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Infarct Diameter for Predicting Cognitive Dysfunction in Ischemic Stroke Survivors in West Nusa Tenggara, Indonesia

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Abstract

Cognitive dysfunction is an important consequence of ischemic stroke, which can progress in the first few years and is primarily determined by clinical factors. This study aimed to investigate the clinical determinants of cognitive dysfunction in stroke survivors in West Nusa Tenggara Province, Indonesia. This cross-sectional study assessed 255 ischemic stroke survivors with a mean age of 57.1±9.3 years old and 29–79 years old, recruited consecutively in three main hospitals in West Nusa Tenggara Province between March 2019 and October 2021. Categorical data collected included age, sex, education level, clinical determinants of ischemic stroke, and cognitive status of the patients. The association between the clinical determinants of ischemic stroke and the risk of cognitive dysfunction in patients was analyzed using logistic regression after adjusting for age, sex, and level of education. The final multiple logistic regression analysis models revealed infarct diameter as the only clinical determinant significantly associated with an increased risk of cognitive dysfunction (OR = 3.14; 95% CI = 1.20–8.23). Thus, a larger infarct diameter is the only clinical determinant of cognitive dysfunction in ischemic stroke survivors in West Nusa Tenggara Province, Indonesia.

Keywords: brain ischemia, clinical determinants, cognitive dysfunction, stroke

Introduction

Cognitive dysfunction is an important consequence of ischemic stroke. Cognitive dysfunction can involve several cognitive domains, including attention, memory, language, perceptual-motor function, and executive function.[1] The prevalence of cognitive dysfunction in ischemic stroke survivors varies and can involve up to 80% of the ischemic stroke survivor population.[2] The prevalence is also high in the early phase of stroke (71.9%).[3] The cognitive domains most often affected by stroke are attention, memory, and executive dysfunction.[4] If not appropriately treated, cognitive dysfunction can progress to dementia after the first few years, characterized by the loss of independence of stroke survivors in carrying out their basic functional and social activities of daily living.[5] However, the cognitive decline found in the early stages of ischemic stroke has been shown to reduce the work productivity of survivors.[6] Thus, post-ischemic stroke cognitive dysfunction has the potential to cause economic and social burdens for families as well as financial burdens for local health authorities and the government.

Post-ischemic stroke cognitive dysfunction is primarily assessed by clinical determinants, including stroke characteristics and well-identified co-existing vascular risk factors (smoking, hypertension, dyslipidemia, overweight, diabetes mellitus, and atrial fibrillation).[7] Stroke characteristics, including infarct size, the affected hemisphere, and the location of the lesion in the brain, describe the extent of the brain area with impaired neural connectivity due to ischemic events regarding the involvement of brain areas that are important in conducting cognitive functions.[8,9] Impaired neural connectivity due to ischemic lesions in the left dorsolateral prefrontal cortex, hippocampus, and frontal insula, structures in the brain responsible for executive function, attention, and memory, is a common finding in ischemic stroke.[10] This fact is relevant to the findings of a previous study that indicated that these three cognitive domains are most frequently impaired in stroke.[4] The identification of these stroke characteristics is particularly important in predicting the severity of post-stroke

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cognitive dysfunction and in planning cognitive rehabilitation strategies specific to the impaired domain.[11] However, the availability of an adequate investigation modality to characterize infarct size and location of ischemic lesions, magnetic resonance imaging, is still limited in most health care facilities in West Nusa Tenggara Province. Head computed tomography scan, which is the gold standard examination for diagnosing acute-phase stroke, despite its relatively wide availability, has limitations in characterizing infarct size in the first few days of ischemic stroke onset.[12]

Smoking, hypertension, dyslipidemia, overweight, diabetes mellitus, and atrial fibrillation are well-known vascular risk factors for ischemic stroke and post-ischemic stroke cognitive dysfunction. A previous study showed that these risk factors could independently cause cognitive dysfunction in the absence of stroke.[13] The presence of these vascular risk factors are related to a pathological neurodegenerative process that disrupts neuronal connectivity in the frontal lobe, resulting in impaired executive function and perceptual-motor function.[14,15] Both hypertension and diabetes mellitus are correlated with beta-amyloid deposition and tau protein phosphorylation, which are hallmarks of Alzheimer's dementia in the absence of stroke.[16,17] Thus, the identification and management of vascular risk factors in ischemic stroke survivors theoretically also has the potential to reduce the occurrence of post-ischemic stroke cognitive dysfunction.

