Correlation between Increased Leukocyte Counts in Patients with Acute Phase Hemorrhagic Stroke with Early Neurological Deterioration Events

Abstract

Stroke is the second most common cause of death and the leading cause of disability worldwide. Hemorrhagic stroke occurs in 15% of stroke cases. Increased leukocyte counts in the acute phase of hemorrhagic stroke are believed to be related to the incidence of early neurological deterioration. This study aims to determine the relationship between increased leukocyte count and early neurological deterioration in hemorrhagic stroke patients while being treated at UKI General Hospital. This research is analytic research with a cross-sectional design. There were 38 research subjects. The sample was selected using total sampling with specified inclusion and exclusion criteria. The study subjects were grouped into leukocytosis with leukocyte values > 11,000/µL blood and normoleukocytes with leukocyte ranges ranging from 4000-11000/µL blood. The data used is secondary data. The results of the study were processed using the SPSS computer program. It was found that early neurological deterioration in patients with leukocytosis was significantly higher than in patients with normoleucosis, with a Relative Risk of early neurological deterioration in patients with leukocytosis of 3.003 (CI 95%); p=0.031). A significant relationship exists between increased leukocyte count (leukocytosis) upon admission and early neurological deterioration while being treated for hemorrhagic stroke patients at the UKI General Hospital.

Keywords*: Leukocytosis, Acute Phase Hemorrhagic Stroke, early neurological deterioration*

Introduction

Stroke is a disease in the form of disturbances in focal and global nerve function that is acute, develops rapidly, can be severe, and lasts for at least 24 hours or can even cause death. [1; 2] Impaired nerve function is caused by impaired blood circulation in the brain. [2] Stroke is the second most common cause of death and the leading cause of disability globally. [3] Stroke is characterized by a neurological deficit caused by acute focal and global injury to the central nervous system by vascular causes such as cerebral infarction and intracerebral hemorrhage resulting in disruption of the blood supply that supplies oxygen and glucose availability. [4] This neurological deficit causes sudden symptoms, including facial or limb paralysis; speech not fluent, speech not clear (pelo), decreased consciousness, and visual disturbances. [5]

Stroke has two main types, namely ischemic stroke and hemorrhagic stroke. Ischemic stroke is a type of stroke caused by reduced or lost blood flow to the parenchyma of the brain, retina, or spinal cord, which can be caused by a blockage or rupture of an artery or vein, while a hemorrhagic stroke is caused by bleeding. [6] Hemorrhagic stroke is a stroke caused by a burst of blood vessels in the brain which results in the discharge of blood fluid and the collection of blood clots in the brain parenchyma, cerebrospinal space, or a combination of both that is not caused by trauma. Intracerebral hemorrhage is the second most common stroke subtype and usually causes severe disability and death. This intracerebral hemorrhage is usually caused by hypertension or other vascular disorders. An intracerebral hemorrhage causes the formation of a hematoma in the brain, which results in pressure on the brain and increased intracranial pressure. [7]

According to a report from the Global Burden of Disease (GBD), 2016 Lifetime Risk of Stroke Collaborators, globally, people aged 25 years and over have a risk of stroke of 24.9%,

an increase of 2.1% from 1990. This estimate includes a higher risk of stroke, almost the same between men and women. [8] Reportedly seven million Americans aged ≥ 20 years had a stroke. This disease is a serious health problem in both developed and developing countries. [9] Based on 2018 basic health research, the prevalence of stroke has increased compared to 2013. The prevalence of stroke has increased from 7% to 10.9%. The prevalence of stroke in 2018 was experienced by people aged ≥ 15 years of 10.9% or an estimated 2,120,362 people. [5] The prevalence of stroke in DKI Jakarta itself is also quite high. The prevalence of stroke based on a doctor's diagnosis in residents aged ≥ 15 years in DKI Jakarta in 2013 was 9.7% and increased in 2018 to 12.2%. [5; 10] Stroke is a non-communicable disease that is an important health problem in Indonesia.

According to the literature, stroke patients with leukocytosis have worse clinical manifestations and prognoses than those without leukocytosis. Inflammatory responses such as leukocytes and cytokines play an important role in stroke in the acute phase, which can exacerbate stroke by accelerating the development of the penumbra into infarction. It is related to the degree of damage and disability resulting from the inflammatory response. [11] Leukocytosis is when the number of leukocytes increases from the average normal limit. The presence of infection and inflammation influences leukocytosis. Inflammation is one of the processes that occur in stroke. In addition, this increase in leukocytes can occur due to bleeding in the body. Several studies have shown that high leukocyte activity can induce the extent of damage to cell death in the brain. Therefore, stroke patients with increased leukocytes usually have poor prognoses and outcomes. Leukocytes tend to be higher in hemorrhagic stroke than in ischemic stroke. [12]

Early neurological deterioration (END) is a decrease in the Glasgow Coma Scale (GCS) score ≥ 3 or death within the first 72 hours after a stroke. [13] END is associated with an increased risk of functional disability and mortality. [14] Despite advances in treating stroke, neurological deterioration is a frequent and rapid complication after intracerebral hemorrhage that occurs spontaneously and produces a poor outcome. END conditions are often associated with baseline hematoma volume, intraventricular hemorrhage, hematoma expanding more than 24 hours, high leukocyte count, and high blood pressure. [15] Based on the description above, it is suspected that leukocytosis in hemorrhagic stroke is associated with the incidence of END. At the UKI General Hospital, no research has been conducted on increasing leukocyte counts in acute-phase hemorrhagic stroke patients and their relationship to END incidence. It makes researchers interested and feel the need to do the research.

