ISSN No:-2456-2165

Correlation between the Leukocyte Levels upon First Hospitalization and Clinical Outcomes in Acute Ischemic Stroke

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Abstract:- Background and Purpose: Based on the high mortality and morbidity rate, stroke is included as a major public health disease. The inflammatory response of stroke is mediated by the immune system. In ischemic stroke, increased expression of various cytokines and chemokines causes leukocyte infiltration into ischemic tissue. It has considered as the main mediator of the response of inflammation and endothelial destruction. Leukocytes assessment upon hospitalisation is expected to define the specific treatment of stroke patients efficiently. This study aimed to identify the correlation between leukocyte level upon hospitalized and clinical outcomes of mild and moderate acute ischemic stroke in neurologic inpatients care at Dr. Soetomo Hospital. Method: A retrospective cross-sectional method was used in this study. Sample data were collected from the stroke registry in the neurologic room at Dr. Soetomo hospital from January to March 2019. Leukocyte levels were collected upon hospitalisation and the clinical outcome of stroke. The data were assessed using the National Institutes of Health Stroke Scale (NIHSS) upon discharge. Data were analysed using SPSS version 24 with p<0.05 as a significant value. Result: From the stroke registry data, it was found that 55 subjects have fulfilled the criteria for this study. Patients with a mild deficit NIHSS clinical outcome with normal leukocyte level showed in 23 (82%) patients, while there were 5 (18%) patients who had leucocytosis. Patients with moderate deficit NIHSS clinical outcomes showed normal leukocyte values in 14 (52%) patients and as many as 13 (48%) patients showed leucocytosis. The chi-square test resulted in a significant value with p-value = 0.017 (RO: 4.27 (95% CI = 1.25-14.56)). Conclusion: There is a correlation between leukocyte values at baseline and clinical outcome of acute ischemic stroke with mild deficits and moderate deficits as assessed by the NIHSS.

Keywords:- *Leukocytes; Ischemic Stroke; Clinical Outcome; NIHSS; Mild and Moderate Deficits.*

I. INTRODUCTION

Due to the high mortality and morbidity rates, stroke has been included as a major disease in the public health sector. Stroke cases tend to increase in old age with a peak age at 75 years and over[1]. The prevalence of stroke shows the same value in both sexes (male and female). In 2013, there were nearly 25.7 million stroke sufferers on a global scale, and about 6.5 million deaths from stroke. Meanwhile, there were 113 million disability-adjusted life-years (DALy) lost due to stroke. The number of new cases reached 10.3 million[1].

Stroke is an acute clinical manifestation due to neurological dysfunction in the brain, spinal cord and retina, either partially or completely, which persists for 24 hours. Generally, stroke can cause death due to vascular disorders[2]. Stroke caused by infarction is proven through radiological, pathological or other evidence that shows ischemia of the brain, spinal cord or retina, hereinafter referred to as ischemic stroke[2].

Above than 60% of population in the world has been diagnosed, the majority of whom are developing economies. In Asia, the prevalence of death from stroke is higher than other regions, such as in Western Europe, America or Australia[1]. The lowest incidence of stroke is in Malaysia (67/100,000 people per year). Meanwhile, the highest figures were recorded in Japan (422/100,000 people per year among men and 212/100,000 people per year among women), as well as in Taiwan (330/100,000 people per year)[1].

ISSN No:-2456-2165

The National Institute of Health in Stroke Scale (NIHSS) worksheet is commonly used as tools to assess the clinical outcome of acute ischemic stroke. The NIHSS is an objective scale in measuring clinical outcomes caused by stroke, as this score can monitor the progress of acute phase of stroke patients and has a high degree of significance among examiners[3]. The NIHSS assessment consisted of (a) Score <5: mild neurological deficit category, (b) Score 6-14: moderate neurological deficit, (c) Score 15-24: severe neurological deficit, (d) Score ≥ 25: very neurological deficit weight. Moreover, the NIHSS assessment is the most widely used measure of neurological severity to determine the feasibility of reperfusion therapy for treating acute ischemic stroke[4].

The immune response after stroke has been known to have a major role in the pathophysiology of cerebral ischemia. Immune mediators activated by brain injury release inflammatory signals, then this triggers a complex series of biochemical and molecular events that are considered to be major contributors to neuronal cell death. The main immune mediators involved include glial cells and infiltrating leukocytes, including neutrophils, monocytes and lymphocytes. The infiltrated leukocytes release inflammatory mediators to the site of the lesion, exacerbating brain injury [5]. The neurological deficit is due to the excitotoxicity cell death of the penumbra which is partly due to leukocyte infiltration. The rise of peripheral leukocyte levels can be associated with poor outcomes of stroke patients with neurological deficits. Nevertheless, The dynamic changes that occur in the leukocyte levels around the time the neurologic deficit begins has examined yet[6].

