Jurnal Ilmiah Mahasiswa Kedokteran Universitas Airlangga

JUXTA: Jurnal Ilmiah Mahasiswa Kedokteran Universitas Airlangga
2024 January, XV (01)

ORIGINAL ARTICLE

Age-Associated with Worsening of Neurological Deficits in Ischemic Stroke Patients in Abdoel Wahab Sjahranie Regional Hospital, Samarinda

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ABSTRACT

Introduction: Treatment of impairment is an important step to prevent advanced neurological deficits in ischemic stroke medicine. Ischemic stroke patients with likely worsening neurological deficits should receive appropriate interventions. Therefore, this study aimed to examine predictors that can identify worsening neurological deficits.

Methods: This study used a cross-sectional design on 74 hospitalized ischemic stroke patients at Abdoel Wahab Sjahranie Regional Hospital, Samarinda, in 2019. The worsening of neurological deficits was based on the progression of the National Institutes of Health Stroke Scale (NIHSS) scores at hospital admission and discharge. Age, hemoglobin level, hematocrit value, gender, smoking history, blood pressure, and hyperglycemic state were based on patient data at the beginning of hospital admission. The Chi-Square and Fisher's exact tests were used in bivariate analysis.

Results: The results showed that age had a significant association with the worsening of neurological deficits in ischemic stroke patients ($p = 0.024$). Hemoglobin level, hematocrit value, gender, smoking history, blood pressure, and hyperglycemic state showed no relationship with worsening neurological deficits in ischemic stroke patients ($p > 0.05$).

Conclusion: Age can serve as a predictor of worsening neurological deficits in ischemic stroke patients, with those aged over 45 years old having a higher risk. Meanwhile, the other factors were not associated with a worsening neurological deficit in ischemic stroke patients.

Highlights:
1. The worsening of neurological deficits in ischemic stroke patients is associated with the patient's age, with those over 45 years old having a higher risk.
2. The worsening of neurological deficits in ischemic stroke patients does not correlate with hemoglobin level, hematocrit value, gender, smoking history, blood pressure, or hyperglycemic state.

ARTICLE INFO

Article history:

Received 22-03-2023
Received in revised form 14-12-2023
Accepted 08-01-2024
Available online 10-01-2024

Keywords:
Age,
Human & medicine,
Ischemic stroke,
Neurological deficit,
Treatment.

Cite this as:
Indria MD, Rachmi E, Hutahaean YO. Age-Associated with Worsening of Neurological Deficits in Ischemic Stroke Patients in Abdoel Wahab Sjahranie Regional Hospital, Samarinda. *JUXTA J Ilm Mhs Kedokt Univ Airlangga* 2024; 15: 34-40.

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JUXTA: Jurnal Ilmiah Mahasiswa Kedokteran Universitas Airlangga
p-ISSN: 1907-3623; e-ISSN: 2684-9453
DOI: 10.20473/juxta.V15I12024.34-40

Introduction

Stroke or central nervous system infarction is defined as central nervous system or retinal cell death caused by ischemia, supported by neuropathological, neuroimaging, and/or clinical evidence of permanent injury.[1] Based on the Global Burden of Disease Stroke Statistics Worldwide 1990–2019, the age-adjusted prevalence of ischemic stroke globally was 77,192,498 people, or 950.97 per 100,000 people. The incidence of ischemic stroke is 62% of all types of stroke.[2] The prevalence of ischemic stroke in Southeast Asia in 2019 was 6,685,553 people. Indonesia ranks the highest in Southeast Asia for incidence (331,149) and prevalence (3,105,438).[3]

Ischemic stroke is a greater contributor to disability than hemorrhagic stroke since it has lesser functional improvement and late-phase recovery.[4] The number of deaths due to ischemic strokes in Indonesia in 2019 was 136,176, and the burden of disability was 3,382.2 per 100,000 people. Based on disability-adjusted life years (DALYs), an ischemic stroke was estimated to cause the loss of 2,957,904 healthy years of life.[2,3,5]