The brain blood supply in adults averages about 50 to 65 ml per 100 grams of brain tissue per minute or about 750 to 900 ml/minute for the whole brain. Thus, the brain, which comprises only about 2 percent of body weight, receives 15 percent of cardiac output at rest because the brain's metabolic demands are very high. Increased carbon dioxide levels in arterial blood entering the brain will increase cerebral blood flow. Carbon dioxide can increase blood flow, starting with its combination with water in body fluids to form carbonic acid; then, the acid dissociates to form hydrogen ions. These hydrogen ions then cause cerebral blood vessel vasodilation, which increases cerebral blood flow to twice normal. [16]

The brain receives its blood supply from two pairs of blood vessels: vertebral and internal carotid arteries. The two pairs of arteries anastomose to each other to form the Willis arteriosus circle. The Circulus of Willis is important in maintaining blood flow to the brain. The circle of Willis is formed from a portion of the internal carotid artery, the left and right anterior cerebral arteries connected by the anterior communicating artery, the posterior communicating artery, and the posterior cerebral artery. [17]

Stroke is a disorder in the form of a neurological deficit characterized by focal acute injury to the central nervous system (CNS) caused by vascular causes such as cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). It is a

major cause of disability and death. [4] According to WHO (World Health Organization), stroke is a disorder of brain nerve function with focal and global clinical signs that lasts more than 24 hours or can cause death caused by vascular disorders. [18] According to the AHA (American Heart Association), stroke is a neurological disorder caused by focal cerebral, spinal, or retinal infarction. [19] Hemorrhagic stroke is characterized by a blood collection around the brain parenchyma and in the ventricular system that is not caused by trauma. According to the Journal of Acute Disease, hemorrhagic stroke is bleeding in a part of the brain due to a rupture of a blood vessel in the brain. [20] Meanwhile, according to the American Heart Association, hemorrhagic stroke is caused by intracerebral or subarachnoid hemorrhage due to the rupture of blood vessels in certain parts of the brain so that blood collects in brain tissues. [21]

Hemorrhagic strokes often occur in the basal ganglia (50%), cerebral lobes (10-20%), thalamus (15%), pons and medulla oblongata (10-20%) and cerebellum (10%). The rupture of degenerating vessels and chronic hypertension causes intracerebral hemorrhage. [22] An acute increase in blood pressure can cause a rupture of normal arterioles and capillaries. A ruptured cerebral artery aneurysm, arteriovenous malformation, vasculitis, cerebral artery dissection, dural sinus thrombosis, or pituitary apopexy usually cause subarachnoid hemorrhage. [23] Other causes of hemorrhagic stroke are vascular malformations, coagulapathies, exogenous substances, metastases and tumors in the brain, infection, and inflammation such as sepsis and arteritis.

Subendothelial fibrinoid necrosis with microaneurysms and focal dilatations can be seen in some patients. Lipohyalinosis is usually associated with a history of chronic hypertension and is most common in non-lobar intracerebral hemorrhage, whereas Cerebral Amyloid Angiopathy is more common in lobar intracerebral hemorrhage. [24] Accumulation of blood in the brain parenchyma occurs rapidly, resulting in brain compression and increased intracranial pressure. Further expansion of the hematoma results in primary damage occurring soon after the onset of bleeding. Mechanical damage to the area around the hematoma is related to the mass of the formed hematoma. [25]

The hematoma results in local edema and nerve damage surrounding the brain parenchyma. The edema usually increases in size within 3 to 12 hours. Perihematoma edema increases within 24 hours, peaks around 5-6 days, and lasts up to 14 days. Further expansion of the edema will result in secondary damage. The primary damage initially causes secondary damage, the body's or tissue's response to the hematoma (e.g., inflammation), and the release of platelets. Release of platelets results in perihematomal edema, excess hemoglobin, heme, free radicals such as Reactive Oxygen Species (ROS), and iron, inducing extensive brain tissue death. [26]

The initial response to a hematoma is a hemostatic mechanism to stop the bleeding. Thrombin plays a role in the hemostatic mechanism. In addition, thrombin can also cause the extent of damage induced by intracerebral hemorrhage. Thrombin induces neuronal or astrocyte apoptosis and activates microglia, contributing to excitotoxicity, inflammation, and blood-brain barrier leakage. The interaction between platelets, collagen, and activated leukocytes results in platelet degranulation and the formation of adhesion molecules in the endothelium. It will trigger the release of eicosanoids and free radicals from granulocytes, increasing oxidative stress in the bleeding microenvironment. Platelets and mast cells contribute directly to the release of activated 5-HT. 5-HT increases vascular permeability and vasoconstriction in large cerebral arteries and vasodilatation in small cerebral arteries. In addition, it contributes to neurogenic inflammation by stimulating sensory fibers of the trigeminovascular system to release substance P in an antidromic manner. [27]

