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Multilevel Analysis of Prognostic Factors for Cognitive Function in Post-Stroke Patients

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ABSTRACT

Background: Stroke is the leading cause of disability and the second leading cause of death worldwide. Post-stroke disability can be in the form of motor, sensory, autonomic, or cognitive impairments. Impaired cognitive function is the leading cause of death and pain in post-stroke patients in the world. Decreased cognitive function is present in more than 70% of post-stroke patients and is associated with disability, independence, and pain. This study aims to analyze the prognosis factors of cognitive function in post-stroke patients.

Subjects and Method: This study used a cross-sectional design conducted in 7 hospitals on the island of Lombok from July to August 2024. A total of 200 post-stroke patients were selected using *stratified random sampling*. The dependent variable in this study was cognitive function examined using the Mini Mental State Examinatio (MMSE) questionnaire. Other independent variables such as age, gender, marital status, pension fund, complications, comorbidities and stroke type were collected using a questionnaire. The data were analyzed using a multilevel double-linear regression model.

Results: The prognosis factor of cognitive function in post-stroke patients was age (b=-0.19; CI 95%=-0.29 to -0.10; p=<0.001), marital status (b=-3.80; CI 95%=-6.72 to -0.88; p=0.011), pension fund (b=-5.88; CI 95%= -8.35 to -3.42; p=<0.001), complications (b=-5.37; CI 95%= -7.34 to -3.39; p=<0.001). While sex, comorbidities, and stroke type did not show a significant relationship with the cognitive function of post-stroke patients. Conversely, there was an influence of doctors treating post-stroke patients on cognitive function (ICC=8.76%).

Conclusion: Age, marital status, pension funds, and complications are prognostic factors in cognitive function of post-stroke patients. Conversely, there is an influence of doctors who treat post-stroke patients on cognitive function.

Keywords: prognosis factors, multilevel analysis, cognitive function, post-stroke patients

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BACKGROUND

Stroke is the leading cause of disability worldwide and the second leading cause of death (Rost et al., 2022). In 2022, the risk of having a stroke has increased by 50% over the past 17 years and now 1 in 4 people are estimated to have a stroke in their lifetime. From 1990 to 2019, there was an increase in stroke incidence by 70%, an increase in stroke mortality by 43%, an increase in stroke prevalence by 102%, and an increase in stroke incidence by 102%. Disability Adjusted Life Years (DALY) by 143% (World Health Organization (WHO), 2022).

Stroke is also the leading cause of death and disability in Indonesia. Compared to countries in Southeast Asia, Indonesia has the highest death rate of 193.3 per 100,000 population and the DALY rate of 3,382.2 per 100,000 population (Venketasubramanian et al., 2022). From the Indonesian Health Survey (SKI) data (2023), the prevalence of stroke in Indonesia is 8.3‰ or around 638,178 people.

Post-stroke disability can be in the form of motor, sensory, autonomic or cognitive disorders (Abdu et al., 2022; Hafdia et al., 2018; Malik & Maulina, 2019). Post-stroke cognitive impairment is all cognitive function problems that occur after the event of a stroke. It can occur immediately after a stroke or late (3-6 months after the stroke event). Impaired cognitive function is the leading cause of death and pain in post-stroke patients in the world. Decreased cognitive function is present in more than 70% of post-stroke patients and is associated with disability, independence and pain (Malik & Maulina, 2019; Rost et al., 2022).

The factors that affect the cognition of post-stroke patients are gender, age, education level, hypertension and diabetes mellitus (Boletimi et al., 2021). Study conducted by Ramadhani et al. (2020) It was found that there was a relationship between age and length of education and cognitive impairment of post-stroke patients while there was no relationship between gender and cognitive impairment. Studies conducted by Chaurasia et al. (2019) only found hypertension and diabetes mellitus as factors influencing cognitive impairment in post-stroke patients (Abdu et al., 2022; Hafdia et al., 2018; Malik & Maulina, 2019). Therefore, this study aims to analyze the prognosis factors of cognitive function in post-stroke patients and explore the contextual influence of neurologists on the cognitive function of post-stroke patients.

SUBJECTS AND METHOD

1. Study design

A cross sectional study was conducted in 7 hospitals on the island of Lombok from July to August 2024.