This study aimed to investigate the clinical determinants of cognitive dysfunction in stroke survivors in West Nusa Tenggara Province, Indonesia. West Nusa Tenggara is a province in Indonesia with a low human development index, where access to health services and the population's education level are also relatively low.[18] Thus, the results of this study will be essential for the government and health authorities in West Nusa Tenggara and other provinces that have similar characteristics in terms of developing promotive, preventive, curative, and rehabilitative strategies to reduce the frequency of post-ischemic stroke cognitive dysfunction.

Method

This cross-sectional study involved ischemic stroke survivors recruited consecutively in the outpatient neurology departments of two general hospitals and one private hospital in Mataram City, West Nusa Tenggara Province. The study was described by neurologists to the patients and their caregivers when they visited the outpatient neurology department at one of the three hospitals where the study was conducted. The study was conducted between March 2019 and October 2021. Due to the coronavirus 2019 (COVID-19) global pandemic situation, this study was temporarily suspended between

$$n = \frac{Z\alpha^2(pq)}{d^2}$$

Formula 1. Sample Size Estimation

April 2020 and February 2021 and continued until September 2021 by implementing a protocol to prevent the transmission of COVID-19. Using Formula 1, where n is sample size, proportion (p) = 20%, q = 1-p, α = 0.05, $Z\alpha$ = 1.96, and margin of error (d) = 0.05, the minimum sample size required in this study was 255.

The inclusion criteria were patients clinically diagnosed with ischemic stroke by a neurologist with or without a head CT scan, aged 18–80 years, and fully conscious. Since a head CT scan is required in the acute-phase ischemic stroke to exclude the presence of a cerebral hematoma, while the cost is relatively expensive, it was not performed for outpatients with clinical symptoms suggestive of an ischemic stroke beyond the acute phase. The exclusion criteria included uncorrected visual and hearing impairments, illiteracy, and a history of diagnosis of dementia and psychiatric disorders before the ischemic stroke.

Categorical data collected in this study were age, sex, education level, and clinical determinants for ischemic stroke, including infarct diameter, hemiparetic side, duration of illness, smoking status, hypertension, dyslipidemia, overweight, diabetes mellitus, atrial fibrillation, and cognitive status of the patients. These data were obtained through interviews with patients and their families, neuropsychological examinations, and medical records. The age of the patients was continuously expressed in years and further categorized into four age groups: less than 40 years, 40–59 years, 60–69 years, and 70–80 years. Sex was categorized as male or female, while the educational level was categorized as elementary school, higher, and college education. Infarct diameter was continuous data expressed in millimeters (mm) and then categorized into small (≤15 mm) and large (more than 15 mm) based on the results of the head CT scan by a radiologist.[19]

The hemiparetic side of the patients was categorized into right and left sides. The duration of illness was expressed in months and then categorized into early-onset (≤3 months from stroke onset) and chronic (more than three months from stroke onset). Regarding smoking status, the patients were categorized into smokers and non-smokers. Overweight was defined as a patient's body mass index (BMI) indicating more than 25 kg/m^2. Dyslipidemia was defined as fasting serum total cholesterol of 240 mg/dL.[20] Hypertension was defined as blood pressure 140/90 mmHg and/or patients taking antihypertensive drugs. In contrast, diabetes mellitus was

defined as fasting blood glucose levels of 126 mg/dL and/or patients taking antidiabetic drugs, as described in previous studies.[3] The presence of atrial fibrillation was determined based on the results of the 12-lead electrocardiography (ECG) examination of the patients reviewed by a cardiologist.

