $\pm$ (5)
<b>Hypertension</b>		
Yes	40 (74.9)	
No	14 (25.1)	
<b>Baseline parameter</b>		
<b>White blood cell counts, /mm<sup>3</sup></b>		
Normal	42 (77.8)	7.87/mm <sup>3</sup> $\pm$ (1.87)
Leukocytosis	12 (22.2)	13.78/mm <sup>3</sup> $\pm$ (4.81)
<b>NIHSS score</b>		
Admission		7 (4–10) (moderate stroke)
Discharge		5 (1–9) (moderate stroke)

**Table 2** WBC Count and Clinical Severity Based on NIHSS Scores for Admission

	Clinical severity based on NIHSS scores for admission					N	p value*
	No stroke symptoms (%)	Minor/mild stroke (%)	Moderate stroke (%)	Moderate to severe stroke (%)	Severe stroke (%)		
Normal	0 (0)	12 (28.6)	30 (71.4)	0 (0)	0 (0)	42	1.000
Leukocytosis	0 (0)	3 (25)	9 (75)	0 (0)	0 (0)	12	
						Total	54

\*p value was calculated using Fisher's Exact test;  $p < 0.05$  is significant.

**Table 3** WBC Count and Clinical Severity Based on NIHSS Scores for Discharge

	Clinical Severity Based on Discharge NIHSS					N	p value*
	No stroke symptoms (%)	Minor/mild stroke (%)	Moderate stroke (%)	Moderate to severe stroke (%)	Severe stroke (%)		
Normal	3 (7.1)	18 (42.9)	21 (50)	0 (0)	0 (0)	42	0.568
Leukocytosis	0 (0)	4 (33.3)	8 (66.7)	0 (0)	0 (0)	12	
						Total	54

\*p value was calculated using Fisher's Exact test;  $p < 0.05$  is significant.

Furlan et al. (2014) showed that higher WBC count on admission in acute ischemic stroke is associated with poorer prognosis with respect to the degree of impairment and disability, risk of further ischemic stroke, and 30-day mortality.<sup>16</sup>

The cause of discrepancy between these findings (Sahan, Bakhshayesh-Eghbali) and findings made to the contrary in other studies (Kammersgaard, Audebert, Nardi, Furlan) may be related to the suggested findings of other mechanisms that contributed to patients with normal WBC count to have the same clinical severity on admission and discharge as patients with leukocytosis. One risk factor that affects the prognosis for and severity of tissue damage that appears following an ischemic stroke is the presence of acute-phase reactants; it has been shown that stroke triggers an acute-phase response.<sup>8,9,11–16</sup> Clinical severity based on NIHSS included several other prognostic factors, including c-reactive protein (CRP), TNF-alpha, IL-6, IL-8, IL-10, and fibrinogen, as reported in the study conducted by Sahan et al. (2013).<sup>11</sup> Particularly in Sahan et al. (2013) and Bakhshayesh-Eghbali (2016), CRP was shown to have greater significant correlation with clinical severity than WBC count by describing that cytokines (TNF-alpha and the interleukins) trigger CRP levels to increase.<sup>11,12</sup> CRP is a serum protein that is produced in the livers of individuals with acute and chronic systemic inflammation. According to Sahan et al. (2013) and Bakhshayesh-Eghbali et al. (2016), increased CRP levels were not only associated with an increased risk of stroke but also with cardiovascular disease, being an important component in determining the prognosis of strokes both atherothrombotic or cardioembolic in origin.<sup>11,12</sup> In both studies, CRP level was statistically significant and WBC count was not.

This study had several important limitations. First and foremost, NIHSS scores were obtained retrospectively because in Indonesia NIHSS is not regularly conducted on the spot as it should be, making this the biggest limitation of this research. The research data were taken from secondary data, so some medical records had incorrect information or lacked supporting details from examinations such as laboratory examinations and head CT-scans. Therefore, several medical records had to be excluded, leading to a small final sample of participants utilized for this study. In addition, the small sample acquired was also due to the restrictions from the inclusion and exclusion criteria. Furthermore, prognosis and functional outcome are typically based on clinical evaluation at day 30 or day 90 of a patient's hospital stay in order to perform continuous evaluation on a patient; however, most hospital stays lasted from 7 to 10 days (an average of

11 days in the present study); therefore, the shorter stay in the hospital turned out to be a critical impediment in performing a thorough clinical evaluation. Stroke onset was a factor not taken into consideration; this is another limitation that may have influenced the research findings. CRP, though a more effective prognostic marker than WBC count as discussed above, is not a routine examination for stroke at Dr. Soetomo Hospital; therefore, there was a limitation in comparing WBC count with other prognostic markers. These limitations overall made it difficult to compare the findings of this research with previous studies.

## CONCLUSION

Data analysis revealed that there was no correlation between WBC count and clinical severity based on NIHSS. Therefore, WBC count itself was not a determining factor in predicting clinical severity in patients with acute ischemic stroke. To highlight the importance of this finding, further studies on WBC as a baseline parameter in predicting clinical severity and outcome should be conducted.

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