



## Prediction score for post-stroke cognitive impairment (PSCI) after acute ischemic stroke

Johan Budiman<sup>1</sup>, Jarir At Thobari<sup>2,3</sup>, Rizaldy Taslim Pinzon<sup>3</sup>

<sup>1</sup>Postgraduate Student in Clinical Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, <sup>2</sup>Department of Pharmacology & Therapy, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, <sup>3</sup>Clinical Epidemiology and Biostatistics Unit (CEBU), Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

### ABSTRACT

Submitted: 2021-03-23  
Accepted : 2022-06-05

It was estimated that patients with ischemic stroke and post-stroke cognitive impairment (PSCI) have been increasing. In addition, this PSCI is often late diagnosed when it has already developed into post-stroke dementia. Only a few studies have developed a scoring system of predictor factors cognitive impairment (CI) for post-acute ischemic stroke in Indonesia. This study aimed to develop a scoring system of predictor factors of CI for post-stroke ischemic patients. The patients included were >18 years old diagnosed with acute ischemic stroke who underwent mini-mental state examination (MMSE) and clock drawing test (CDT) examination on day-30 at Bethesda Hospital Yogyakarta. It was retrospective cohort study design and samples were obtained from the stroke registry and medical records. Patients who had a history of CI and incomplete medical records were excluded. The results of MSSE and CDT at day-30 were the outcomes of this study. To evaluate the relationship between the independent variable and the dependent variable, chi-squared tests were performed followed by multivariate logistic regression analysis with Hosmer-Lemeshow tests with backward likelihood-ratio (LR) method and by assessing the final area under the curve (AUC) model. The final model was transformed into a scoring system to determine the value of probability prediction of PSCI, the optimal cut-off point, the sensitivity value and specificity value of the cognitive impairment scoring system at day-30 after acute ischemic stroke. A total of 140 subjects were included in the study with an average age of 62.8 years, 86 (61.4%) males and 54 (38.6%) females. Ninety-one subjects (65%) experienced post-stroke CI. The multivariate analysis showed age >70 years, education level  $\leq 6$  years, modified ranking score (mRS) >3 at diagnosis, Barthel index score  $\leq 4$  at diagnosis, the number of multiple lesions and the location of lesion in the cortex were independent predictor factors affecting CI 30 days after acute ischemic stroke. The developed predictor score obtained AUC discrimination value of 82.6% (95%CI:0.757-0.896) and calibration value of  $p > 0.366$ . The scoring system had a value range of 0-7, and with a cut-off  $\geq 1$ , it had a sensitivity value of 86.8% and a specificity value of 59.2%. It can be concluded that the predictor score has a good performance in predicting the occurrence of PSCI at day-30 after acute ischemic stroke.

### ABSTRAK

Penderita stroke iskemik dan gangguan kognitif pasca stroke (*post-stroke cognitive impairment*/PSCI) diperkirakan terus meningkat. Selain itu, PSCI ini sering terlambat didiagnosis ketika sudah berkembang menjadi demensia pasca stroke. Hanya sedikit penelitian yang mengembangkan sistem penilaian faktor predictor gangguan kognitif (*cognitive impairment*/CI) untuk pasca stroke iskemik akut di Indonesia. Penelitian ini bertujuan untuk mengembangkan sistem penilaian faktor predictor CI pada pasien iskemik pasca stroke. Pasien yang termasuk berusia >18 tahun didiagnosis stroke iskemik akut yang menjalani pemeriksaan *mini-mental state examination* (MMSE) dan *clock drawing test* (CDT) pada hari ke 30 di RS Bethesda Yogyakarta. Penelitian ini menggunakan rancangan studi kohort retrospektif dan sampel diperoleh dari catatan stroke dan rekam medis. Pasien yang memiliki riwayat CI dan catatan medis yang tidak lengkap dikeluarkan. Hasil MSSE dan CDT pada hari

### Keywords:

Prediction score;  
acute ischemic stroke;  
cognitive impairment;  
post-stroke cognitive  
impairment;  
PSCI score

