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Original Article

Severity of White Matter Lesions Correlate with Small Vessel Ischemic Stroke

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Abstract

Background: Stroke is the third leading cause of death globally. White matter lesions (WMLs) are often observed on brain imaging such as magnetic resonance imaging (MRI) in healthy elders and are considered as stroke predictors. Increased WMLs volume also affects small vessel stroke with worse disability. This study aimed to explore the correlation between WMLs severity and small vessel stroke subtype in acute ischemic stroke patients.

Methods: A cross-sectional descriptive study was conducted using medical record data from June 2018 to October 2022. Simple randomized sampling was used, including stroke patients at Siloam Hospital, Jember, Indonesia. The Fazekas scale categorized WMLs, and magnetic resonance angiography (MRA) confirmed small vessel stroke etiology-based subtype. Two-tailed Spearman's Rank-Order Correlation Coefficient test was employed to describe the relationship between WMLs severity and small vessel stroke subtype.

Results: From a total of 65 acute ischemic stroke patients, 39 patients were included, predominantly females (62%), aged less than 55 years old (44%) with a history of hypertension (54%) and diabetes mellitus (59%). Small vessel stroke subtype was found in 64% of patients. There was a positive correlation between WMLs and the small vessel stroke subtype in acute ischemic stroke patients (p=0.02), suggesting that a higher Fazekas scale correlated with the small vessel subtype.

Conclusion: The higher the severity of WMLs, the greater the correlation with small vessel stroke subtype. Early detection of small vessel ischemic stroke in patients with severe WML may contribute to early diagnosis and prompt treatment of ischemic stroke.

Keywords: Acute ischemic stroke, Fazekas scale, small vessel disease, white matter lesions

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Introduction

Stroke is the third leading cause of death in developing countries, with a death rate of 10%, after coronary heart disease and cancer.[1] One of the crucial factors in treating ischemic stroke is time. Ischemic stroke patients lose 190,000 brain cells and over 14 billion neuronal networks every minute.[2] Acute ischemic stroke patients treated in less than 72 hours will have better neurological function, daily activities, and motor function compared to patients treated within 72 hours to a week. Early rehabilitation has a significant role in improving post-stroke outcomes and helping patient revert to a normal life.[3] Intravenous tissue-type plasminogen activator (IV-tPA) has been proven to be more beneficial for small vessel stroke instead of large vessel strokes, therefore increasing the urgency for clinicians to be able to determine the stroke subtype.[4] White matter lesions (WMLs) are often observed on brain magnetic resonance imaging (MRI) of the healthy older adults and are considered to be predictors of stroke and dementia risk, as well as markers of

various pathological conditions.[5] WMLs are found in 44% of strokes patients and 50–75% of vascular dementia patients. Stroke patients with WMLs are more vulnerable to experiencing cognitive decline.[6] WMLs are best seen as hyperintensities in FLAIR and T2-weighted MRI sequences. Any process that damages the chemical composition, destruction, or ischemia of myelinated axons could result in WMLs.[7] A study showed that brain hypoperfusion and decreased cerebral blood flow are the consequences of WMLs rather than causes, supporting the hypothesis that WMLs increase the risk of stroke, not vice versa.[8] A cohort study has suggested that WMLs are associated with the escalation risk of ischemic stroke in patients with atrial fibrillation taking anticoagulant drugs.[9] WMLs have a vital role as a stroke risk factor and doubles the mortality risk in stroke patients. An increase in WMLs volume is also related to worse functional disruption.[10]

The severity of WMLs is related to the size of the damaged tissue due to the ischemic as well as infarct expansion and higher NIHSS scores in stroke patients. WMLs cause damage to white matter tracts in the intra and interhemispheric that can lead to loss of neuronal integrity function. This mechanism can result in loss of brain plasticity and compensation mechanism so that even a small stroke can cause a relatively large functional deficits.[11] The severity of WMLs can negatively impact the brain's ability to tolerate ischemic effects. Higher levels of WMLs severity may lead to worse and more persistent clinical deficits in acute infarct patients and are associated with worse outcomes, including decreased physical function, quality of life, stroke recurrence, and death. Therefore, WMLs should not be considered as minor findings that have no clinical significance but should be given more attention to prevent stroke events.[12,13]

An increase in WMLs volume also affects small vessel stroke with worse disability. In small vessel stroke patients, higher WMLs volumes are related to higher NIHSS scores at the onset.[14] WMLs severity is also related to the small vessel stroke subtype and has larger progressivity than other stroke subtypes.[15] WMLs are related to small vessel stroke and, therefore, support the hypothesis of small vessel pathogenesis.[16]

The aim of the study was to explore the correlation between WMLs severity and small vessel stroke subtype in patients with acute ischemic stroke. By discovering the relationship between the WMLs severity and small vessel stroke subtype, clinicians may detect patients at higher risk for acute small vessel ischemic stroke, determine treatment effectively, and estimate patient's prognosis as WMLs worsen the stroke outcomes.