Ischemic stroke is associated with pro-oxidant and pro-inflammatory leukocyte activation which is accelerated by thrombin and is seen in the formation of leukocytes. The results of the study conducted showed that the total leukocyte and neutrophil levels has an important role in determining the outcome of ischemic stroke[7]. A research by Husna et al 2015 states that the number of leukocytes has a significant relationship with NIHSS discharge and repair[8]. Furthermore, regarding the condition of leucocytosis, the study of Westendorp WF et al, (2015) stated that the administration of preventive antibiotics did reduce infection rates, however it has not increased the functional outcomes of acute stroke patients, nor did they shorten the length of stay or reduce hospital mortality[9].

This study aims to determine the correlation between leukocyte levels and clinical outcomes in ischemic stroke patients assessed by NIHSS. Moreover, this study can be used as a preliminary study to support the efficient treatment of acute ischemic stroke in the neuro-care ward.

II. METHODS

An analytic study with a retrospective cross sectional approach was used in this research. The objective is to determine the correlation between leukocyte levels and clinical outcomes of acute ischemic stroke patients. The study period was conducted from January to March 2019. The primary data was from the Stroke registry. The study population was acute ischemic stroke patients who underwent treatment in the ward, Seruni A Room in the Neurology Section of Dr. Soetomo Surabaya. The data collected included leukocyte values at the time of initial hospitalized, gender, age, incidence of infection and NIHSS scores when the patient was discharged from the hospital.

The leukocyte level is included as an independent variable in this study. The researchers used the standard haematology test of the Clinical Pathology Laboratory of RSUD Dr. Soetomo with normal leukocyte level: 3300-10000/mm3 or SI: 3.3-10x103/uL, and leucocytosis (leukocyte count>10x103/uL). The level of leukocytes was routinely checked on the day of hospitalized.

Clinical outcomes of acute ischemic stroke patients studied were assessed using The National Institute of Health in Stroke Scale (NIHSS) worksheet. The NIHSS assessment includes: (a) Score <5: mild neurological deficit, (b) Score 6-14: moderate neurological deficit, (c) Score 15-24: severe neurological deficit, (d) Score ≥ 25: very severe neurological deficit[4]. The assessment result included in the study was the NIHSS with mild deficit ischemic stroke and moderate deficit which was the dependent variable.

The collected data was analyzed using the Statistical Package for the Social Sciences (SPSS) v22 for Windows (IBM Inc., Chicago, IL). Chi-square test with the calculation of odds ratios and 95% confidence intervals (95% CI) was used to determine the correlation. Meanwhile, the Spearman test was to determine the strength of the correlation with significantly of P-value <0.05.

III. RESULTS

This study involved 55 patients with the number of male patients (63.6%) which is higher than women (36.4%). The majority of patients were aged between 61-70 years (27.3%) compared to other age groups. The research sample obtained 37 (67.3%) samples with normal blood leukocytes (Leukocyte value 3300-10000/mm3). Meanwhile, 18 (32.7%) samples were recorded with high leukocyte levels (leucocytosis with a leukocyte value > 10,000/mm3). From all research subjects, the normal leukocyte value was more than the leucocytosis value. The number of subjects with a clinical outcome of ischemic stroke with a mild deficit NIHSS value of 28 patients and a moderate deficit of 27 patients.(Table 1)

In patients with mild deficit NIHSS values, as many as 23 (82%) patients had normal leukocyte values, while patients with leucocytosis were as many as 5 (17%) patients. In patients with moderate deficit NIHSS, normal leukocyte values were experienced by 14 (52%) patients and leucocytosis was experienced by 13 (48%) patients. It can be concluded that the number of patients with normal leukocytes in NIHSS mild deficit while out is higher than the time of entry.

In the Chi Square statistical test, there was a significant value of p=0.017 which indicates that the correlation between the leukocyte level and the clinical

ISSN No:-2456-2165

outcome of acute ischemic stroke, mild deficit and moderate deficit was significant (OR: 4.27 (95%CI: 1.25-14.56)). The Spearman correlation value of 0.323 indicates that the direction of the correlation is positive with weak correlation strength (Table. 2).