ke 30 merupakan hasil dari penelitian ini. Untuk mengetahui hubungan antara variabel bebas dan variabel terikat dilakukan uji chi-kuadrat dilanjutkan dengan analisis regresi logistik multivariat dengan model uji Hosmer-Lemeshow dengan metode *backward likelihood-ratio* (LR) dan dengan menilai model akhir *area under the curve* (AUC). Model akhir ditransformasikan menjadi sistem penilaian untuk menentukan nilai prediksi probabilitas PSCI, titik potong optimal, nilai sensitivitas, dan nilai spesifisitas sistem penilaian gangguan kognitif pada hari ke-30 pasca stroke iskemik akut. Sebanyak 140 subjek dilibatkan dalam penelitian dengan usia rata-rata 62,8 tahun, 86 (61,4%) laki-laki dan 54 (38,6%) perempuan. Sembilan puluh satu subjek (65%) mengalami CI pasca stroke. Analisis multivariat menunjukkan usia >70 tahun, tingkat pendidikan 6 tahun, skor rankin termodifikasi (*modified ranking score/mRS*) >3 saat diagnosis, skor indeks Barthel 4 saat diagnosis, jumlah lesi multipel, dan lokasi lesi di korteks merupakan faktor prediktor independent yang mempengaruhi CI 30 hari setelah stroke iskemik akut. Skor prediktor yang dikembangkan diperoleh nilai diskriminasi AUC sebesar 82,6% (95%CI:0,757-0,896) dan nilai kalibrasi  $p > 0,366$ . Sistem penilaian memiliki rentang nilai 0-7, dan dengan *cut-off* 1, memiliki nilai sensitivitas 86,8% dan nilai spesifisitas 59,2%. Dapat disimpulkan bahwa skor prediktor memiliki kinerja yang baik dalam memprediksi terjadinya PSCI pada hari ke 30 pasca stroke iskemik akut.

## TRODUCTION

Stroke is the second leading cause of death and the third-ranking cause of disability in the world.<sup>1,2</sup> The prevalence of stroke in Indonesia has increased from 7 to 10.9% and it is the highest cause of disability among people aged  $\geq 60$  years old.<sup>3</sup> Post-stroke disability is not only a physical disability (motoric) but also involves cognitive impairment (CI). Post-stroke cognitive impairment (PSCI) is part of vascular cognitive impairment (VCI) which includes all CI (vascular dementia and CI no dementia) caused by or associated with vascular factors (cerebrovascular).<sup>4</sup>

The prevalence of PSCI varies from 20 to 80% among countries depending on population, race, and diagnostic criteria.<sup>5,6</sup> As many as 61.7% of post-stroke patients in Indonesia experienced CI based on data from the Basic Health Research (*Riset Kesehatan Dasar/Riskesdas*) in 2013.<sup>7</sup> A research conducted at Dr. Sardjito General Hospital, Yogyakarta in 2000 showed that acute ischemic stroke plays a role in CI with the result that 80.6% of patients with acute ischemic stroke aged  $\geq 65$  years old have decreased cognitive function.<sup>8</sup>

Patients with PSCI have reportedly returned to normal or progressively worsened into dementia.<sup>9</sup> A study

conducted by Suda *et al.*<sup>10</sup> in Japan in 2020 showed that CI can appear immediately after minor ischemic stroke on the fifth day with a prevalence of 63.3% and is associated with decreased function of daily activities. Post-stroke cognitive impairment is an important problem for stroke patients, but not many are aware of it so it is often discovered late when it has developed into post-stroke dementia (PSD).<sup>11</sup> Cognitive impairment after acute ischemic stroke have not been widely reported in Indonesia. Accordingly, a multidomain screening tool is needed to predict PSCI earlier in order to prevent the development of PSD and hopefully improve the recovery of stroke patients. This study aimed to develop a CI predictor scoring system in acute ischemic stroke patients and estimate the magnitude of risk factors to predict CI after acute ischemic stroke.

## MATERIALS AND METHODS

### Design of study

This an observational study used a retrospective cohort design involving patients aged >18 years with the clinical diagnosis of acute ischemic stroke and radiological head CT-scan at Bethesda Yogyakarta Hospital from December 30<sup>th</sup>, 2019 to November 14<sup>th</sup>, 2020.

## Procedure

The inclusion criteria for study subjects were patients aged >18 years diagnosed with acute ischemic stroke with the first attack and onset <24 h at Bethesda Yogyakarta Hospital. The exclusion criteria were diagnosed with transient ischemic attack (TIA), had a history of previous cognitive and psychiatric disorders, and incomplete medical records, which did not include complete data on all variables of this study. The calculation of the minimum sample size in this study used the hypothesis testing research formula with descriptive sensitivity, namely 140 subjects. The results of the mini-mental state examination (MMSE) and the clock drawing test (CDT) on day-30 were the outcomes of this study.

This study has received ethical approval from the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta with number: KE/FK/1005/EC/2020 and licensing of research institutions from RS Bethesda Hospital Yogyakarta with No.118/KEPK-RSB/IX/20.

## Statistical analysis

Statistical analysis was performed using the SPSS version 26 (IBM Corp., Chicago) data package program. Predictor factor analysis used bivariate analysis with the chi-squared method. Variables with a  $p < 0.25$  were followed by multivariate logistic regression analysis with Hosmer and Lemeshow tests and backward likelihood ratio (LR) until the variables with each  $p < 0.2$  became the final model. The Hosmer-Lemeshow tests used a  $p > 0.05$  as statistically significant (calibration) and an area under the curve (AUC) value  $> 0.80$  was considered strong or equal to the expected value (discrimination). Furthermore, the final model was transformed into a scoring

system, to assess the PSCI probability prediction, and optimal cutoff point, while the sensitivity and specificity scores for acute ischemic PSCI scores were determined.