2. Population and sample

The study population consisted of post-stroke patients who were treated in outpatient polyclinics in 7 hospitals on the island of Lombok. A total of 200 respondents were selected using stratified random sampling spread across 7 hospitals. Respondents were taken 14-15 from each neurologist.

3. Study variables

The dependent variable is cognitive function. The independent variables were age, gender, marital status, pension fund, complications, comorbidities and stroke type. In addition, neurologists are also included as contextual variables

4. Operational definition of variables

Cognitive function: a thought process i.e. the ability of the individual to relate and assess and consider an event assessed by the MMSE

Age: number of years the study subject was born.

Gender: the biological classification of a person based on the physical and genetic characteristics he or she has.
Marital status: a person's circumstances related to marriage
Pension Fund: income received by pensioners every month as a guarantee of old age and appreciation for the employee's services over the years of service.
Complications: health problems or conditions that arise as a result of stroke disease.
Comorbidities: suffering from one of the comorbidities before experiencing a stroke such as hypertension, diabetes mellitus, and heart rhythm disorders
Stroke Type: Classification of stroke based on the cause and mechanism of impaired blood flow to the brain.
Neurologist: education by doctors specializing in the diagnosis and treatment of nervous system disorders (strokes)

5. Study instruments

The study instrument used for data collection is using a questionnaire. Cognitive function variables were measured using the Mini-Mental State Examination (MMSE) questionnaire. The independent variables, namely age, gender, marital status, pension fund, complications, comorbidities, and stroke type, were taken using a questionnaire.

6. Data analysis

Univariate analysis described the characteristics of study variables such as age, education, occupation, gender, marital status, pension fund, complications, comorbidities, and stroke type in frequency and percentage. Bivariate analysis was carried out to see the relationship between independent variables (age, gender, marital status, pension fund, complications, comorbidities and stroke type) and cognitive function using the Chi-Square test at a confidence level of 95% (CI 95%).

The multivariate analysis used multilevel double linear regression performed at two levels: individual (age, gender, marital status, pension fund, complications, comorbidities and stroke type) and contextual (neurologist). Intraclass Correlation Coefficient (ICC) is used to measure the contribution of individual and contextual variables to cognitive function. This analysis was processed using Stata 13.

7. Study ethics

Study ethics include informed consent, anonymity, and confidence. Handled with care during the study process. The author has received a letter of ethical eligibility from the Study Ethics Commission of the Faculty of Medicine, Al-Azhar Islamic University on June 10, 2024 with the number 038/EC-03/FK-06/UNI-ZAR/VI/-2024.

RESULTS

This study was carried out from July to August 2024 on 200 post-stroke patients treated by 14 neurologists spread across 7 hospitals on the island of Lombok.

1. Sample characteristics

Table 1 shows that post-stroke patients have an average age of 59.89 (mean 59.89, SD 11.30) and an average MMSE score of 18.34 (mean 18.34, SD 8.37). Table 2 shows 200 post-stroke patients, from the education level of 23 bachelors (11.5%), 2 diplomas (1%), 60 high school equivalents (30%), 19 junior high school equivalents (9.5%), 57 elementary schools (28.5%), and not schooling/not completing elementary school as many as 39 (19.5%). In terms of education, 24 are pensioners (12%), 13 Civil Servants (6.5%), 40 farmers (20%), 61 self-employed (30.5%), and 62 are not working (31%). A total of 123 study subjects were male (61.5%), 77 female (38.5%), 169 married (84.5%), 31 unmarried/ widowed/ widowed (15.5%). Of the 200 study

subjects, 44 had a pension fund (22%), 156 did not have a pension fund (78%), 98 had complications due to stroke (49%), 102 had no complications (51%), 175 had comorbidities (87.5%), 25 had no comorbidities (12.5%), 34 had hemorrhage type (17%) and 166 had ischemic type (83%).