After intracerebral hemorrhage, red blood cells that have accumulated in the parenchyma will undergo lysis within hours or days. This releases hemoglobin into the

extracellular space. The hemoglobin molecule has four heme and globin rings, with each heme ring consisting of a porphyrin ring with iron in the center. Bleeding, ischemia, edema, and mechanical damage result in the release of heme from hemoglobin. Once released, the iron in the heme subunit is oxidized from ferrous (2+) to ferric (3+). Hemoglobin is endocytosed into macrophages and monocytes by CD163. Iron bound to heme via CD163 will reach neurons, thereby increasing neurotoxicity. Iron toxicity results from the formation of free radicals through the Fenton reaction. Iron will react with hydrogen peroxide to form ROS based on the reaction below: [28]

$$Fe^{2+} + H_2O_2 \quad \blacktriangledown \quad Fe^{3+} + OH + OH^-$$

The above process causes the formation of lipid peroxidation, which causes further damage. Free radical damage to lipids, DNA, and proteins results in the death of neurons, glia, and endothelial cells. Damage to the endothelial cells and the neurovascular unit triggers a series of inflammatory reactions that lead to disruption of the blood-brain barrier, development of perihematomal edema, neuronal death, and brain damage secondary to intracerebral hemorrhage. Hemorrhagic stroke induces an inflammatory reaction by activating microglia and leukocytes and releasing inflammatory mediators. Leukocytes interact with platelets, endothelium, and coagulation factors to play a role in hemostasis. Leukocytes stimulate macrophages to release proinflammatory mediators and result in secondary brain damage. The blood-brain barrier is broken after the onset of intracerebral hemorrhage, resulting in an influx of leukocytes into the perihematoma area. Neutrophils are the first leukocytes to enter the brain after the onset of intracerebral hemorrhage. Neutrophils will release TNFα and proinflammatory proteases and produce Reactive Oxygen Species (ROS). Neutrophils and monocytes are the predominant leukocytes that cross the blood-brain barrier after intracerebral hemorrhage. Monocytes are leukocytes whose surface contains many anticoagulant factors, such as inhibition of the TF pathway, endothelial protein C receptors, and thrombomodulin which physiologically can inhibit thrombus formation and increase fibrinolysis. [29] Leukocytes can further break down the blood-brain barrier and exacerbate secondary brain damage.

Leukocytes are usually called white blood cells. Leukocytes numbered at least 4000-11000/mm3. Leukocytes are produced in the bone marrow and consist of granulocytic and mononuclear. Unlike red blood cells, leukocytes have a nucleus, and most leukocytes can move like amoebae and penetrate capillary walls. [30] Leukocytes play an important role in the body's immune system and protect the body from infection. An increase in the number of leukocytes in the blood manifests as an infection in the body. Leukocytes are divided into two based on the presence or absence of granules, namely granulocytes, and agranulocytes. Granulocytes are classified into neutrophils, eosinophils, and basophils. At the same time, agranulocytes are classified into lymphocytes and monocytes.

Neutrophils are the body's first defense mechanism when a foreign object enters or the tissue is damaged. Neutrophil activation plays a role in effectively fighting the infection together with monocytes and macrophages through phagocytosis or the release of oxygen radicals, proteases, or peroxidases. Eosinophils play a role in fighting parasitic and worm infections. Basophils synthesize and store histamine and heparin, potent chemicals that are released when appropriate stimuli occur. The release of histamine is important in allergic reactions, while heparin speeds up the clearance of fat particles from the blood after we eat a fatty meal. Heparin also functions as an anticoagulant. Lymphocytes play a role in the body's immune response to fight viral and bacterial infections. Monocytes are the largest blood cells and function as the second layer of the body's defense, which can phagocytize and are a group of macrophages. [31]

Leukocytes are the fewest blood cells (about one white blood cell for every 700 red blood cells). Under normal circumstances, about two-thirds of leukocytes in the blood are granulocytes, mainly neutrophils, while one-third are agranulocytes, mainly lymphocytes. Although leukocyte levels vary, abnormalities in leukocyte production can occur that are out of control, namely, leukocyte levels that are too low or too high. Leukopenia decreases white blood cells to less than 4,000 per mm3. Leukopenia can occur because there is a disorder in the spinal cord that slows down or even stops the production of white blood cells when exposed to toxic chemicals or excessive radiation. A decrease in the number of leukocytes can result in a decrease in phagocytic cells, namely neutrophils, and macrophages, which greatly reduce the body's defense ability against invading microorganisms. Leukocytosis is an increase in the white blood cell count of more than 11,000 per mm3 in a non-pregnant adult. An increase in the number of leukocytes indicates an infection and inflammation and plays a role in vascular injury and atherogenesis which is the development of an atherosclerotic plaque rupture and thrombosis. A high leukocyte count is related to the extent of the infarction that occurs, this is often characterized by increased peripheral leukocytosis, and the most common are neutrophils. [32]