## RESULTS

A total 163 subjects who met the inclusion criteria during the period of 30 December 2019 to 14 November 2020 were recruited in this study. Total sampling was conducted and 23 subjects were excluded because the medical record contained incomplete data and had a previous history of CI. The basic characteristics of the subjects are detailed in TABLE 1. The results of the CI assessment of acute ischemic stroke in this study are shown in TABLE 2. Study subjects on day-30 were assessed by MMSE and CDT. The results of the MMSE assessment showed that 58.6% of subjects experienced acute ischemic PSCI and CDT results showed 45.7% experienced acute ischemic PSCI. In this study, those who were declared to have CI after acute ischemic stroke were those with MMSE values  $\leq 25$  and or CDT  $\leq 2$ . After the assessment, it was found that there were 91 subjects (65%) who experienced PSCI incidents and 49 subjects (35%) who did not experience PSCI events. The basic characteristics of the subjects were obtained through descriptive analysis. In this study, the incidence of PSCI occurred in study subjects who had an average age of  $64.8 \pm 10.16$  years with the proportion predominantly women (68.5%) and educational level of  $\leq 6$  years (90.3%).

The final results of the multivariate analysis obtained 6 variables, namely age  $> 70$  years, education level  $< 6$  years, mRS score  $> 3$ , BI score  $\leq 4$ , the number of multiple lesions, and the presence of lesions in the cortex location which were statistically selected to be developed into a scoring system with the AUC discrimination value of 0.826 (95%CI: 0.757-0.896;  $p=0.000$ ) and the Hosmer and Lemeshow test calibration value

of  $p = 0.366$ . In the multivariate logistic regression analysis with the backward LR method, the results of the final stage used  $p < 0.20$  which was concluded as

statistically significant. The results of the bivariate analysis and the final results of the backward LR multivariate logistic regression analysis are shown in TABLE 3.

TABLE 1. Basic characteristics of subjects

Basic characteristics	Total (n=140)	PSCI		p
		Presence n=91 (65%)	Absent n= 49 (35%)	
Age (mean ± SD years)	62.8±10.4	64.8±10.16	59.1±10.03	0.001 <sup>a</sup>
Gender [n (%)]				
• Female	54 (38.6)	37 (68.5)	17 (31.5)	0.489 <sup>b</sup>
• Male	86 (61.4)	54 (62.8)	32 (37.2)	
Education [n (%)]				
• ≤6 years	31 (22.1)	28 (90.3)	3 (9.7)	0.001 <sup>b</sup>
• >6 years	109 (77.9)	63 (57.8)	46(42.2)	
Hypertension [n (%)]				
• Yes	74 (52.9)	46 (62.5)	28 (37.8)	0.456 <sup>b</sup>
• No	66 (47.1)	45 (68.2)	21 (31.8)	
Diabetes mellitus [n (%)]				
• Yes	43 (30.7)	29 (67.4)	14 (32.6)	0.687 <sup>b</sup>
• No	97 (69.3)	62 (63.9)	35 (36.1)	
Hyperlipidemia [n (%)]				
• Yes	99 (70.7)	64 (64.6)	35 (35.4)	0.892 <sup>b</sup>
• No	41(29.3)	27 (65.9)	14 (34.1)	
Smoking [n (%)]				
• Yes	59 (42.1)	39 (66.1)	20 (33.9)	0.816 <sup>b</sup>
• No	81 (57.9)	52 (64.2)	29 (35.8)	
At day on admission				
• NIHSS score (median IQR)	6(4–8)	6(5–9)	5(4–6)	0.001 <sup>c</sup>
• mRS score (median IQR)	3(3–4)	4(3–4)	3(2–3)	0.000 <sup>c</sup>
• Barthel index score (median IQR)	4(2–8)	3(1–6)	7(4–10)	0.000 <sup>c</sup>
Number of lesions [n (%)]				
• Multiple	56 (40)	48 (85.7)	8 (14.3)	0.000 <sup>b</sup>
• Single	84 (60)	43 (51.2)	41 (48.8)	
Location of lesions [n (%)]				
• Cortex	56 (40)	43 (76.8)	13 (23.2)	0.017 <sup>b</sup>
• Subcortex	84 (60.0)	48 (57.1)	36 (42.9)	
Cerebral atrophy [n (%)]				
• Yes	41(29.7)	33 (80.5)	8 (19.5)	0.013 <sup>b</sup>
• No	99 (70.3)	58 (58.6)	41 (41.4)	
At 30 day after admission				
• MMSE score (median IQR)	24(19-27)	21(17-23)	27(26-28)	0.000 <sup>c</sup>
• CDT score (median IQR)	3 (1-4)	1 (0-3)	4 (3-4)	

<sup>a</sup>: t-test independent, <sup>b</sup>: Chi-squared test, <sup>c</sup>: Mann-Whitney test

TABLE 2. The outcome of patients with CI 30 days after acute ischemic stroke

PSCI day-30	n = 140 (%)
MMSE [n (%)]	
• $\leq 25$	82 (58.6)
• $> 25$	58 (41.4)
CDT [n (%)]	
• $\leq 2$	64 (45.7)
• $> 2$	76 (54.3)
CI [n (%)]	
• MMSE $\leq 25$ and/or CDT $\leq 2$	91 (65)
• MMSE $> 25$ and CDT $> 2$	49 (35)

Note: CI: cognitive impairment; CDT: clock drawing test; MMSE: mini-mental state examination; PSCI: post-stroke cognitive impairment.