Table 1. Categorical characteristics of post-stroke patients in hospitals on Lombok Island (N=200)

Variable	Mean	SD	Min.	Max.
Age (years)	59.89	11.30	14	85
MMSE	18.34	8.37	0	30

Table 2. Characteristics of post-stroke patients in hospitals in Lombok Island Categorical Data (N=200)

Variable	Frequency (N)	Percentage (%)
Education		
Bachelor	23	11.5
Diploma	2	1
High school equivalent	60	30
Junior high school equivalent	19	9.5
Elementary school	57	28.5
Not in school/not graduating from elementary school	39	19.5
Work		
Pension	24	12
ANS	13	6.5
Farmer	40	20
Self employed	61	30.5
Not working/not working	62	31
Gender		
Man	123	61.5
Woman	77	38.5
Marital status		
Marry	169	84.5
Unmarried/Widowed/Widowed	31	15.5
Pension Fund		
Exist	44	22
None	156	78
Complications		
None	102	51
Exist	98	49
Comorbid		
None	25	12.5
Yes	175	87.5
Stroke type		
Bleeding	34	17
Ischemic	166	83

2. Bivariate Analysis

Table 3 shows that there is a negative relationship between comorbidities and cognitive function of post-stroke patients, but it is not statistically significant. Post-stroke patients who have comorbidities will experience a decrease in MMSE score of 3.26 (b= -3.26; CI 95%= -6.77 to 0.24;

p=0.068). Likewise, a negative relationship between stroke type and cognitive function was obtained, but it was not statistically significant. Post-stroke patients who suffer from hemorrhagic stroke will experience a decrease in MMSE scores of 0.27 (b= 0.27; CI 95%= -2.84 to 3.38; p=0.863).

Table 3 shows that there is a negative relationship between age and cognitive function of post-stroke patients and the relationship is statistically signi-ficant. Each increase in age of 1 year will be followed by a decrease in MMSE score by 0.15 times (b= -0.15; CI 95%= -0.26 to -0.05; p=0.003). Female post-stroke patients will experience a decrease in MMSI score of 2.56 (b= -2.56; CI 95%= -4.94 to -0.18; p=0.035).

Data analysis showed that there was a negative relationship between marital status and cognitive function of post-stroke patients and the relationship was statistically significant. Post-stroke patients who do not have a partner will experience a decrease in MMSE scores by 5.10 times (b= -5.10; CI 95%= -8.25 to -1.94; p=0.002). Data analysis also showed that there was a negative relationship between pension funds and cognitive function of post-stroke patients and the relationship was statistically significant. Post-stroke patients who do not have a pension fund will experience a decrease in MMSE score of 6.46 times (b= -6.46; CI 95%= -9.13 to -3.78; p=<0.001).

Table 3 shows that there is a negative relationship between complications and cognitive function of post-stroke patients and the relationship is statistically significant. Post-stroke patients who had complications experienced a decrease in cognitive function by 5.97 times (b= -5.97; CI 95%= -8.16 to -3.79; p=<0.001).

Table 3. Bivariate analysis of age, sex, marital status, pension funds, complications, comorbidities and stroke type on the cognitive function of post-stroke patients

Independent variables	b	CI 95%		p
		Lower limit	Upper limit	
Age (years)	-0.15	-0.26	-0.05	0.003
Gender (female)	-2.56	-4.94	-0.18	0.035
Not married	-5.10	-8.25	-1.94	0.002
No pension fund	-6.46	-9.13	-3.78	<0.001
There are complications	-5.97	-8.16	-3.79	<0.001
There are comorbidities	-3.26	-6.77	0.24	0.068
Non-hemorrhagic stroke	0.27	-2.84	3.38	0.863

3. Multivariate Analysis

Table 4 shows the results of multilevel multiple linear regression analysis of prognostic factors of cognitive function in post-stroke patients in hospitals on Lombok Island. Data analysis showed that there was a negative relationship between age and cognitive function of post-stroke patients and the relationship was statistically significant. Each 1-year increase in the age of post-stroke patients will be followed by a decrease in MMSE score of 0.19 (b= -0.19; CI 95%= -0.29 to -0.10; p <0.001).

There was a negative relationship between sex and cognitive function in post-stroke patients, but it was not statistically significant. Female post-stroke patients experienced a decrease in MMSE scores of 1.46 (b= -1.46; CI 95%= -3.68 to 0.75; p= 0.195). Data analysis also showed that there was a negative relationship between marital status and cognitive function of post-stroke

patients and the relationship was statistically significant. Post-stroke patients who do not have a partner will experience a decrease in MMSE scores by 3.80 times (b= -3.80; CI 95%= -6.72 to -0.88; p=0.011).