Post-ischemic stroke disability affects the quality of life of patients and their families in physical, emotional, psychological, cognitive, social, and economic aspects. Some patients live with long-term limitations that result in lost productivity. The economic burden for treatment and rehabilitation, as well as additional costs, are very high.[6,7] The burden of ischemic stroke disability is exacerbated by the frequent incidence of ischemic stroke in elderly individuals as well as in the unemployed.[8]

The World Health Organization's (WHO) International Classification of Functioning, Disability, and Health (ICF) stated that neurological disorders can have three effects, changes in body structure and function (impairment), daily and instrumental activities, and taking part in life roles (work, family, fun, and travel).[9] Effective treatment of ischemic stroke in the impairment dimension will prevent further disturbances affecting the other dimensions. To improve the accuracy of personalized treatment plans, clinicians need tools to predict whether an ischemic stroke patient will deteriorate after hospital admission or during therapy. This approach will help allocate ischemic stroke management resources to patients who will benefit optimally.[10]

The ideal marker should be easily accessible, fast, safe, and inexpensive. Tools that were potential in predicting the worsening of ischemic stroke were hemoglobin levels and hematocrit values because the procedure is cheap and requires a simple laboratory. Other factors such as age, gender, smoking history, blood pressure, and hyperglycemic state have a high possibility of being associated with worsening neurological deficits in ischemic stroke patients. Ischemic stroke patients with likely worsening neurological deficits should receive appropriate interventions.[9] Therefore, this study aimed to examine predictors that can identify worsening neurological deficits.

This study was conducted in East Borneo. Although the prevalence and disability rate of ischemic stroke in East Borneo are not yet available, the prevalence of stroke of all types in East Borneo (14.7 per 1,000 population) is higher than in Indonesia (10.9 per 1,000 population).[11] Abdoel Wahab Sjahranie Regional Hospital, Samarinda, the main referral hospital in East Borneo, was appointed as the research location. Abdoel Wahab Sjahranie Regional Hospital, Samarinda, recorded 79.07% of all stroke types from January 2014 to April 2015, which showed the magnitude of ischemic stroke in East Borneo.[12]

Methods

This study used a cross-sectional design from a medical record with purposive sampling. The samples for this study were ischemic stroke patients who were hospitalized at Abdoel Wahab Sjahranie Regional Hospital, Samarinda, in 2019. The age of the selected patients was at least 18 years old. Ischemic stroke patients who were pregnant, had congenital heart disease, and had comorbidities (tuberculosis, pneumonia, chronic obstructive pulmonary disease (COPD), cancer, and heart failure) either before or during treatment were excluded.

Neurologists assessed neurological deficits based on the National Institutes of Health Stroke Scale (NIHSS) score.[13] The worsening of neurological deficits in ischemic stroke patients was determined by analyzing the NIHSS scores on admission and discharge from the hospital. The NIHSS score of the neurological deficit assessment was categorized as follows, mild (score 5), moderate (score 6–14), moderate-severe (score 15–24), and severe (score 25).

If the NIHSS score at discharge was higher than at admission, the neurologic deficit was categorized as worsening. The neurologic deficit was defined as not worsening if the NIHSS score at discharge remained constant or decreased compared to admission. Age, gender, smoking history, hemoglobin level, hematocrit value, blood pressure, and hyperglycemic status were obtained from the medical record on the first day of hospital admission. Submission of ethical permits, data collection, processing, and preparation were performed from July to September 2022. The research data was processed using Statistical Package for the Social Sciences (SPSS) version 26.[14] The Chi-Square test or Fisher's Exact test were used in bivariate analysis.

Results

This study recruited 74 ischemic stroke patients based on inclusion and exclusion criteria. The degree of neurological deficit in ischemic stroke patients upon hospital admission showed that the majority of patients (31 patients/41.9%) had mild neurological deficits (NIHSS score 5) and a minority of patients (9 patients/12.1%) had severe neurological deficits (NIHSS score 25). Based on Table 1, at the time of discharge from the hospital, most of the ischemic stroke patients had improved neurological deficits, as indicated by the increasing number of patients with mild neurological deficits (46 patients/62.2%) and patients who had improved NIHSS scores (66 patients/89.2%).