TABLE 3. Results of bivariate and multivariate analyses of CI after acute ischemic stroke

Variable	Bivariate Analysis			Multivariate Analysis			
	p	OR	95%CI	p	OR	95%CI	B coefficient/ Standard Error
Age (years)							
• $> 70$	0.003	3.75	1.51–9.26	0.046	2.93	1.01–8.47	1.08/0.54
Gender							
• Female	0.489	1.29	0.62–2.65				
Education							
• $\leq 6$ years	0.001	6.81	1.95–23.78	0.016	5.48	1.38–21.81	1.70/0.70
Hypertension							
• Yes	0.456	0.76	0.38–1.54				
Diabetes mellitus							
• Yes	0.687	1.16	0.54–2.50				
Hyperlipidemia							
• Yes	0.892	0.94	0.44–2.03				
Smoking							
• Yes	0.816	1.08	0.53–2.20				
NIHSS score on admission							
• $\geq 7$	0.004	3.09	1.40–6.80				
mRS score on admission							
• $> 3$	0.000	4.40	2.00–9.69	0.170	2.17	0.71–6.60	0.77/0.56
Barthel Index score on admission							
• $\leq 4$	0.000	5.62	2.62–12.06	0.058	2.82	0.96–8.24	1.03/0.54
Number of lesion							
• Multiple	0.000	5.72	2.41–13.54	0.053	2.68	0.98–7.30	0.98/0.51
Location of lesion							
• Cortex	0.017	2.48	1.16–5.28	0.132	2.06	0.80–5.32	0.72/0.48
Cerebral atrophy							
• Yes	0.013	2.91	1.22–6.95				

After the final model was transformed into a scoring system by utilizing the B and SE values in the multivariate TABLE, a cognitive impairment score system was formed after acute ischemic stroke with a score range of 0–7 where the optimal cutoff point was  $\geq 1$  with a sensitivity

value of 86.8%, specificity of 59.2% and the predicted PSCI event probability value of 40.49%. The scoring system and the probability value for the occurrence of PSCI are shown in TABLE 4, 5 and FIGURE 1.

TABLE 4. Acute ischemic PSCI scoring system.

Variable	Score
Age	
• $\leq 70$ years	+0
• $> 70$ years	+1
Level of education	
• $> 6$ years	+0
• $\leq 6$ years	+2
Score of mRS	
• $\leq 3$	+0
• $> 3$	+1
Score of Barthel index	
• $> 44$	+0
• $\leq 44$	+1
Number of lesions	
• Single	+0
• Multiple	+1
Location of lesions	
• Subcortex	+0
• Cortex	+1

The maximum score is 7. A score of 1 or higher is at risk of developing PSCI significantly

TABLE 5. The sensitivity, specificity, NPV and PPV of PSCI scoring system.

Cut-point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
$\geq 0$	95.6	40.8	75.0	83.3
$\geq 1$	86.8	59.2	79.5	69.0
$\geq 2$	60.4	87.8	90.1	54.4
$\geq 3$	40.7	91.8	90.4	45.4
$\geq 4$	26.4	100	100	42.2
$\geq 5$	12.1	100	100	37.9
$\geq 6$	3.3	100	100	35.7
$\geq 7$	0.0	100	100	35.0