IV. DISCUSSION

Research has been carried out on 55 subjects of acute ischemic stroke patients who were treated at Dr. Hospital. Soetomo during the period from January to March 2019 through stroke registry data. General characteristics of study subjects included age, sex and incidence of infection during treatment. As explained by Patricia et al, (2013) that factors that can cause stroke divides into modifiable and non-modifiable factors. Factors that cannot be modified consist of age and gender, while factors that can be modified include hypertension, diabetes mellitus, lipid profile, alcohol consumption and smoking[3].

In this study, the average age of the patients was 57.42 ± 12.36 years, the mean age of the patients was in accordance with the epidemiological research regarding the predictors of stroke which said that the largest age group was in the 45-65 year age group[10]. One of the strongest risk factor of ischemic stroke is age. On the other words, as age increases, the incidence of stroke also increases[3]**.** When a person turns 55 years old, the incidence will double every decade[3]. Gender characteristic data is also one of the unmodifiable risk factors for stroke. This is in accordance with a study by Ahaangar AA, et al. (2018) who proved that men have a 30% more risk of having a stroke than women[11]**.** According to Patricia et al. (2013), most patients with ischemic stroke are male [3].

The incidence of pneumonia in this study was experienced by 2 patients (3.6%) with NIHSS scores of 5 and 13. This included the criteria for being discharged from the hospital and there were 1 (1.8%) patients with an NIHSS score of 7 at the time of discharge, which means a moderate deficit. The explanation of this phenomenon is that post-stroke, patient immobility, mechanical ventilation, and any fixed tube or catheter equipment can increase the risk of infection. Moreover, aspiration, a common cause of pneumonia, can occur due to a combination of decreased level of consciousness. Besides brain injury conditions will be followed by decreased immunity as a form of cellular adaptation to survive[12].

In this study, it was found that at the time of hospitalized, many patients had high leukocyte level, as well as the number of leukocytosis. This is consistent with the characteristics of stroke, which is a condition where rapid development is possible resulting a damage of the ischemic zone of brain tissue. Inflammation in the early phase of cerebral ischemia enhances the damage to post-ischemic brain regions. This will also cause necrotic tissue in the ischemic penumbra. The acute and prolonged inflammatory response is characterized by the rapid activation of young cells through the production of proinflammatory mediators. Moreover, it can be produced by infiltration into the brain of various types of inflammatory cells, including leukocytes. Furthermore, brain tissue exposed to ischemia or reperfusion elicits an acute inflammatory response characterized by leukocyte infiltration in post-ischemic tissue[13].

The early post-stroke response is also facilitated by disruption of the blood-brain barrier and infiltration of leukocytes and neutrophils which can lead to cerebral edema and secondary infarction. About couple of days after infarction, the inflammatory process will be sustained by lymphocytes, following by T-helper type 1 (TH1) lymphocytes secrete interleukin (IL)-1β, interferon (IFN)-γ, and macrophage inflammatory protein (MIP), all of which promote the response persistent inflammation[13]. Circulating leukocytes and platelets adhere to the activated endothelium, migrate into the parenchyma and play a role in neuronal inflammation around ischemic areas[14].

Similarly, leukocytes produce proinflammatory factors in ischemic areas of the brain. Platelet activators will be produced when leukocytes have activated by phospholipase, which drives to vasoconstriction and platelet aggregation. Then, leukocyte infiltration continuing exacerbates neuronal injury by activating proinflammatory factors in and around the penumbra and infarct nucleus. All of these inflammatory cells play an important role in initiating and exacerbating the pathological response to stroke and in maintaining brain cell homeostasis[15].

In this study, there was a correlation between leukocyte values and clinical outcomes of acute ischemic stroke NIHSS mild deficit and NIHSS moderate deficit, patients with normal leukocytes at the beginning of admission had better clinical manifestations (NIHSS mild deficit) than patients with leucocytosis at first hospitalized time. Chi Square statistical test showed that patients with high leukocyte level will be at risk of experiencing poor clinical outcomes as much as 4 times compared to patients who enter with normal leukocyte. Based on the Spearman correlation test, it shows a positive correlation with weak correlation strength. The correlation between first hospitalized leucocytes and clinical outcomes is supported by previous studies that obtained prognostic values of leukocytosis at the first hospitalized for short-term neurological outcomes. The study suggested that hospitalized time of leukocytosis is defined not only as an independent indicator of initial stroke severity, but also the disability possibility and lowest clinical outcomes after 72 hours. An elevated leukocyte levels at first hospitalized time indicates a risk factor for bad prognosis in acute ischemic cerebral patients[13].