The majority of ischemic stroke patients had normal hemoglobin levels (55 people/74.3%) and normal hematocrit values (53 people/71.6%). Based on the WHO classification of the degree of anemia, 2 people had moderate anemia (Hb 8–10.9 g/dL), 15 people had mild anemia (Hb 11–12.9 g/dL), and only 1 person had severe anemia (Hb <8 g/dL).

Based on Table 1, the characteristics of ischemic stroke patients in this study were in the age range of 30–86 years old, with 48 people (64.9%) in the age group of 46–65 years old (middle adults). Ischemic stroke was slightly more common in male (42 people/56.8%). Almost all of the patients had no history of smoking (69 patients/93.2%). A history of hypertension was found in 52 patients (70.3%), and impaired hyperglycemic status was identified in 22 patients (29.7%).

Table 1. Characteristics of ischemic stroke patients

	n	%
Hemoglobin levels		
Low	18	24.3
Normal	55	74.3
High	1	1.4
Hematocrit value		
Low	19	25.7
Normal	53	71.6
High	2	2.7
Age		
≤45 years old	7	9.5
46-65 years old	48	64.9
≥66 years old	19	25.7
Gender		
Man	42	56.8
Woman	32	43.2
Smoking history		
Smoking	5	6.8
No smoking	69	93.2
Blood pressure		
Hypertension	52	70.3
No hypertension	22	29.7
Hyperglycemic status		
Hyperglycemic	22	29.7
No hyperglycemic	52	70.3
Admission NIHSS score		
Score <5	31	41.9
Score 6-14	22	29.8
Score 15-24	12	16.2
Score >25	9	12.1
Discharge NIHSS score		
Score <5	46	62.2
Score 6-14	17	22.9
Score 15-24	5	6.8
Score >25	6	8.1
Worsening of neurological deficit		
Getting worse	8	10.8
Not getting worse	66	89.2

Source: Research data, processed

From the analysis results in Table 2, the Chi-Square test and Fisher's Exact test showed worsening of ischemic stroke neurological deficits. Bivariate analysis showed a significant relationship between age and worsening of neurological deficits ($p = 0.024$). Compared to the age group of 45 years or younger, ischemic stroke patients in the age group over 45 years old had a 5.7 times higher risk of experiencing worsening neurological deficits. Hemoglobin level, hematocrit value, gender, history of smoking, history of hypertension, and hyperglycemic status were not associated with worsening of the neurological deficit ($p > 0.05$).

Discussion

Based on the cause, ischemic stroke can be classified into four categories, large vessel atherosclerosis, small vessel occlusion (lacunar), cardioembolic stroke, stroke with other etiologies, and stroke with an undetermined etiology.[10,15] In this study, 44.6% of patients had an NIHSS score of less than 7, which is based on previous studies related to the type of lacunar occlusion.[16] Patients with mild neurological deficits generally account for 46-57% of types of ischemic stroke admitted to several hospitals in Indonesia.[13,17] Most of the patients in this study were discharged from the hospital with an NIHSS score of less than 5 or mild neurological deficits. Four patients had NIHSS admission and discharge scores that remained constant, and two patients had NIHSS scores that worsened, but all were still in the category of mild to moderate neurological deficits. These results are consistent with the characteristics of the lacunar type, which has a shorter hospital stay, lower mortality, and a lower NIHSS at discharge.[15]

Ischemic stroke management at Abdoel Wahab Sjahranie Regional Hospital, Samarinda, showed significant success, with 89.2% of patients showing an increase in the NIHSS score based on Table 1, and 24.3% of patients improved without neurological deficits upon discharge from the hospital. These results are related to the hospital's efforts to improve time efficiency through stroke centers, which are supported by the availability of neurologists, magnetic resonance imaging (MRI), multi-slice computed tomography (MSCT), and optimization of fast lanes between triage and neurologists.[18] Nonetheless, 8 ischemic stroke patients (10.8%) worsened, most of whom remained in the same neurological deficit category between admission and discharge (1 mild, 3 moderate, 2 severe, and 1 very severe).