The cognitive status of the participants was assessed using the Indonesian version of the Montreal Cognitive Assessment (MoCA-Ina), a neuropsychological test instrument for evaluating cognitive function that has been validated for the Indonesian population.[21] This instrument has a maximum score of 30. By using a cut-off value of 26 for the standard score, cognitive status was categorized into normal (MoCA-Ina score $\geq$ 26) and dysfunctional (MoCA-Ina score less than 26). An additional score of 1 was assigned to participants with elementary- and highschool-level education as a correction factor for the effect of education level on their performance in the neuropsychological test.

The first analysis was conducted to investigate the sociodemographic characteristics and cognitive status of the participants. At this stage, continuous age data were presented as means and standard deviations. In contrast, data on the categorical variables of age, sex, education level, and cognitive status of the patients were presented as proportions. The second analysis examined the relationship between each clinical determinant of ischemic stroke and the frequency of cognitive dysfunction in ischemic stroke survivors. At this stage, the association between categorical data of infarct diameter, hemiparetic side, duration of illness, smoking status, hypertension, dyslipidemia, overweight, diabetes mellitus, atrial fibrillation, and the frequency of cognitive dysfunction in stroke survivors was analyzed using simple binary logistic regression and crude odds ratio (OR) with 95% confidence interval (CI). In the third analysis, each clinical determinant showing a p-value<0.25 in the second analysis was assigned to the final model of multiple logistic regression analysis to examine its association with the frequency of cognitive dysfunction in stroke survivors after adjustment for age, sex, and education level and the results were reported as adjusted OR with 95% CI.

Results

During the study, 314 patients were identified as having an ischemic stroke. Of these, 59 did not meet the inclusion criteria. Thus, 255 ischemic stroke patients were involved in this study, with a mean age of 57.1$\pm$9.3 years and between 29–79 years. Of the 255 patients, 197 underwent a head CT scan to confirm the diagnosis of ischemic stroke, while 58 did not undergo a head CT scan because their ischemic stroke was beyond the acute phase when they were recruited. Table 1 shows the sociodemographic characteristics and cognitive status of the subjects. This study showed that the proportion of subjects with post-stroke cognitive dysfunction was high (79.6%). Sociodemographically, most patients were in the productive age group, male, and with a high school education level.

Table 2 shows the results of a simple binary logistic regression analysis that examined the relationship between clinical variables and frequency of cognitive dysfunction in ischemic stroke survivors. The analysis showed that infarct diameter (OR = 3.42; 95% CI = 1.33–8.78), hypertension (OR = 2.02; 95% CI = 0.96–2.43), and atrial fibrillation (OR = 4.24; 95% CI = 0.94–19.15) were eligible clinical variables to be assigned in the final model of multiple logistic regression analysis (p-value<0.25). Although of the three variables, infarct diameter was the only variable that exhibited a significant relationship. Hypertension and atrial fibrillation also modulated the increased risk of cognitive dysfunction in the patients.

Table 3 shows the results of the final multiple logistic regression analysis models that examined the relationship between eligible clinical variables in simple binary logistic regression analysis and the frequency of cognitive dysfunction in ischemic stroke survivors after adjustment for age, sex, and education level. The analysis showed that infarct diameter was the only clinical determinant that was significantly associated with an increased risk of cognitive dysfunction in ischemic stroke survivors (OR = 3.14; 95% CI = 1.20–8.23). Consistent with the simple logistic regression analysis results, subjects with larger infarct diameters had a higher risk of developing cognitive dysfunction after ischemic stroke.