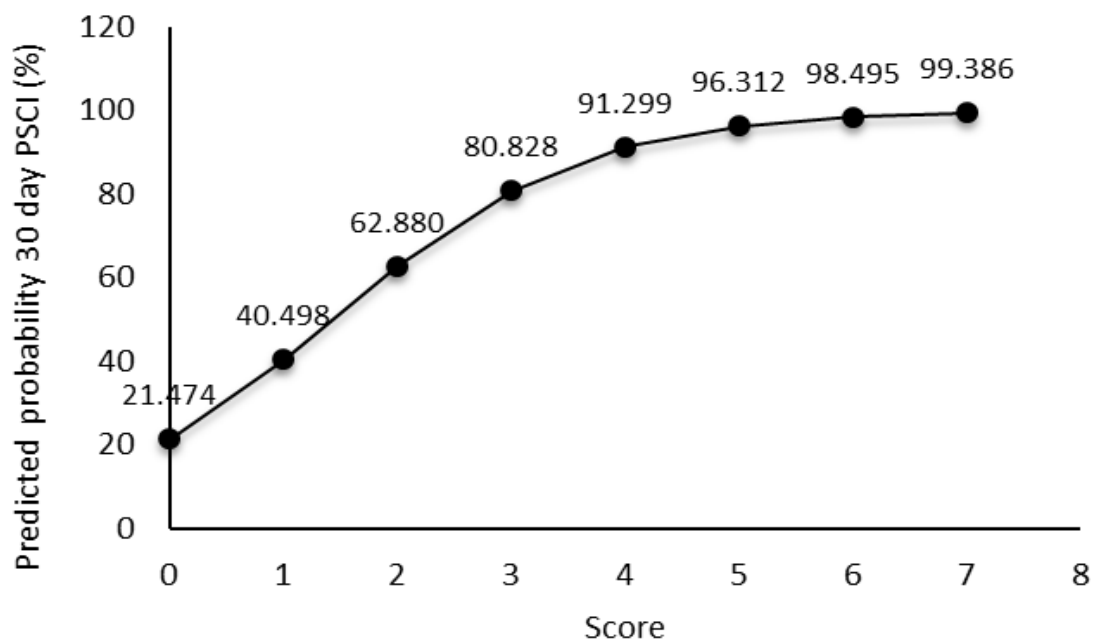


FIGURE 1. PSCI probability prediction graph at day-30.

## DISCUSSION

Acute ischemic PSCI is increasing but is often identified late when it has progressed to post-stroke dementia. In this study, it was found that 65% of patients with acute ischemic stroke experienced CI on the 30th day after acute ischemic stroke. Most of those who experienced acute ischemic PSCI at age >70 years, education level  $\leq 6$  years, had a BI score  $\leq 4$  and mRS score  $> 3$  at diagnosis, had multiple lesions, and the presence of lesions in the cortex on CT-scan result of the head which are predictors of CI after acute ischemic stroke. In addition, the main result of this study is the developed predictor score has a good performance in predicting the occurrence of CI at day-30 after acute ischemic stroke as indicated by the AUC discrimination value of 0.826 (95% CI: 0.75–0.89) and the Hosmer-Lemeshow test calibration value of  $p=0.366$ . This scoring system has a value range of 0–7, with a cutoff  $\geq 1$  having sensitivity value of 86.8%, specificity of 59.2%, and predictive value of the PSCI event probability of 40.49%.

The output observed in this study was the PSCI incident. The incidence of PSCI ranges between 20%–80%, which varies between countries depending on population, time of observation, and outcome criteria.<sup>6</sup> The incidence of PSCI in this study was 65%. These results are similar to those of the study conducted by Yang *et al.*<sup>14</sup> in 2020 in China which reported the results of the PSCI incidence rate at day-30, specifically 62.5%. In addition, the results of previous studies that have been done at RS Bethesda Yogyakarta by Pinzon *et al.*<sup>15</sup> in 2018 obtained the PSCI incidence rate of 68.2%. Different results were seen in study conducted by Chander *et al.*<sup>16</sup> in 2017 in Singapore who reported the PSCI incidence rate was lower at 37.32%. The different results in this study were likely due to several differences, namely, the study used a mild ischemic stroke type, the time was observed at the 3rd month and the observed outcome criteria were only using MMSE.

The results of the analysis of this study showed that acute ischemic stroke patients aged > 70 years were

significantly associated with the incidence of PSCI having an OR value of 2.9 times higher to experience PSCI events. These results are similar to studies conducted by Godefroy *et al.*<sup>17</sup> in 2018 which showed stroke patients aged >70 years have an OR value of 2.5 times higher incidence of PSCI. This condition indicates that as age increases, changes in the structure of the brain tissue can result in decreased cognitive function and the ischemic stroke incidence causes hypoperfusion of brain tissue, thereby accelerating the process of cognitive decline.<sup>18</sup>

The results of this study show there were as many as 90.3% of patients with acute ischemic stroke with an education level of  $\leq 6$  years who experienced CI with OR value of 5.4 times higher to experience PSCI. This is similar to the results of research conducted by Chander *et al.*<sup>16</sup> in 2017, where 85.9% of ischemic stroke patients with an education level of  $\leq 6$  years experienced CI with OR value of 1.76 times higher to experience PSCI. In addition, research in Korea in 2019 showed that low levels of education were associated with an increased risk of PSCI and this condition was related to the cognitive reserve (CR) theory. The CR is the ability of the brain's endurance (capacity) to slow down or minimize damage to brain tissue. Although the exact mechanism is not clearly known, it is believed that the level of education and work affects the resilience of the neuropathological process where each individual has a different number of synapses and volume of brain tissue in maintaining the neuropathological process. Patients who had an ischemic stroke with an education level of  $\leq 6$  years have fewer synapses and a smaller volume of brain tissue, making it less effective at resisting tissue damage.<sup>19</sup>