Data analysis showed that there was a negative relationship between pension funds and cognitive function of post-stroke patients and the relationship was statistically significant. Post-stroke patients who do not have pension funds will experience a decrease in MMSE scores of 5.88 times (b= -5.88; CI 95%= -8.35 to -3.42; p=<0.001). There was a negative association between complications and cognitive function in post-stroke patients and the association was statistically significant. Post-stroke patients who have complications will experience a decrease in MMSE by 5.37 times (b= -5.37; CI 95%= -7.34 to -3.39; p<0.001).

There was a negative relationship between comorbidities and cognitive function of post-stroke patients, but it was not statistically significant. Post-stroke patients who have comorbidities will experience a decrease in MMSE score of 2.19 (b= -2.19; CI 95%= -5.33 to 0.94; p=0.169). There was a negative relationship between stroke type and cognitive function, but it was not statistically significant. Post-stroke patients who suffer from hemor-rhagic stroke will experience a decrease in MMSE score of 0.29 (b= 0.29; CI 95%= -2.34 to 2.93; p=0.824). The results of this multilevel linear regression analysis showed that there was a contextual influence of doctors treating post-stroke patients on cognitive function (ICC=8.76%).

Table 4 Multilevel double linear regression analysis of cognitive function prognosis factors in post-stroke patients

Independent variables	b	CI 95%		p
		Lower limit	Upper limit	
Fixed Effect				
Age (years)	-0.19	-0.29	-0.10	<0.001
Gender (female)	-1.46	-3.68	0.75	0.195
Not married	-3.80	-6.72	-0.88	0.011
No pension fund	-5.88	-8.35	-3.42	<0.001
There are complications	-5.37	-7.34	-3.39	<0.001
There are comorbidities	-2.19	-5.33	0.94	0.169
Non-hemorrhagic stroke	0.29	-2.34	2.93	0.824
Random effect				
Treating specialist doctors				
Var (constanta)	4.72			
Var (residual)	47.08			
N observation 200				
Log likelihood = -668.98				
LR test vs. linear regression, p=1.000				
Inter Class Corelation (ICC)=8.76%				

DISCUSSION

a. Effect of age on cognitive function

Age is the main risk factor for stroke, as we age there is a decrease in vascular elasticity and an increase in the prevalence of vascular diseases such as hypertension and atherosclerosis (Srilestari, 2022). Study by Dichgans (2019) states that about 30-40% of stroke patients experience signi-ficant cognitive impairment within 6 months of stroke, with advanced age as an important predictor of this cognitive decline.

Age is also a determining factor in the outcome of cognitive recovery in post-

stroke patients. Older patients have a higher risk of developing more severe cognitive impairment, slower recovery, and a greater risk of vascular dementia. Due to decreased neuroplasticity and increased susceptibility to vascular brain damage (Dichgans, 2019).

The analysis in this study showed that every 1-year increase in the age of post-stroke patients would be followed by a decrease in MMSE score of 0.19. In line with the study of Filler et al. (2024) who found that increasing age every year will increase cognitive function impairment in post-stroke patients. Kaddumukasa et al. (2023), stating that increasing age increases the risk of cognitive dysfunction in post-stroke patients (OR=1.04; 95%CI= 1.00 to 1.07; p=0.026). Likewise with the study of Huang et al. (2023) The prevalence of cognitive dysfunction was found in post-stroke patients aged >60 years (40.73%), and statistically significant in patients aged 70-79 years (OR=3,973; 95%CI=2,346 to 6,729; p <0.001).

b. Effect of gender on cognitive function

Epidemiologically, women tend to experience more severe strokes and higher mortality rates than men (Phan et al., 2019). One of them is caused by the hormone estrogen, which is thought to have a protective effect on the brain, before menopause. After menopause, estrogen levels decrease, women become more susceptible to post-stroke cognitive impairment. Study by Lisabeth et al. (2009) showed that postmenopausal women had a higher risk of cognitive decline after stroke compared to premenopausal women and men.

Structural differences in the brains of men and women are also mentioned to be one of the factors that affect the relationship between sex and cognitive function after stroke. Men tend to have more white tissue (White Matter) that plays a role in information processing while women have more gray networks (gray matter), which plays a role in deeper cognitive function, but is more susceptible to stroke damage (Gall et al., 2012).