Discussion

This study aimed to investigate the clinical determinants of cognitive dysfunction in ischemic stroke survivors in West Nusa Tenggara, a province in Indonesia with a low human development index. This study revealed that a larger infarct diameter was the major deter-

Table 1. Subjects Characteristics (n = 255)

Variable	Category	n (%)
Age (Mean±SD)		57.1±9.3
Age group	<40 years	6 (2.4)
	40–59 years	144 (56.5)
	60–69 years	82 (32.2)
	≥70 years	23 (9.0)
Sex	Male	178 (69.8)
	Female	77 (30.2)
Education level	College	78 (30.6)
	High school	102 (40.0)
	Elementary school	75 (29.4)
Cognitive impairment	Cognitive impaired	203 (79.6)
	Cognitive intact	52 (20.4)

Note: SD = Standard Deviation

Table 2. Simple Binary Logistic Regression Showing Variables Associated with Cognitive Dysfunction in the Subjects

Clinical Variable	n	Category	Cognitive Status n (%)		Crude OR (95% CI)	p-value
			Cognitive Intact	Cognitive Impaired		
Infarct diameter	197	Small	37 (26.2)	104 (73.8)	3.42 (1.33–8.78)	0.010*
		Larger	6 (10.7)	50 (89.3)	Reference	
Hemiparetic side	255	Right	29 (21.8)	104 (78.2)	1.18 (0.62–2.25)	0.607
		Left	23 (18.9)	99 (81.1)	Reference	
Duration of illness	255	Early-onset	29 (23.2)	96 (76.8)	1.23 (0.65–2.33)	0.524
		Chronic	23 (17.7)	107 (82.3)	Reference	
Smoking status	255	Smokers	17 (19.5)	70 (80.5)	0.77 (0.36–1.64)	0.505
		Non-smokers	35 (20.8)	133 (79.2)	Reference	
Hypertension	255	Yes	37 (17.8)	171 (82.2)	2.02 (0.96–2.43)	0.064*
		No	15 (31.9)	32 (68.1)	Reference	
Dyslipidemia	255	Yes	27 (19.7)	110 (80.3)	1.17 (0.61–2.25)	0.635
		No	25 (21.2)	93 (78.8)	Reference	
Overweight	255	Yes	19 (17.8)	88 (82.2)	1.27 (0.66–2.42)	0.472
		No	33 (22.3)	115(77.7)	Reference	
Diabetes mellitus	255	Yes	14 (19.7)	57 (80.3)	1.00 (0.49–2.07)	0.983
		No	38 (20.7)	146 (79.3)	Reference	
Atrial fibrillation	255	Yes	2 (7.7)	24 (92.3)	4.24 (0.94–19.15)	0.061*
		No	50 (21.8)	179 (78.2)	Reference	

Notes: *eligible for final model of multiple logistic regression analysis, OR = Odds Ratio, CI = Confidence Interval

Table 3. Final Model Logistic Regression Analysis Showing Variables Associated with Cognitive Dysfunction in the Subjects after Adjustment for Age, Sex, and Education Level

Clinical Variable	n	Category	Cognitive Status n (%)		Adjusted OR (95% CI)	p-value
			Cognitive Intact	Cognitive Impaired		
Infarct diameter	197	Small	37 (26.2)	104 (73.8)	3.14 (1.20–8.23)	0.020*
		Larger	6 (10.7)	50 (89.3)	Reference	
Hypertension	255	Yes	37 (17.8)	171 (82.2)	1.43 (0.51–4.01)	0.501
		No	15 (31.9)	32 (68.1)	Reference	
Atrial fibrillation	255	Yes	2 (7.7)	24 (92.3)	7.76 (0.96–62.59)	0.054
		No	50 (21.8)	179 (78.2)	Reference	