One of the tools that can be used to assess the functional level of stroke patients is the BI score and the mRS score. The BI score of  $\leq 4$  (total dependence) at

diagnosis in this study was shown to be a significant predictor of CI after acute ischemic stroke with a value of  $p:0.05$ . In addition, the mRS score  $>3$  at diagnosis (moderate to severe disability) for those who cannot meet basic life needs without the help of others has also been shown to be associated with the incidence of PSCI. Research conducted by Monfort *et al.*<sup>20</sup> in 2008 reported that decreased cognitive function affects the independence of stroke patients in their daily activities and increases the risk of post-stroke disability. Another study conducted by Khedr *et al.*<sup>21</sup> in 2009 showed that a low BI score was significant as a predictor of PSCI. This condition showed that the BI score  $\leq 4$  and the mRS score  $>3$ , when diagnosed with cognitive performance disorders as a whole, resulted in subjects being unable to carry out daily activities which required higher cognitive function for motor control, organization, problem-solving, and memory.<sup>22</sup>

The number of multiple stroke lesions is significant as a predictor factor and can increase the risk of PSCI by 3.06 times higher than with a single lesion. These findings are consistent with research conducted by Godefroy *et al.*<sup>17</sup> in 2018 in Paris which showed that the number of multiple stroke lesions was significant as a predictor factor and could increase the risk of PSCI by 3.78 times higher (95% CI:1.6–8.9,  $p=0.002$ ) compared to the single lesion. This finding suggests that the number of multiple stroke lesions at multiple locations can lead to a more progressive deficit in cognitive function than a single lesion. Compensation of the brain in developing plasticity and repairing the infarcted brain tissue becomes inefficient.<sup>23</sup>

The acute ischemic stroke patients with the location of the lesion in the cortex experienced the majority of PSCI events (76.8%) and increased the risk of PSCI 2.06 times higher than subcortical lesions. This result does not differ from the results of the study conducted by



Zhang *et al.*<sup>24</sup> in 2012 in China where stroke patients with a location of cortical lesions had a 1.5 times higher risk of PSCI incidence than subcortical lesions and it was reported that cortical location was a predictor of PSCI. This condition is because the location of the lesion in the cortex (cortex-subcortex) is more at risk of causing damage to neural networks such as frontal-subcortical circuits which play an important role in cognitive function in the three domains, namely memory, speed of processing information, and executive function.<sup>23</sup> In this study, the majority of acute ischemic stroke patients were located in the subcortex of 84 (60%) and those who had PSCI were 48 (57.1%). This finding suggests that acute ischemic stroke patients who have lesions located in the subcortex also need more attention because the frequency of cases is large and few of them experienced PSCI events. This finding is supported by a study conducted by Grau-Olivares *et al.*<sup>25</sup> in 2009 that showed lesions in the subcortex that were considered mild can cause MCI in 55% and dementia in 33%–67%.

There are several scores that have been developed in other countries as a comparison in this study, namely the SIGNAL2, CHANGE, and GRECogVASC. The SIGNAL2 score was developed and validated in Singapore by Chander *et al.*<sup>26</sup> in 2015 where the SIGNAL2 score had an AUC value of 0.829 (95% CI: 0.77–0.88) and was effective in identifying patients at risk for PSCI at 3–6 months after stroke. Chander *et al.*<sup>16</sup> in 2017 further developed and validated the CHANGE score which had an AUC value of 0.82 (95% CI: 0.76–0.88) and was effective in screening ischemic stroke patients who were at risk for PSCI up to 18 months after stroke. Another study conducted in Paris by Godefroy *et al.*<sup>17</sup> in 2018 developed and validated the GRECogVASC score which had an AUC value of 0.793 (95% CI: 0.745–0.842) and was effective in

screening ischemic stroke patients who were at risk for PSCI at the 6<sup>th</sup> month after stroke.

The difference between this study and the comparative studies above is that the subjects of this study are patients with acute ischemic stroke for the first time with mild to moderate severity, including variables from clinical factors (NIHSS score, BI score and mRS score at diagnosis), and neuroradiological variables which were assessed. Based on the head CT scan, the observation time for PSCI events was 30 days and the outcome criteria were assessed using MMSE and CDT. The parallel equations of this study with the comparative research above are the place of research in the hospital. In the development of the model, the value of  $p \leq 0.20$  was concluded as statistically significant, and the score developed had a good performance with a value of AUC  $\geq 0.8$ .