Methods

This was a cross-sectional descriptive study, using medical record data from Siloam Hospital Jember collected between June 2018 and October 2022. The study obtained ethical approval from the Ethics committee of the Faculty of Dentistry, Universitas Jember (No.1748/UN25.8/KEPK/DL/2022).

The inclusion criteria were data from patients with acute ischemic stroke confirmed by MRI, showing hyperintensity on Diffusion-weighted Imaging (DWI), T2-weighted, and Fluid-Attenuated Inversion Recovery (FLAIR) sequences, as well as hypointensity on Apparent Diffusion Coefficient (ADC) and T1-weighted sequences. Patients with low-quality images due to movement or metal artifacts, patients with brain hemorrhage, and tumors were excluded.

Patient characteristics data were collected such as age, gender, history of diabetes mellitus and hypertension. Furthermore, the severity WMLs was measured using the Fazekas scale divided into Fazekas grade 0, 1, 2, and 3; while the small vessel stroke subtype was divided into 'yes' and 'no' groups. Based on the severity, the Fazekas scales evaluated WMLs in the periventricular and deep white matter areas.[17] In the periventricular area, Fazekas grade 0 was designated as no lesion, grade 1 as thin pencil lining, grade 2 as smooth halo, and grade 3 as irregular with extension into deep white matter. In the deep white matter area, Fazekas grade 0 was designated as normal; grade 1 as punctate foci; grade 2 as early confluent foci, and grade 3 as wide confluent area.[18] Magnetic resonance angiography (MRA) examination results confirmed small vessel stroke etiology-based subtypes to localize the occluded artery.

The collected data was tested using the Two-tailed Spearman's Rank-Order Correlation Coefficient to determine the correlation between two variables. The results were significant if the p-value was below 0.05. The correlation coefficient (r) was interpreted as a strong correlation with a correlation coefficient of 0.00 to 0.20 as almost no correlation, 0.21 to 0.40 as a weak correlation, 0.41 to 0.60 as a medium correlation, as 0.61 to 0.80 as a strong correlation, and 0.81 to 1.00 as a perfect correlation.

Table 1 Characteristics of Patients with Acute Ischemic Stroke at Siloam Hospital Jember, Indonesia from June 2018 to October 2022

Characteristic	White Matter Lesions Severity (Fazekas)								Total		p-value
	0		1		2		3				
	n	%	n	%	n	%	n	%	n	%	
Gender											
Male	-	-	7	47	7	44	1	14	15	38	0.36
Female	1	100	8	53	9	56	6	86	24	62	
Age (year)											
≤55	1	100	14	93	1	6	1	14	17	44	
56–65	-	-	1	7	10	63	1	14	12	31	0.00*
66–75	-	-	-	-	5	31	3	43	8	21	
>75	-	-	-	-	-	-	2	18	2	5	
Hypertension											
Yes	1	100	4	27	11	69	5	71	21	54	0.02*
No	-	-	11	73	5	31	2	29	18	46	
Diabetes mellitus											
Yes	-	-	8	53	10	63	5	71	23	59	0.04
No	1	100	7	47	6	38	2	29	16	41	

Results

Of the 65 data on patients with acute ischemic stroke, only 39 data were included in this study where the patients predominantly females (62%) aged under 55 years (44%). Hypertension and diabetes mellitus were prevalent in 54% and 59%, respectively.

The was a significant relationship between WMLs severity and small vessel stroke subtype (p=0.02), however, the correlation coefficient was +0.35, suggesting a weak correlation.