The analysis in this study did not find a difference between female and male post-stroke patients with the incidence of cognitive decline. This result is in line with the study conducted by Ramadhani and Hutagalung (2020), no sex relationship with cognitive function impairment in post-stroke patients with a value of p=0.673.

In contrast to the study conducted by Kaddumukasa et al. (2023), more female stroke patients experienced a decline in cognitive function. Likewise with the study conducted by Utami et al. (2024), stating that female post-stroke patients are 1.28 times more likely to develop cognitive impairment than male counterparts (aOR= 1.28; 95% CI=1.16 to 1.42; p<0.001). Women tend to experience more severe cognitive decline and slower recovery than men. A study by Merriman et al. (2019) It examined stroke outcomes in more than 2,000 patients and found that women tended to have greater difficulties in cognitive recovery related to memory, attention, and executive function than men.

c. Effect of marital status on cognitive function

Marital status has a significant influence on the cognitive function of post-stroke patients. Married patients tend to have better cognitive recovery outcomes, largely due to social and emotional support from their partner. In contrast, patients who are single, divorced, or widowed/widowed are more prone to more severe cognitive decline, especially due to social isolation and stress (Dupre & Lopes, 2016).

In this study, post-stroke patients who do not have a partner will experience a decrease in MMSE scores of 3.80. In line with Dupre and Lopes' study (2016) who found that someone who is not married or who has become a widower is more at risk of dying from a stroke. In contrast to the study conducted by Kaddumukasa et al. (2023), there was no difference in marital status on the incidence of cognitive decline (p=0.285).

d. Effect of pension funds on cognitive function

Stroke not only affects people affected by stroke but also their families, especially economic problems. If the person affected by the stroke is the backbone of the family, the family's source of income can be reduced to non-existent. Meanwhile, if a family member suffers from a stroke, the additional expenses will increase the family's economic burden (Akhvlediani et al., 2022). With a sufficient economy, it can reduce the economic burden on families, improve the quality of rehabilitation, and get better health services so that it can affect the cognitive recovery outcomes of post-stroke patients. Pension funds are one of the economic aspects (Kamel et al., 2017).

Data analysis in this study showed that there was a negative relationship between pension funds and cognitive function of post-stroke patients and the relationship was statistically significant. Post-stroke patients who do not have pension funds will experience a decrease in MMSE score of 5.88. Study of Tian et al. (2024) stated that a person with low socioeconomic status is at higher risk of developing cognitive function impairment after stroke (OR=2.09, 95%CI=1.57 to 2.78).

e. Effect of complications on cognitive function

Stroke can cause a variety of complications, these complications have a significant influence on cognitive function. Stroke itself can cause direct damage to brain tissue, but the various complications that arise after a stroke can also worsen cognitive impairment. Complications such as infections, seizures, depression, and advanced vascular diseases often contribute to poorer recovery, both physically and cognitively. Infections and seizures can cause additional brain damage, while depression and vascular comorbidities worsen cognitive recovery and increase the risk of dementia (Chohan et al., 2019).

The analysis in this study showed that there was a negative association between complications and cognitive function of post-stroke patients and that the relationship was statistically significant. Post-stroke patients who have complications will experience a decrease in MMSE score of 5.37. One complication of stroke is seizures, van Tuijl et al's study. (2020) reported that patients with post-stroke epilepsy had low MMSE scores. It can be concluded that stroke complications in the form of seizures are related to cognitive impairment in post-stroke patients.

f. Effect of comorbidities on cognitive function

Comorbidities or the presence of other medical conditions that accompany stroke, such as diabetes, hypertension, and heart disease, have a significant impact on the cognitive function of post-stroke patients. Hypertension is one of the most common comorbidities found in stroke patients, and has been shown to have a significant impact on cognitive function after stroke. Chronic hypertension damages the blood vessels of the brain, leading to impaired blood supply and accelerating a decline in cognitive

function (Filler et al., 2024). Study by Iadecola et al. (2016) showed that patients with hypertension were more likely to experience more extensive microbrain damage after stroke, which contributed to cognitive impairment, especially in terms of memory and information processing speed.