There are several factors that cause the incidence of PSCI to increase and develop into PSD, namely delays in recognizing CI in post-stroke patients, high stroke severity, and post-stroke patients' non-compliance for rehabilitation. Accordingly, the importance of the predictor score developed by the researcher can be used by clinicians as a basis for knowing stroke patients who are at high risk of CI at day-30 after acute ischemic stroke. At this time, the best course of action in preventing the incidence of PSCI is lifestyle modification by increasing physical exercise, a healthy diet and smoking cessation to reduce stroke severity, prevent stroke complications and prevent recurrent stroke events.<sup>27</sup> In addition, citicoline oral therapy can be given as an effort to prevent PSCI from getting worse or developing into PSD. A study conducted by Cotroneo *et al.*<sup>28</sup> in 2013 stated that after giving citicoline orally at a dose of 500 mg 2 times a day for 9 months, there was an increase in the MMSE score by 0.5 points compared to those who did not

receive therapy. Evaluation at 9 months showed a decrease in MMSE score in the group that did not receive citicoline therapy. From this study, it is known that citicoline administration is effective and safe for elderly patients with mild vascular CI.

This study some weaknesses including (1) there was no adjustment of the MMSE and CDT score assessments with the patient's education level, and (2) there was a possibility of selection bias in the subjects included in the study because the previous history of CI was only based on the nurse's alloanamnesis of the patient's family, (3) the research subjects obtained were ischemic stroke patients with mild to moderate severity so that the NIHSS score variable at diagnosis and cerebral atrophy could not represent the ischemic stroke patient population, (4) the concluded values were statistically significant in developing the predictor model using  $p < 0.2$ , and (5) external validity had not been carried out in other hospitals.

## CONCLUSIONS

The developed predictor score had a good performance in predicting the occurrence of cognitive impairment on the day-30 after acute ischemic stroke. Results in this study suggest further research should be conducted with external validity in another hospital with a prospective design and a longer monitoring time, specifically, 1, 3, and 6 months after acute ischemic stroke.

## ACKNOWLEDGMENTS

We would like to thank the Director of Bethesda Hospital, Yogyakarta for permission to conduct study at the relevant hospitals and also the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada/ Dr. Sardjito General Hospital, Yogyakarta for permission for this study.

## REFERENCES

1. Donkor ES. Stroke in the 21st century: a snapshot of the burden, epidemiology, and quality of life. *Stroke Res Treat* 2018. 2018:3238165. <https://doi.org/10.1155/2018/3238165>
2. Truelsen T, Begg S, Mathers C. The global burden of cerebrovascular disease. *Glob Burd Dis* 2000; 1-67.
3. Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan RI. Laporan Riskesdas 2018. *J Chem Inf Model*. 2018; 53(9):181-222. from: [http://www.yankes.kemkes.go.id/assets/downloads/PMK No. 57 Tahun 2013 tentang PTRM.pdf](http://www.yankes.kemkes.go.id/assets/downloads/PMK%20No.%2057%20Tahun%202013%20tentang%20PTRM.pdf)
4. Sachdev PS. Vascular cognitive disorders. In: Fillit H, Rockwood K, Young YB editors. *Brocklehurst's textbook of geriatric medicine and gerontology* 8<sup>th</sup> eds. Amsterdam: Elsevier Inc.; 2020. 410-420.
5. Sun JH, Tan L, Yu JT. Post-stroke cognitive impairment: epidemiology, mechanisms and management. *Ann Transl Med* 2014; 2(8):80. <https://doi.org/10.3978/j.issn.2305-5839.2014.08.05>
6. Lo JW, Crawford JD, Desmond DW, Godefroy O, Jokinen H, Mahinrad S, *et al*. Profile of and risk factors for poststroke cognitive impairment in diverse ethnoregional groups. *Neurology* 2019; 93(24):E2257-71. <https://doi.org/10.1212/WNL.00000000000008612>
7. Riset Kesehatan Dasar. Penyajian pokok-pokok hasil riset kesehatan dasar 2013. 2013.
8. Setyopranoto I, Lamsudin R, Dahlan P. Peranan stroke iskhemik akut terhadap timbulnya gangguan fungsi kognitif di RSUP Dr Sardjito Yogyakarta. *B Neuro Sains* 2000; 2:227-34.
9. Tham W, Auchus AP, Thong M, Goh ML, Chang HM, Wong MC. *et al*. Progression of cognitive impairment after stroke: one year results from a longitudinal study of Singaporean