Notes: *significant association (p-value<0.05), OR = Odds Ratio, CI = Confidence Interval

minant of cognitive dysfunction after ischemic stroke in the patients studied. This result conformed to a study on ischemic stroke patients in Yogyakarta, an urban area in Indonesia with a high human development index.[22] The large infarct diameter represents the severity of both the pathological process in the brain and the disruption of its neuronal connectivity. Thus, large infarct size in the brain region responsible for the conduction of cognitive function will result in dysfunction in these cognitive domains.[23] This finding emphasized the importance of head CT examination in early-phase stroke, not only to determine the appropriate initial treatment for ischemic stroke but also to predict the vulnerability of ischemic stroke patients to suffer from cognitive dysfunction by characterizing the infarct diameter based on this examination. Since a head CT scan was not performed in 58 patients because their stroke was beyond the acute phase, this fact implied the magnitude of the challenge for health authorities in the province of West Nusa Tenggara Province in the management of stroke and cognitive dysfunction after ischemic stroke. Since all patients in this study were members of the National Health Insurance (NHI) and head CT scans were also covered by this insurance, the absence of head CT scans in some patients might be due to the low level of knowledge of the patients and lack of access to adequate healthcare facilities for head CT scans. In general, the problems described above are common in populations living in areas with a low human development index characterized by the low level of education of the population and their lack of access to available healthcare facilities.[24]

This study also demonstrated that the proportion of ischemic stroke survivors with cognitive dysfunction was high (79.6 %). A previous study investigating the prevalence of post-stroke cognitive dysfunction in the subacute phase showed similar results.[3] In general, the prevalence

of post-stroke cognitive dysfunction is in the range of 20–80 %, and this variation is highly dependent on the population studied and the diagnostic criteria used.[2] The high proportion of post-ischemic stroke cognitive dysfunction and the proportion of male stroke survivors of productive age shown in this study indicated a high potential for public health problems that could be caused by post-stroke cognitive dysfunction in the future. Considering that condition, cognitive dysfunction that is not appropriately managed in the early phase of stroke in 30% of cases progresses to dementia and this condition will result in a loss of work productivity for survivors. The problem of post-ischemic stroke cognitive dysfunction has the potential to add to the socioeconomic burden of the family.[5] Moreover, since the prevalence and incidence of stroke in Indonesia are quite high and most ischemic stroke patients are highly dependent on the National Health Insurance provided by the government, the problem of cognitive dysfunction as a complication of ischemic stroke also has the potential to increase the burden of financing treatment by the government.[25] Thus, local health authorities must educate the public, especially those at high risk, about the importance of stroke prevention, recognize the signs and symptoms of stroke, and disseminate information about adequate health facilities for stroke treatment. Furthermore, the adequacy of the availability of cognitive rehabilitation facilities for stroke patients needs to be considered by both local health authorities and healthcare providers.

The results of this study also indicated that neither the hemiparetic side representing contralateral cerebral hemisphere involvement nor the duration of illness was associated with an increased proportion of stroke survivors with cognitive dysfunction. These results were consistent with the following previous studies. Regarding cerebral hemisphere involvement, Dacosta-Aguayo, *et al.*,[26] demonstrated that an ischemic lesion in one hemisphere leads to impaired functional integrity in the contralateral hemisphere. Regarding the duration of illness, Douiri, *et al.*,[27] showed that the prevalence of post-stroke cognitive dysfunction in both the early and chronic phases of the stroke was similar. The clinical significance of these findings was that cognitive function should be evaluated in every ischemic stroke patient, regardless of the hemisphere involved. These findings were also clinically significant in that the cognitive dysfunction found in ischemic stroke survivors, if not treated adequately, will tend to be relatively stable until the duration of illness enters the chronic phase, which is certainly related to a poor prognosis for these stroke survivors.[28] Thus, early identification and management of cognitive dysfunction in stroke survivors is an important part of the curative and rehabilitative strategy for post-stroke cognitive dysfunction. Local health authorities should develop such strategy to enable patients to obtain optimal clinical outcomes.