Early neurological deterioration is associated with an increased risk of disability and death. Early neurological deterioration is a decrease in the Glasgow Coma Scale score of ≥ 3 or death within 72 hours after stroke. END is associated with a poor prognosis in stroke patients. Multifactorial factors cause early neurological deterioration. Atherosclerosis of the large arteries and the development of symptomatic arterial occlusion are frequently associated with END. In addition, clinical, hemodynamic, bleeding, biochemical, metabolic, and vascular reactions are associated with early neurological deterioration. Early neurological deterioration may occur due to the mechanism of collateral circulation failure in patients with intracranial or extracranial great vessel stenosis or occlusion, development of thrombosis in ischemic areas, development of cerebral edema in patients with stroke and hemorrhage transformation, seizures, excitotoxicity, and inflammatory reactions. [33]

Several studies on early neurological deterioration identified predictors of early neurological deterioration, including hematoma volume, intraventricular hemorrhage, hematoma expansion within 24 hours, increased white blood cells, and high blood pressure. According to the study of Shoujian et al., other predictors of END include an extension of subarachnoid hemorrhage and left hemisphere hematoma. Left hemisphere hematomas were shown to have more severe clinical features with lower GCS and higher NIHSS scores. Early neurological deterioration associated with subarachnoid hemorrhage is thought to be associated with an inflammatory process and hydrocephalus. [34] Early neurological deterioration occurs mostly in progressive strokes. Therefore, it is necessary to be able to assess the risk of END in the hospital to improve clinical skills and determine the initial treatment of stroke.

Rupture of the blood vessel wall in hemorrhagic stroke will result in blood seepage and the formation of a hematoma resulting in primary damage after the onset of bleeding. The formation of a hemorrhagic stroke zone will result in the entry of metabolic products into the circulation system, which will then activate hormones and release leukocytes from the bone marrow into the bloodstream. The bone marrow is primarily filled with neutrophils so that leukocytosis appears as a shift in cell numbers, and activated neutrophils then migrate to the hemorrhagic stroke zone via positive chemotaxis. In addition to neutrophils, lymphocytes increased significantly within 24 hours after bleeding and peaked at 3–7 days. Neutrophils and lymphocytes play an important role in brain tissue damage. Stroke patients with leukocytosis usually have a much worse prognosis and outcome than those without elevated leukocytosis. It can be caused by the accumulation of leukocytes, which disrupts brain microcirculation and causes secondary brain damage. According to research by Yunisa and

Ayu, leukocyte numbers tend to be higher in hemorrhagic strokes than in ischemic ones. Yunisa and Ayu explained further that the accumulation of leukocytes, especially neutrophils, in acute inflammation would result in more widespread tissue damage in the brain, which results in clinical deterioration of the patient. [35] Other studies also stated that the larger the lesion volume, the higher the number of leukocytes in both hemorrhagic and ischemic strokes, which leads to a poor prognosis. Existing studies show increased END rates and significantly worse outcomes in stroke patients with high leukocyte counts. [6]

Based on the background of this study, the formulation of the problem in this study was formulated as follows: Is there a relationship between an increase in leukocyte count in acute phase hemorrhagic stroke patients and the incidence of END at the UKI General Hospital for the period January 2016 - December 2019? The aim of the study, namely to determine whether there is a relationship between an increase in leukocyte count in acute phase hemorrhagic stroke patients and the incidence of END at the UKI General Hospital for the period January 2016 - December 2019.

Research Method

This research is a retrospective study using a cross-sectional research design. The research was conducted using medical record data at UKI General Hospital. The study was conducted from December 2020 to February 2021. The population that became the object of this study were all patients diagnosed with Hemorrhagic Stroke by a neurologist via CT-Scan and treated at the UKI General Hospital from January 2016 to December 2020. The samples studied from this study were acute-phase Hemorrhagic Stroke patients who came to UKI General Hospital from January 2016 to December 2020, taking into account the inclusion and exclusion criteria. In this study, samples were obtained by tracing patient medical records. Samples were collected and selected using a total sampling technique in acute-phase hemorrhagic stroke patients according to the inclusion criteria. The research instruments used in this study were patient medical records and SPSS version 25. Data was collected by taking secondary data from the medical records of acute-phase hemorrhagic stroke patients. To obtain secondary data, data selection was carried out according to the study's inclusion criteria at UKI General Hospital. The data obtained from the samples were processed using the Statistical Product for Service Solution (SPSS) Version 25 program. The data obtained entered the editing stage, in which the data obtained would be adjusted to the established inclusion and exclusion criteria. Coding of data aims to make it easier to take samples and analyze data by giving codes in the form of numbers. The data will be grouped based on predetermined criteria, namely normoleukocytes (4000-11000 cells/µL), leukocytosis (> 11,000 cells/µL), and early neurological deterioration. Tabulated research data were analyzed using Univariate analysis to determine the frequency distribution of each variable. The analysis technique used was bivariate analysis to determine the relationship between leukocyte count in the acute phase of hemorrhagic stroke and Early Neurological Deterioration. The hypothesis test used in this research is chi-square.