Delays in coming to the hospital and management of stroke units that are not yet optimal are associated with the worsening functional outcome of ischemic stroke patients.[19] These delays often occur in referred patients due to a lack of knowledge about symptoms at the onset and ignorance of emergency response services. Stroke management is related to time efficiency, hence it needs to be improved in coordination between central-peripheral health facilities, availability of neurologists, as well as computed tomography (CT)-scan/stroke unit facilities needed in many hospitals, and optimization of fast lanes between triage staff and neurologists.[20] Therefore, patients experience worsening because the ischemic stroke management system in Indonesia is not optimal.

Table 2. Chi-Square test and Fisher's Exact test worsening of ischemic stroke neurological deficit

	Criteria	Worsening of neurological deficit				p-value	Relative risk	95% Confidence interval	
		Getting worse		Not getting worse				Lower	Upper
		n	%	n	%				
Hemoglobin level	Low	2	2.7	16	21.6	1,000	1,037	0.229	4,693
	Normal-high	6	8.1	50	67.6				
Hematocrit value	High	0	0	2	2.7	1,000	1,125	1,037	1,221
	Normal-low	8	10.8	64	86.5				
Age	<45 years old	3	4.1	4	5.4	0.024	5.743	0.052	0.579
	>45 years old	5	6.7	62	83.8				
Gender	Man	4	5.4	38	51.4	0.720	0.762	0.206	2,816
	Woman	4	5.4	28	37.8				
Smoking history	Smoking	0	0	5	6.7	1,000	1.131	1.039	1.232
	No smoking	8	10.8	61	82.5				
Blood pressure	Hypertension	7	9.5	45	60.8	0.422	2,962	0.387	22,665
	No hypertension	1	1.3	21	28.4				
Hyperglycemic status	Hyperglycemic	2	2.7	20	27.0	1,000	0.788	0.171	3,605
	No hyperglycemic	6	8.1	46	62.2				

Source: Research data, processed

Table 2 showed that age was associated with worsening neurological deficits in ischemic stroke patients (p = 0.024). Patients over 45 years old had a 5.74 times higher risk of worsening neurological deficits compared to those less than 45 years old. Previous studies have supported this phenomenon. Anxiety about getting an ischemic stroke is higher in older people, which is a risk factor that cannot be changed. Older people also have worse neurological deficits and disabilities.[21,22] A systematic review in the young-adult (<45 years old) group showed a prevalence of ischemic stroke at 21–77.9% and a mortality rate of 0.7/100,000 in the population. The increasing number of hospitalized young-adult ischemic stroke patients is associated with obesity, hypertension, diabetes, smoking, alcohol, and other risk factors.[23,24] The incidence of ischemic stroke based on age between 46 and 90 years old is about 85.6%.[25] Older age is associated with declining body function, an aggravating factor in ischemic stroke patient outcomes. Changes in structural and functional microcirculation are mediated by endothelial dysfunction, neurovascular disorders, and cerebral auto-regulation disorders.[26]

Based on Table 2, hemoglobin levels in ischemic stroke patients were not associated with worsening neurological deficits (p = 1,000). Anemia increases the risk of ischemic stroke 1.6 times and the risk of mortality 1.5 times when an ischemic stroke occurs.However, previous studies reported that the risk of post-surgical ischemic stroke death is more related to the degree of hemoglobin reduction than to the hemoglobin level.[27] Compared to an acute decrease in hemoglobin, chronic anemia may give the body an opportunity to adapt, thereby reducing the risk of death. The brain autoregulation mechanism in ischemic stroke patients is still effective at hemoglobin levels ≥8 mg/dL and worsens in severe anemia with extremely low hemoglobin levels (Hb <8 g/dL).[17,28] In this study, it was not explored whether the anemia was acute or chronic, and the number of patients with severe anemia was only 1, thus further exploration was needed.