Basically, pathophysiological leukocytosis in stroke will be worse for clinical outcomes. The mechanism of significantly decreases leukocyte deformation capacity followed by significantly increased adhesion and aggregation functions. Then, it induces cerebral microcirculation disorders and limits collateral circulation. Adhesion of leukocytes to the surface of vascular endothelial cells causes the formation of small embolism, obstructs small blood vessels, induces microcirculation disorders and decreased cerebral blood flow. Two types of leukocytes adhere to the surface of vascular endothelial cells

and activate each other in brain tissue; it generates and releases oxygen free radicals, vasoactive substances such as leukotrienes and platelet activating factor. Then it decreases endothelial cell viability, induces platelet aggregation and vasoconstriction, and directly damages brain cells. At the same time, these substances damage the blood-brain barrier, further exacerbating brain edema and resulting in more severe brain injury[16].Brain injury after ischemic stroke or hemorrhagic stroke is able to activate and infiltrate the inflammatory cells into the brain. The literature from Shi K et al. (2018) showed that the expansion of stroke lesions and exacerbates neurological deficits can be promoted by inflammation in the brain during acute stroke[17].

Chen J. (2018) explained that the prognostic test for the value of leukocytes at first hospitalization can predict the neurological prognosis and the amount of leukocytes levels, which is associated with poor functional outcomes[18]. The studies of Kumar AD, et al (2013) and Nikanfar M. (2012) stated that increased leukocyte levels at first hospitalization predict neurologic deficits and are associated with poor outcomes and increased leukocyte values are associated with poor outcomes and higher rates of morbidity[6,19].

Husna M. (2013) said that leucocytes had a significant relationship with discharge NIHSS. Hence, acute ischemic stroke patients with normal leukocyte levels tend to have better improvement and clinical manifestations based on the NIHSS outgoing category than patients with leucocytosis[8].

The limitations of this study are that we did not analyze the factors that can co-exist and cause poor outcomes in the acute phase of ischemic stroke. Besides, blood sampling to measure the leukocyte value at first hospitalized was too various.

V. CONCLUSIONS

There is a correlation between the value of leukocytes at baseline with mild and moderate clinical outcomes in acute ischemic stroke patients. Leucocytosis level at first hospitalized time was associated with clinical outcome ($p = 0.017$). A high leucocyte value at hospitalized time would have a risk of experiencing poor clinical outcomes as much as 4 times compared to normal leukocyte values.

Author Contributions: Conceptualization, D.T.L., M.S.A and M.B.; methodology, M.S.A and M.B; software, D.T.L.; validation, D.T.L., M.S.A and M.B.; formal analysis, D.T.L.; investigation, D.T.L. and M.S.A.; resources, M.S.A. and M.B.; data curation, M.B.; writing—original draft preparation, D.T.L.; writing—review and editing, M.S.A and M.B.; visualization, D.T.L..; supervision, M.S.A. and M.B.; project administration, D.T.L.; funding acquisition, D.T.L., M.S.A and M.B.. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study had got an ethical approval from ethical committee of Dr. Soetomo General Hospital (no.1239/KEPK/VI/2019

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available based on a request to the corresponding author.

Acknowledgments: none

Conflicts of Interest: The authors declare no conflict of interest.

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Characteristics	Total (N:55) (%)	Mean (Min-Max±SD)
Gender		
- Women	20 (36.4)	
- Men	35 (63.6)	
Age		57.42 (30-83±12.36)
<=40 years	4 (7.3)	
41-50 years	13 (23.6)	
51-60 years	14 (25.5)	
61-70 years	15 (27.3)	
>70 years	9 (16.4)	
Infection		
- Pneumonia	2 (3.6)	
- Urinary tract infections	1 (1.8)	
Leukocyte		9325.46(5400-18100)
- Normal	37 (67.3)	
- Leucocytosis	18 (32.7)	
NIHSS Final		5.53(2-14±3.39)
- Mild Degree	28 (51)	
- Moderate Degree	27 (49)	

Table 1. Sample characteristics from the stroke registry

Deficit Neurology		Mild	Moderate	Total	*p*	OR(95%CI)	r
Leucocyte	**Normal**	23	14	37	0.017	4.27(1.25-14.56)	0.323
	Leucocytosis	5	13	18			
	Total	28	27	55			

Table 2. Chi-Square Test and Correlation Coefficient of Leukocyte level