Result and Discussion

Based on the results of medical record data collection conducted at the UKI General Hospital, it was found that there were 39 hemorrhagic stroke patients 2016-2019 from January 2016 to December 2019. The study subjects who met the inclusion criteria were 38 of the 39 patients who were diagnosed with hemorrhagic stroke by CT scan. The bleeding volume variable cannot be measured because the medical record data does not attach the examination results, especially regarding the bleeding volume and diameter in hemorrhagic stroke patients.

In this study, the age of the patients was divided into six age groups, namely <40 years, 41-45 years, 46-50 years, 51-55 years, 56-60 years, and>60 years. Based on the data, most hemorrhagic strokes occurred in the age group >60 years, namely 13 people (34.2%). The age group of hemorrhagic stroke patients was the least in the age group <40 years, which was two people (5.3%). The distribution of the age groups of the respondents is shown in Table 1.

Table 1. Distribution of Research Subjects by Age

Age	Frequency (Patient)	Percentage (%)
<40	2	5,3
41-45	6	15,8
46-50	6	15,8
51-55	5	13,2
56-60	6	15,8
>60	13	34,2
Total	**38**	**100,0**

The results showed that the number of male hemorrhagic stroke patients was 25 (65.8%), while female patients were 13 people (34.2%). Based on the results of this study, it showed that there were more male patients than female patients. The gender distribution of the respondents is in Table 2.

Table 2. Distribution of Research Subjects by Gender

Gender	Frequency (Patient)	Percentage (%)
Male	25	65,8
Female	13	34,2
Total	**38**	**100,0**

Based on the results of research conducted by researchers, it was found that 13 patients (34.2%) had hemorrhagic strokes patients who experienced END. The distribution of research subjects based on their END status can be seen in Table 3.

Table 3. Distribution of research subjects based on END status

END	Frequency	Percentage (%)
Yes	13	34,2
No	25	65,8
Total	**38**	**100,0**

Based on the medical history of hemorrhagic stroke patients, hypertension is the most common history of disease in patients, namely 16 people (42.1%). The distribution of research subjects based on medical history can be seen in Table 4.

Table 4. Distribution of research subjects based on medical history

Disease History	Frequency	Percentage (%)
Hypertension (HT)	16	42,1
Diabetes Mellitus (DM)	7	18,4
History of HT and DM	6	15,8
No history of the disease	9	23,7

The distribution of research subjects based on the Glasgow Coma Scale (GCS) score obtained that the highest initial GCS score was 13-15, namely 25 people (65.8%), and the highest GCS score ≤ 72 hours was 3-12 (52.6%). The distribution of research subjects based on the Glasgow Coma Scale (GCS) score can be seen in Table 5.

Table 5. Distribution of research subjects based on GCS scores

Glasgow Coma Scale	Frequency	Percentage (%)
Early GCS		
13-15	25	65,8
3-12	13	34,2
GCS ≤ 72 hours		
13-15	18	47,4
3-12	20	52,6

Based on the operational definition, leukocyte data can be divided into normoleukocytes and leukocytosis. Based on these data, 20 hemorrhagic stroke patients had an increased leukocyte count (52.6%), and 18 had normal leukocyte counts (47.4%). Hemorrhagic stroke patients with the highest leukocyte count were 33,000/µL of blood, and the lowest leukocyte count was 5,400/µL of blood with an average leukocyte count of 13,210.53/µL. The distribution of research subjects based on leukocyte values can be seen in Table 6.

Table 6. Distribution of research subjects based on leukocyte values

Leukocyte Value	Frequency	Percentage (%)
Normoleukocytes	18	47,4
Leukocytosis	20	52,6
Total	**38**	**100,0**

The END characteristics in this study showed that the average age of subjects with END was 56.62 years, while patients without END had an average age of 54.28. Based on the Independent T-Test test results, the value of Sig. (2-tailed) of 0.511, where this value is greater than 0.05. So, there is no significant difference between the average age of patients with END and non-END events at the UKI General Hospital. The END characteristics of research subjects can be seen in Table 7.

Table 7. Characteristics of END research subjects

Characteristics	END (n=13)	Not END (n=25)	p
Age, years, mean	56,62	54,28	0,511

Unpaired t-test

Research subjects with male gender experienced more END than female gender, namely 12 people. Based on the medical history of the study subjects with a history of diabetes, two people experienced END. Subjects with a history of hypertension were found more in subjects with END than those with Diabetes Mellitus, namely four people. The END characteristics of research subjects can be seen in Table 8.