Based on Table 2, the Chi-Square and the Fisher's Exact tests showed worsening of ischemic stroke neurological deficits, but hematocrit was not associated with worsening of neurologic deficits in ischemic stroke patients (p = 1,000). These results are inconsistent with previous studies, which showed that a low hematocrit, especially less than 32%, increases the risk of ischemic stroke mortality, both during hospitalization, 30 days, 90 days, and 1 year after stroke.[29] Low hematocrit has a detrimental effect on vascular function because high hematocrit is needed to induce the endothelial nitric oxide (NO) and endothelial nitric oxide synthase (eNOS) production.[30] However, high hematocrit increases protein infiltration into the vessel wall, triggers platelet adhesion to the sub endothelium, and increases the risk of blood flow stagnation, which increases the risk of atherosclerosis.[31] Previous studies showed similar results to this study, that hematocrit was not associated with the short-term outcomes of ischemic stroke patients,[32] and was not associated with ischemic stroke mortality in the first 30 days.[29] The mean age of the patients in this study, as stated by Ozaita, *et al*. (1987)[33] and Bhatia, *et al*. (2004)[34], were in the same range (59.46 + 11.64, 60.9 + 12.8, and 59.4 + 11.2 years old, respectively), which is younger than 67.9 years old, the average age in a study conducted by Sico, *et al*. (2018).[29] The average age of the sample needs to be considered. Worsening ischemic stroke may be related to hematocrit levels in the older group of patients because the effects of low or high hematocrit on dysfunction of smooth muscle and vascular structures have lasted longer and physiological degeneration of the body has advanced. This assumption needs to be investigated further by comparing the effects of hematocrit between the younger and older age groups.

In this study, worsening of ischemic stroke neurological deficit was not associated with gender (p = 0.720). The ischemic stroke patients in this study were dominated by male (56.8%), consistent with several other studies in Indonesia.[5,35] Men were found to be more susceptible to ischemic stroke, and the onset tends to be at a younger age than women.[36] Nevertheless, related to the worsening of ischemic stroke during the hospitalization period, this study proves that men are no different from women. The results of this study are supported by previous studies that showed no difference in mortality between the sexes at hospitalization[37] and 3 months after an ischemic stroke.[38] Studies in the 45-74 years old age group also reported that gender did not affect mortality or recovery of brain function at the end of the acute ischemic stroke period.[39] However,

several studies showed that women experience higher mortality during ischemic stroke treatment in hospitals,[37,40] worse functional outcomes,[41] and worse locomotor function at 1 and 5 years of follow-up after ischemic stroke.[42]

Differences in ischemic stroke outcomes based on gender are influenced by gene-related mechanisms, sex-related steroid hormones, and social culture.[27,36] While genetic elements are constant, sex steroid hormones are dynamic throughout the human life cycle. Thus, the relationship between sex and ischemic stroke severity will be influenced by which phase of the life cycle is observed. In addition, socioeconomic factors affect the incidence of ischemic stroke in women but not in men,[29] which raises the notion that the relationship between gender and ischemic stroke incidence will be different in certain socioeconomic groups. The relationship between gender and ischemic stroke outcomes may also be clearer when considering confounding factors, such as age and degree of severity.[43]

Table 2 showed that there was no relationship between smoking (p = 1,000) and worsening of ischemic stroke during hospitalization. Smoking increases the risk of worsening vascular conditions through two mechanisms, the induction of atherosclerosis and pro-coagulant conditions. The pro-coagulant state is characterized by increased platelet aggregation, increased fibrinogen concentration, decreased fibrinolysis, polycythemia, and increased blood viscosity.[44] The relationship between smoking and atherosclerosis is more related to the incidence and recurrence of ischemic stroke.[45,46] Meanwhile, the effect of smoking on pro-coagulant conditions can be quickly reversible within days after quitting smoking,[45] which certainly happened when patients were hospitalized. Therefore, active smoking (continuing to smoke after ischemic stroke) is associated with functional outcomes and functional independence 3 months after ischemic stroke, compared to non-smokers and former smokers.[44] Smoking is also associated with poor functional recovery in patients on thrombolytic therapy.[47] The interpretation of this study needs to consider that the smoking history was based on the confession of the patient or the patient's family. Therefore, there was a possibility that the patient had a smoking history but denied it.