The study also revealed that well-identified vascular risk factors for ischemic stroke, including smoking, hypertension, dyslipidemia, overweight, diabetes mellitus, and atrial fibrillation, were not significantly associated with an increased risk of cognitive dysfunction in ischemic stroke survivors. However, hypertension and atrial fibrillation appeared to modulate the risk of cognitive dysfunction in stroke survivors, and an insignificant association between these two vascular risk factors. Previous studies have shown mixed results regarding the association between these vascular risk factors and the frequency of cognitive dysfunction associated with ischemic stroke.[4,29] Theoretically, these risk factors can cause post-stroke cognitive dysfunction, both independently and through their interactions with each other.[30] Given that vascular risk factors, including smoking, hypertension, dyslipidemia, overweight, diabetes mellitus, and atrial fibrillation, generally exist long before the occurrence of stroke. The early identification and adequate management of these vascular risk factors are essential as part of a strategy to prevent ischemic stroke and post-stroke cognitive dysfunction. Moreover, the identification of these vascular risk factors is generally possible in almost all existing healthcare facilities. In this regard, the role of healthcare workers in primary health care (PHC) facilities in supporting appropriate education, detection, and management strategies for these vascular risk factors also needs to be optimized by local health authorities.

The results of this study are important to add to previous studies related to the clinical determinants of cognitive dysfunction in patients with ischemic stroke. Furthermore, the results of this study can be used as a basis for developing promotive, preventive, curative, and rehabilitative strategies for cognitive dysfunction after ischemic stroke in the population of stroke survivors in West Nusa Tenggara and other provinces in Indonesia with similar characteristics. However, this study had some limitations. First, the timing of the head CT scans of the patients varied significantly. Given that ischemic lesions can evolve at any time in the first few weeks after stroke onset, this variation in the timing of the CT scan of the head may affect the accuracy of measuring the diameter of the brain infarct. Second, given that this study used a cross-sectional design and the study patients did not have data on their cognitive status before the stroke, it was impossible to determine precisely whether current cognitive dysfunction was a pre-existing condition or a direct impact of stroke. Information related to the history of cognitive dysfunction before stroke obtained in this study was based only on the patients' caregivers' information and was generally subjective. A longitudinal study is recommended for investigating the impact of the clin-

ical determinants identified in this study on the progression of cognitive dysfunction in ischemic stroke survivors.

Conclusion

This study revealed the infarct diameter as the only significant determinant of cognitive dysfunction in ischemic stroke survivors in West Nusa Tenggara Province, Indonesia. A larger infarct diameter is associated with an increased risk of cognitive dysfunction in ischemic stroke survivors. These results add to previously reported data related to the clinical determinants of cognitive dysfunction in the ischemic stroke patient population in Indonesia and other developing countries. These results can also be considered a basis for developing promotive, preventive, curative, and rehabilitative strategies for cognitive dysfunction after ischemic stroke in a population of stroke survivors in West Nusa Tenggara and other provinces in Indonesia with similar characteristics.

Abbreviations

COVID-19: coronavirus disease 2019; CT: Computed Tomography; BMI: Body Mass Index; ECG: Electroencephalography; MoCA-Ina: Indonesia version of Montreal Cognitive Assessment; OR: Odds Ratio; CI: Confidence Interval; NHI: National Health Insurance; PHC: Primary Health Care.

Ethics Approval and Consent to Participate

This study was conducted after obtaining ethical approval from the Ethics Committee for Health Research of the University of Mataram (registration number: 401/UN/18.F7/ETIK/2018). Each participant provided written informed consent before participation.

Competing Interest

The authors declare that there are no significant competing financial, professional, or personal interests that might have affected the performance.

Availability of Data and Materials

Data and materials of this study are available from the corresponding author for reasonable request and non-commercial purposes.

Authors' Contribution

HSH conceptualized and designed the study. HSH, SAP, YI, HA, and FIM analyzed and interpreted the study results. HSH drafted the manuscript. HSH, SAP, YI, HA, and FIM revised the manuscript.

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