Table 8. Characteristics of END research subjects

Characteristics	END (n=13)	Not END (n=25)	P
Gender			
Male	12 (92,3%)	13 (52,0%)	0,015
Female	1 (7,7%)	12 (48,0%)	
Hypertension	4 (30,8%)	12 (48,0%)	1,000
Diabetes mellitus	2 (15,4%)	5 (20,0%)	

Chi-Square Test

The independent variable in this study was the leukocyte count at hospital admission with onset ≤ 7 days, while the dependent variable was the incidence of END while hospitalized. The results of the research data obtained were then carried out by testing the

hypothesis with the Chi-Square test using a statistical program, and the following data were obtained:

Table 9. Effect of Leukocyte Counts at Hospital Admission on the Incidence of Early Neurological Deterioration

Leukocyte Number Category	END state		P	RR (IK = 95%)
	Yes n (%)	No N (%)		
Leukocytosis	10 (76,9%)	10 (40,0%)	0,031	3,003
Normoleukocytes	3 (23,1%)	15 (60,0%)		
Total	**13**	**25**		

Bivariate analysis to determine whether or not there was a difference in leukocyte values between acute phase hemorrhagic stroke patients who had END and those who did not have END. Based on the processed data, it can be seen that three patients (23.1%) in the normoleukocyte category experienced END, while ten patients (76.9%) in the leukocytosis category experienced END. Based on the Chi-Square Test, the significance value obtained from the Chi-Square test is 0.031 ($p < 0.05$). This result means that statistically, there is an effect of an increase in leukocyte count upon admission to the incidence of Early Neurological Deterioration in hemorrhagic stroke patients. The relative risk score (RR) indicates the strength of the relationship in a cross-sectional study design. The relative risk figure (RR) obtained from the calculation is 3.003 with a 95% confidence interval. It means that patients with leukocyte counts of more than 11,000/µL of blood or patients with leukocytosis are three times more likely to experience END events compared to patients who have normal leukocyte counts or normoleukocytes with leukocyte counts ranging from 4,000/µL of blood to 11,000/µL of blood.

Based on medical record data, the youngest age group of hemorrhagic stroke patients at UKI General Hospital is <40 years old, while the oldest age group is >60. The most common age group of hemorrhagic stroke patients was the age group over 60 years, with 13 people (34.2%), and the age group with the least number of hemorrhagic stroke patients was less than 40 years old, with two people (5.3%). The average age of hemorrhagic stroke patients is 55.08 years. This study's results align with several previous studies, which stated that the average age of incident hemorrhagic stroke was 54.2 years and 53.84 years. [49] In a study conducted by Sanyasi et al. at Bethesda Hospital Yogyakarta, it was found that the most common age profile of hemorrhagic stroke patients was ≥ 60 years of 56.1% and under <60 years of 45.5%. [50] Similar results were also found in a study conducted by Badriyah et al. at RSHS Bandung, where the prevalence of stroke increased with age; namely, the highest age profile of stroke patients was the 55-64 age group of 33.3%. While the lowest prevalence is in the age group of 15-24 years of 0.6%. The incidence of stroke increases with age, doubling after age 45 to 85 years.

Based on research conducted by Budi et al., the incidence of hemorrhagic stroke occurred mostly in the old adult age group, namely 51-55 years (37.5%), and the least in the 31-35 years age group, namely 4.2%. The increasing number of hemorrhagic strokes is caused by an unhealthy lifestyle, such as a diet that contains a lot of fat, a lack of exercise, and a history of stress that triggers hypertension. Hypertension is a risk factor for intracerebral hemorrhagic stroke at a younger age. [36] Meanwhile, in elderly hemorrhagic stroke patients, the main risk factor for hemorrhagic stroke is a degenerative process. Degenerative processes in blood vessels in the brain include thickening of the intima of blood vessels, endothelial dysfunction, decreased elasticity of blood vessels, and increased blood-brain barrier permeability. The increased incidence of hemorrhagic stroke at 55 years and

over tends to be caused by hemodynamic factors such as high systemic arterial blood pressure, where the elasticity of the brain's blood vessels has been reduced, and the inability to withstand increased blood pressure. The results of this study indicate that the incidence of hemorrhagic stroke in patients treated at the UKI General Hospital occurs at an age that is not much different when compared to the results of studies elsewhere.

Based on the medical record data taken, it was found that 25 (65.8%) male patients suffered more hemorrhagic strokes compared to 13 (34.2%) female patients. This study aligns with research conducted by Mahayani et al., which stated that the number of hemorrhagic stroke patients was higher in male patients, namely 60%, and in female patients, namely 40%. [37] Another study that showed that the number of male patients was far more than female patients was shown by a study conducted by Khan et al. This study found that of 53 hemorrhagic stroke patients, there were 40 male patients and 13 female patients. [38]

Based on research conducted by Irsyad et al., the incidence of hemorrhagic stroke was more common in men, 110 people (67%), and women, 53 people (32%). Sex hormones play a role in the occurrence of these differences. Several studies have stated that estrogen positively affects the brain's blood vessels. Certain risk factors influence each gender. [39] It relates to a study by Roquer et al., which found that risk factors for alcohol consumption, smoking habits, and atherosclerotic disease were higher in men than women.