Diabetes is also a comorbidity that is often found in stroke patients, and is closely related to cognitive decline. Diabetes can accelerate damage to the brain's blood vessels, causing microcirculation disorders that restrict blood flow to vital brain tissue. Chronic hyperglycemia caused by diabetes causes oxidative stress and inflammation in the brain, which can exacerbate the damage caused by stroke (Mosenzon et al., 2023). In addition, heart disease, especially atrial fibrillation and heart failure, also contributes to cognitive impairment in post-stroke patients. Heart disease can cause embolisms or blockages in the blood vessels of the brain that increase the risk of recurrent strokes, which in turn worsens cognitive function. Atrial fibrillation, for example, increases the risk of cerebral embolism, which often leads to a more extensive stroke and is more destructive to cognitive function (Kamel et al., 2017).

The results of this study showed that comorbidities decreased MMSE scores, but were not statistically significant. Kaddumukasa et al. (2023) showed that the presence of comorbidities in the form of hypertension and atrial fibrillation was not associated with decreased cognitive function in post-stroke patients. In contrast to the findings by Utami et al. (2024) that there is a relationship between hyper-tension and diabetes mellitus and cognitive impairment in post-stroke patients. Post-stroke patients with hypertension are 1.56 times at risk of cognitive dysfunction and post-stroke patients with diabetes mellitus are at 1.58 times at risk of cognitive dysfunction

g. Effect of stroke type on cognitive function

Non-hemorrhagic stroke and hemorrhagic stroke have different mecha-nisms in affecting cognitive function. Non-hemorrhagic stroke occurs when blood flow to the brain is blocked by a blockage (thrombus or embolus), causing damage to brain tissue due to lack of oxygen. Cognitive deficits that arise in ischemic stroke are highly dependent on the location and size of the ischemic lesion (Wijaya, 2013).

A hemorrhagic stroke occurs when a blood vessel in the brain ruptures, causing bleeding in the brain tissue (intracerebral hemorrhage) or in the space between the brain and its protective layer (subarachnoid hemorrhage). Although less common compared to ischemic strokes, hemorrhagic strokes tend to have a higher mortality rate and lead to more severe cognitive deficits (El Husseini et al., 2023).

The results of this study showed that non-hemorrhagic stroke decreased MMSE scores, but it was not statistically significant. In line with Kaddumukasa study et al. (2023), there was no difference between hemorrhagic and non-hemorrhagic stroke types on the incidence of cognitive decline (p=0.953).

h. Contextual effect of neurospecialist doctors on cognitive function

Stroke is a disease that causes disability mainly. This can be prevented with quick and appropriate handling. Since a person is suspected of having a stroke, it is necessary to establish a diagnosis so that treatment can be given immediately. Fast and appropriate treatment is carried out by neurologists, especially those who have received special training for stroke (Nouh et al., 2022).

In line with the results of this study, the results of this multilevel linear regression analysis show that there is a contextual

influence of doctors who treat post-stroke patients on the cognitive function of post-stroke patients (ICC=8.76%). This figure is in the benchmark rule of thumb of 8-10%, which means that as much as 8.76% of the variation in cognitive function of post-stroke patients is determined by the doctor who treats the post-stroke patient. In contrast to the study conducted by Chew et al. (2021) There was no difference between hospitals that had neurologists or not with cognitive outcomes and complications that occurred in stroke patients.

The obstacles experienced by several countries, including Indonesia, Malaysia, Pakistan and other developing countries, are the availability of human resources (neurologists). In Indonesia, the number of human resources owned is 1,200 neurologists and 56 neurointerventionists, but they are not evenly distributed throughout Indonesia, most of them practice on the island of Java. Population to neurological ratio 1:108, with neurointerventions 1: 4,500 and neurosurgery 1:1,350 (Venketasubramanian et al., 2022b). A similar situation also occurs in Malaysia with a ratio of 1:323,000, mostly practiced in urban areas (Tan & Venketasubramanian, 2022). Similarly, in Pakistan the ratio of neurologists is 1:1,000,000 (Tan & Venketasubramanian, 2022). Neurological availability is vey important in reducing the incidence of stroke (Venketasubramanian et al., 2022b).

AUTHOR CONTRIBUTIONS

All authors have made meaningful and significant contributions to data analysis and the preparation of the final manuscript.

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CONFLICTS OF INTEREST

There is no conflict of interest in this study.

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