Discussion

In this study, acute ischemic stroke patients are predominantly females, and moreover, the WMLs severity groups are more prevalent in females, similar to a previous study showing that the percentage of all WMLs severity grades is higher in females.[19] However, another study has shown a contradictory result, reporting that WMLs are correlated with male,[20] or otherwise no difference between the WMLs severity and gender.[21] In general, ischemic stroke is more prevalent in females due to the life expectancy of females.[22]

Interestingly, most of the patients (44%) are in the age group below 55 years. Most studies have shown an older age group for ischemic stroke and WMLs, which progressing with age with a mean age of 60 to 70 years.[20] Hypertension and diabetes mellitus have been found in the majority of patients. Previous studies have shown a correlation between WMLs severity and increased blood pressure. There is a strong relationship between the increasing severity of WMLs and diastolic and systolic blood pressure.[23] Hypertension is not only associated with the first appearance of WMLs, but also with its progressivity. Hyaline degeneration and thickening of inner wall occur in chronic hypertension, especially in intracranial arterioles and deep perforating

Table 2 Correlation between White Matter Lesions Severity and Small Vessel Stroke Subtype among Patients with Acute Ischemic Stroke

Vessel Stroke Subtype	White Matter Lesions Severity (Fazekas)								Total		p-value
	0		1		2		3				
	n	%	n	%	n	%	n	%	n	%	
Yes	0	0	14	36	8	21	3	8	25	64	
No	1	3	1	3	8	21	4	10	14	36	0.02
Total	1	3	15	38	16	41	7	18	39	100	

Note: Fazekas 0 is no lesion, grade 1 as thin pencil lining, grade 2 as smooth halo, and grade 3 is irregular with extension to deep white matter

arteries. This mechanism leads to reduced cerebral blood flow and collateral circulation, which induces white matter damage.[24] This is reinforced by another study, reporting a correlation between systolic and diastolic blood pressure and WMLs progressivity. The WMLs progressivity is also slower in patients with controlled hypertension compared to the uncontrolled hypertension group.[25]

Diabetes mellitus has been found to correlate with the WMLs severity as it causes loss of white matter integrity. High glucose levels cause a shift in microglia/macrophage polarization to a proinflammatory phenotype that induces impaired differentiation of the oligodendrocyte precursor cells (OPCs). Diabetes mellitus causes loss of white matter repair function in ischemic stroke patients.[26]

The WMLs severity may negatively affect the brain's capacity to tolerate ischemic damage, thereby increasing the risk of acute ischemic stroke. It is known that the WMLs severity can increases the possibility of incomplete infarct turning into complete infarct, thus causing worse and persistent clinical deficits in acute infarct patients. Normally, new infarcts tend to be asymptomatic, especially several days after an ischemic stroke occurs. In patients with extensive WMLs, the brain is impaired in tolerating the effects of ischemic and loses the capacity to compensate for the loss of brain function. Hence, in patients with extensive WMLs, new infarct may grow into symptomatic infract.[12]

In the current study, 64% of acute stroke ischemic patients were in the small vessel stroke group. This finding is similar to previous studies showing the association of WMLs between with small vessel stroke subtypes. WMLs volume is a marker of higher severity of cerebral small vessel disease.[15] Detached from the weak correlation, this result prove that higher WMLs grade based on Fazekas score correlate with small vessel stroke subtype in acute ischemic stroke patients. This result is in line with the previous study, showing that in acute ischemic stroke patients, the WMLs burden is most severe in patients with a small vessel subtype. Higher WMLs severity, assessed by CT and MRI, is related to the small vessel stroke. Using the semiquantitative Fazekas scale , WMLs grade also correlate with small vessel stroke with more WMLs progression and prediction of new small infarct formation. In addition, using semi-automated volumetric analysis of WMLs severity, WMLs was also found to be correlated with small vessel stroke because it had the highest burden compared to other stroke subtypes.[15] However, the Fazekas scale is a semiquantitative visual rating scale with less accurate WML measurements than quantitative volumetric calculations. The Fazekas scale used is also not divided into periventricular and deep white matter area, which may interfere with the results. Nevertheless, the Fazekas scale is the most recommended visual rating scale as it is the most effective and simple scale to use in general research.[18]

This study also highlighted that patients with small vessel stroke subtypes also had the highest WMLs burden among other acute ischemic stroke subtypes. Hypertension and previous stroke history were correlated independently with a more significant WMLs burden in small vessel stroke patients.[16]

The small sample size in this study limits the study. The scant amount of acute ischemic stroke patients who underwent MRI imaging might be due to the arrival time of ischemic stroke patients, being mostly outside the acute phase. MRI imaging is considered expensive, hence, it is not accessible to all economic groups. Another limitation is the possibility of bias since there was no adjustment of the result for age and gender. Data on other confounding factors were not available in this study due to the lack of data in the medical records, such as NIHSS score, smoking activity, physical activeness, psychosocial stress, and others.

In conclusion, white matter lesions severity correlates with small vessel stroke subtype in acute ischemic stroke patients. The higher the WMLs severity, the more it is related to small vessel stroke subtype. This result may help determine the prognosis and treatment of patients with WMLs in acute ischemic stroke, and require further research to exclude the confounding factors.

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