The risk of stroke is 20% higher in men than women, but after age 55, the risk of stroke is higher in women than men. Although men are more prone to hemorrhagic stroke than women at a younger age, after women enter menopause, there is no significant difference between the number of male and female patients. Postmenopausal women have a higher incidence of hemorrhagic stroke than pre-menopausal women. It is because, during pre-menopause, women are protected by the hormone estrogen, which plays a role in increasing HDL and lowering LDL, thereby preventing the formation of atherosclerosis. Risk factors in the form of the individual's own behavior in the form of lifestyle and previous medical history related to vascular disease are the most important factors to be reviewed.

Based on the results of the Glasgow Coma Scale (GCS) score data study, as many as 25 people (65.8%) had a GCS score of 13-15 at baseline, and as many as 18 people (47.4%) had a GCS score of 13-15 during the period 72 hour time. Then seven patients experienced a decrease in GCS $\leq$ 72 hours, so the final GCS score was 3-12. This group is at risk of experiencing END, especially if you enter with an initial GCS score of 13-15. This study showed a GCS score of $\leq$ 12 within 72 hours of acute phase hemorrhagic stroke, defined as END. Glasgow Coma Scale (GCS) can be used to observe patients who experience END and assess the severity of stroke patients. Research conducted by Lord et al. in 2015 showed that 22.8% of hemorrhagic stroke patients who experienced END had a GCS score at initial admission of $\leq$13. Hemorrhagic Stroke Patients with a GCS score $\leq$13 at admission have 0.77 times the risk of experiencing END. Higher GCS scores are associated with better clinical outcomes in stroke. [40]

Subjects who experienced END had an average age of 56.62 years, and those who did not experience END had an average age of 54.28 years. Based on the results of the unpaired T-test, it was found that there was no significant difference in the mean age of the subjects between END and not END ($p = 0.511$). A previous study conducted by Helbok et al. found that the average age of hemorrhagic stroke patients who experienced END was 57 years, and those who did not experience END were 52 years. [41] Based on research conducted by Shkirkova et al. in 2018 stated that the average age of hemorrhagic stroke patients who experienced END was 65.7 years, and those who did not experience END was 64.9 years. Ischemic and hemorrhagic strokes correlate positively with age; the higher a person's age, the higher the risk of stroke. The risk of poor outcomes in stroke increases after age 60. As a person's age increases, the possibility of experiencing permanent neurological damage will be

higher. The results of this study indicated that subjects with the male sex experienced more END, namely 12 people (92.3%), compared to women, namely one person (7.7%). Differences in activity could cause it. Based on the results of the Chi-Square Test, sex characteristics had a significant relationship with the incidence of END (P=0.015). In contrast to the study conducted by Du et al., which stated that there was no significant relationship between gender and the incidence of END. According to Huang et al., men's and women's antioxidant activity differences affect END risk. This difference is associated with differences in hormone levels. Estrogen can directly regulate the post-stroke immune response through steroid hormone receptors in cells in the brain to reduce the risk of infection and worsening of neurological damage. [42]

Based on a history of hypertension, 22 patients who had a history of hypertension experienced hemorrhagic stroke. According to Soewarno et al., hypertension is a strong factor in hemorrhagic stroke. In this study, four patients (30.8%) had a history of hypertension and experienced END. Patients with a history of hypertension are 4.76 times more likely to experience a hemorrhagic stroke than those without a history of hypertension. It is very important to know these risk factors to prevent hemorrhagic stroke so that the patient's quality of life increases and patient mortality decreases. Hypertension plays a role in forming atherosclerosis which causes blood vessels to narrow and plaque formation. Chronic hypertension can cause endothelial dysfunction. Endothelial dysfunction will result in reduced NO (Nitric Oxide) production, which regulates the dilation and constriction of blood vessels. Reduced NO production will cause proinflammatory, procoagulant, and prothrombotic effects, which can change the structure of blood vessels and hyalinization in the muscle layer of cerebral blood vessels. These structural changes result in blood vessels being unable to dilate and constrict normally during fluctuations in systemic blood pressure. If there is an increase in systemic blood pressure, the perfusion pressure on the capillary walls becomes high, resulting in hyperemia, edema, and possible cerebral hemorrhage. [43]

Based on a history of diabetes mellitus, it was found that 13 subjects had a history of diabetes mellitus. According to Gaillard and Miller's research, diabetes mellitus is also a risk factor for hemorrhagic stroke. In END patients, two people had a history of diabetes. Patients with a history of diabetes mellitus have a 1.6 times risk of experiencing a hemorrhagic stroke compared to patients who do not have a history of diabetes mellitus. [44] Based on the Chi-Square test results, there was no significant relationship between patients with a history of hypertension and DM and END (p=1,000). The results of a study conducted by Shkirkova et al. stated that there was no relationship between a history of diabetes and END (p=055), in contrast to hypertension which had a significant relationship with the incidence of END in hemorrhagic stroke patients (p=0.01).