This study showed that the worsening of neurological deficits in ischemic stroke was not related to blood pressure (p = 0.422) (Table 2). The results of this study may be related to the patient's blood pressure data taken at the initial admission to the hospital. Hence. the increase in blood pressure could be a response to an ischemic stroke. Increased blood pressure is a characteristic of the majority of ischemic stroke patients, which can persist several days after stroke onset and is not related to the blood pressure history or stroke etiology.[48] Compared to blood pressure, wide blood pressure variation (BPV) is associated with worsening functional outcomes in the first 7 days and 3 months after acute stroke.[49,50] Brain autoregulation is disrupted in the stroke area. If the area of healthy penumbra tissue around the ischemic core cannot regulate properly, it may be more likely to be hurt by changes in cerebral perfusion, which is linked to a wide BPV.[51] The timing of blood pressure measurement also affects the relationship between blood pressure and stroke outcomes. Studies that measured blood pressure early in stroke onset demonstrated a positive association between systolic blood pressure variation and poor long-term functional outcome, while those that measured blood pressure more than 12 hours from stroke onset reported no or weak association with outcome.[52] Meanwhile, in this study, there was no information about how many hours after stroke onset the patient came to the hospital.

Based on Table 2, worsening of ischemic stroke neurological deficit was not associated with hyperglycemic status (p = 1,000). Most stroke patients have hyperglycemic stress, which is associated with cortisol and epinephrine release.[53,54] Elevated glucose is related to the early volume of infarct tissue in the acute phase and becomes an early infarct development indicator, worse outcomes, and high mortality risk.[54,55] Hyperglycemia often happens in the early phase of a stroke attack in diabetic patients or non-diabetic patients. It induces anaerobic metabolism mechanisms, elevated lactate, calcium overload, and declined mitochondrial function, leading to lipid membrane destruction and umbra and penumbra neuron cell death.[55,56] There is no significant difference in diabetic and non-diabetic ischemic stroke patient outcomes.[57] Diabetic hyperglycemia is proven by a history of diabetes diagnosis, a positive fasting blood glucose examination, and an oral glucose tolerance test. The value of HbA1c >6.5% is the gold standard for diagnosing diabetic hyperglycemia.[58] However, HbA1c is not the main examination in the research institution, except for specific conditions. The patient's history determines the hyperglycemia status on admission. Non-fasting blood glucose levels were not used in this study in consideration of bias if there were no classic diabetic symptoms.

Strength and Limitations

The strength of this study was the use of many variables as factors that were considered to influence the worsening of ischemic stroke neurological deficits compared to other studies. The limitation in this study was that many ischemic stroke patients arrived more than 24 hours after onset, hence the NIHSS score at hospital admission was not the patient's condition on the first day of ischemic stroke. Therefore, NIHSS hospital admission time was not only influenced by the severity and location of the blockage but also by the length of time the patient had not received proper management.

Conclusion

Ischemic stroke patients treated at Abdoel Wahab Sjahranie Regional Hospital, Samarinda, aged >45 years old were 5.7 times more likely to have poor outcomes than young people. It is linked to changes in the structure and function of the microcirculatory system caused by endothelial dysfunction, neurovascular disturbances, and poor brain autoregulation. Hemoglobin level, hematocrit value, gender, smoking history, blood pressure, and

hyperglycemic status did not exacerbate neurological deficits in ischemic stroke patients upon discharge from the hospital. It is needed to use larger samples in future studies to look into the link between hemoglobin levels and both low and high hematocrit values. This will help to prove the idea that hemoglobin levels affect changes in hematocrit values in people who have had an ischemic stroke.

Acknowledgments
The authors would like to thank the staff of Abdoel Wahab Sjahranie Regional Hospital, Samarinda, for their assistance in conducting this study.

Conflict of Interest
The authors declared there is no conflict of interest.

Funding
This study did not receive any funding.

Ethical Clearance
This study was ethically approved by the Health Research Ethics Commission of Abdoel Wahab Sjahranie Regional Hospital, Samarinda (No. 110/KEPK-AWS/VII/2022) in July 2022.

Authors' Contributions
Designed the study and drafted the manuscript: MDI, ER, YOH. Collected data and performed a background literature review: MDI, ER, YOH. Performed statistical analysis: MDI. Supervised results and discussion: MDI, ER, YOH. All authors contributed and approved the final version of the manuscript.

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