Patients with DM have an increased incidence of cardiovascular atherosclerosis and peripheral arterial and cerebrovascular disease. Several studies have shown that elevated glucose at admission is associated with expansion, larger hematoma size, perihematomal edema, cell death, and increased risk of poor outcome, and it is a strong predictor of 30-day mortality in patients with hemorrhagic stroke. Diabetes Mellitus causes intracellular acidosis, which damages neurons, glial tissue, and vascular tissue, so hyperglycemia is associated with worse outcomes and mortality in hemorrhagic stroke patients. [6] This study showed that three patients in the normoleukocyte category experienced END (23.1%), while ten patients (76.9%) in the leukocytosis category experienced END. The significance number obtained from the Chi-Square test is 0.031 ($p < 0.05$). These results mean that statistically, there is an effect of an increase in leukocyte count upon admission to the incidence of Early Neurological Deterioration in acute phase hemorrhagic stroke patients at the UKI General Hospital. In addition, the relative risk figure obtained is 3.003 with a 95% confidence interval. It means that patients with leukocyte counts of more than 11,000/µL of blood or

patients with leukocytosis are three times more likely to experience END events compared to patients who have normal leukocyte counts or normoleukocytes with leukocyte counts ranging from 4,000/µL of blood to 11,000/µL of blood.

Based on research conducted by Sun et al., it was shown that leukocyte counts > 10,000/mL3 at admission or in the first 72 hours are associated with subacute damage. In addition, the results of this study indicated that leukocytosis had a strong relationship with worsening clinical conditions, such as a decrease in GCS (p=0.05). Leukocyte accumulation results in disruption of brain microcirculation and results in secondary brain damage. This study shows that hemorrhagic stroke patients with an increased leukocyte count are five times at risk of experiencing END compared to patients who do not have an increased leukocyte count. [45] Following intracerebral hemorrhage, peripheral leukocytes are activated in response to inflammation. Various immune system components, such as neutrophils, macrophages, active microglia, proinflammatory cytokines, and complement components, will induce an inflammatory reaction in the hematoma and the surrounding area. TNF and IL-1 will be released in response to brain injury and as a trigger for leukocyte production. This factor is a feedback mechanism that starts with inflammation in the tissue, then continues to generate large numbers of leukocytes to eliminate the cause of inflammation.

The formation of a hemorrhagic stroke zone will result in the entry of metabolic products into the circulation system, which will then activate hormones and release leukocytes from the bone marrow into the bloodstream. The bone marrow is primarily filled with neutrophils so that leukocytosis appears as a shift in cell numbers, and activated neutrophils then migrate to the hemorrhagic stroke zone via positive chemotaxis. According to a study conducted by Sun et al., neutrophil infiltration can increase gradually within one day after bleeding and reach a peak in 2-3 days. [46] Neutrophils secrete and release various proteolytic enzymes and proteases that can damage brain tissue directly. In addition, lymphocytes increased significantly within 24 hours after ICH and peaked at 3-7 days. It suggests that leukocytes, especially neutrophils and lymphocytes, play an important role in early brain tissue damage caused by cerebral vascular bleeding. The results of this study were supported by Yunisa and Ayu, who, in their research, stated that the tendency for leukocyte numbers to be higher in hemorrhagic strokes compared to ischemic strokes. Yunisa and Ayu explained further that the accumulation of leukocytes, especially neutrophils, in acute inflammation would result in more widespread tissue damage in the brain, which results in clinical deterioration of the patient. [47] Other studies also stated that the larger the lesion volume, the higher the number of leukocytes in both hemorrhagic and ischemic strokes, which leads to a poor prognosis. Based on various previous studies, the average shows that hemorrhagic stroke patients with high leukocyte counts usually have a much worse prognosis and outcome. Several studies have also stated that there is a relationship between leukocytosis and clinical deterioration in patients. It is also related to research conducted by Mohamed et al. in 2021, which stated that Early Neurological Deterioration often occurs after hemorrhagic strokes and is associated with a longer hospital stay, poor functional recovery, and death. [48] It was further explained that it was suspected that increased leukocyte activity in stroke patients would induce death of more extensive brain tissue so that the patient's prognosis would be worse and patient mortality would also increase.

Conclusion

Based on the results of data analysis and discussion that has been carried out in this study, it can be concluded that: a) The number of incidents of acute phase hemorrhagic stroke is higher in male patients, and most are in the age group >60 years with an average age of hemorrhagic stroke patients is 55, 08 years; b) The total number of acute phase hemorrhagic stroke patients who experienced END was 13 people; c) The number of acute phase

hemorrhagic stroke patients with normoleukocytes who experienced END was three people; d) The number of acute phase hemorrhagic stroke patients with leukocytosis who experienced END was ten people; and e) There is a significant relationship between increased leukocyte count on admission and END in hemorrhagic stroke patients while being treated at the General Hospital of the Indonesian Christian University. Therefore, health workers are advised to provide education and outreach about a healthy lifestyle more often so that the incidence and END in hemorrhagic stroke patients can decrease. In addition, the community is advised to adopt a healthy lifestyle by controlling weight, doing moderate exercise, limiting food consumption which increases the risk of hemorrhagic stroke, and frequently controlling blood pressure and blood glucose.

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