- stroke patients. *J Neurol Sci* 2002; 203-204:49-52.  
[https://doi.org/10.1016/s0022-510x\(02\)00260-5](https://doi.org/10.1016/s0022-510x(02)00260-5)
10. Suda S, Nishimura T, Ishiwata A, Muraga K, Aoki J, Kanamaru T, Suzuki K, *et al.* Early cognitive impairment after minor stroke: associated factors and functional outcome. *J Stroke Cerebrovasc Dis* 2020; 29(5):104749.  
<https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104749>
  11. Kosgallana A, Cordato D, Chan D, Yong J. Use of cognitive screening tools to detect cognitive impairment after an ischaemic stroke: a systematic review. *SN Compr Clin Med* 2019; 1(4):255-62.  
<https://doi.org/10.1007/s42399-018-0035-2>
  12. Yang YM, Zhao ZM, Wang W, Dong FM, Wang PP, Jia YJ, *et al.* Trends in cognitive function assessed by a battery of neuropsychological tests after mild acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2020; 29(7):104887.  
<https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104887>
  13. Kwon HS, Lee D, Lee MH, Yu S, Lim JS, Yu KH, *et al.* Post-stroke cognitive impairment as an independent predictor of ischemic stroke recurrence: PICASSO sub-study. *J Neurol* 2020; 267(3):688-93.  
<https://doi.org/10.1007/s00415-019-09630-4>
  14. Lee SY, Kim DY, Sohn MK, Lee J, Lee SG, Shin YI *et al.* Determining the cut-off score for the Modified Barthel Index and the Modified Rankin Scale for assessment of functional independence and residual disability after stroke. *PLoS One* 2020; 15(1):0226324.  
<https://doi.org/10.1371/journal.pone.0226324>
  15. Pinzon RT, Sanyasi RDL, Totting S. The prevalence and determinant factors of post-stroke cognitive impairment. *Asian Pacific J Heal Sci* 2018; 5(1):78-83.  
<https://doi.org/10.21276/apjhs.2018.5.1.17>
  16. Chander RJ, Lam BYK, Lin X, Ng AYT, Wong APL, Mok VCT, *et al.* Development and validation of a risk score (CHANGE) for cognitive impairment after ischemic stroke. *Sci Rep* 2017; 7(1):12441.  
<https://doi.org/10.1038/s41598-017-12755-z>
  17. Godefroy O, Yaiche H, Taillia H, Bompaire F, Nedelec-Ciceri C, Bonnin C, *et al.* Who should undergo a comprehensive cognitive assessment after a stroke?: a cognitive risk score. *Neurology* 2018; 91(21):e1979-87.  
<https://doi.org/10.1212/WNL.0000000000006544>
  18. Yang T, Sun Y, Lu Z, Leak RK, Zhang F. The impact of cerebrovascular aging on vascular cognitive impairment and dementia. *Ageing Res Rev* 2017; 34:15-29.  
<https://doi.org/10.1016/j.arr.2016.09.007>
  19. Shin M, Sohn MK, Lee J, Kim DY, Lee SG, Shin YI, *et al.* Effect of cognitive reserve on risk of cognitive impairment and recovery after stroke: the KOSCO study. *Stroke* 2020; 51(1):99-107.  
<https://doi.org/10.1161/STROKEAHA.119.026829>
  20. Chodosh J, Miller-Martinez D, Aneshensel CS, Wight RG, Karlamangla AS. Depressive symptoms, chronic disease, and physical disabilities as predictors of cognitive functioning trajectories in older Americans. *J Am Geriatr Soc* 2010; 58(12):2350-7.  
<https://doi.org/10.1111/j.1532-5415.2010.03171.x>
  21. Khedr EM, Hamed SA, El-Shereef HK, Shawky OA, Mohamed KA, Awad EM, *et al.* Cognitive impairment after cerebrovascular stroke: relationship to vascular risk factors. *Neuropsychiatr Dis Treat* 2009; 5:103-16.  
<https://doi.org/10.2147/ndt.s4184>

22. Mohd Zulkifly MF, Ghazali SE, Che Din N, Singh DKA, Subramaniam P. A review of risk factors for cognitive impairment in stroke survivors. *Sci World J* 2016; 2016:3456943. <https://doi.org/10.1155/2016/3456943>
23. Saczynski JS, Sigurdsson S, Jonsdottir MK, Eiriksdottir G, Jonsson PV, Garcia ME, *et al.* Cerebral infarcts and cognitive performance: importance of location and number of infarcts. *Stroke* 2009; 40(3):677-82. <https://doi.org/10.1161/STROKEAHA.108.530212>
24. Zhang Y, Zhang Z, Yang B, Li Y, Zhang Q, Qu Q, *et al.* Incidence and risk factors of cognitive impairment 3 months after first-ever stroke: a cross-sectional study of 5 geographic areas of China. *J Huazhong Univ Sci Technolog Med Sci* 2012; 32(6):906-11. <https://doi.org/10.1007/s11596-012-1056-9>
25. Grau-Olivares M, Arboix A. Mild cognitive impairment in stroke patients with ischemic cerebral small-vessel disease: a forerunner of vascular dementia? *Expert Rev Neurother* 2009; 9(8):1201-17. <https://doi.org/10.1586/ern.09.73>
26. Kandiah N, Chander RJ, Lin X, Ng A, Poh YY, Cheong CY, *et al.* Cognitive Impairment after Mild Stroke: Development and Validation of the SIGNAL2 Risk Score. *J Alzheimers Dis* 2016; 49(4):1169-77. <https://doi.org/10.3233/JAD-150736>
27. Mijalovic MD, Pavlovic A, Brainin M, Heiss DW, Quinn JT, Hansen IBH, *et al.* Post-stroke dementia: a comprehensive review. *BMC Med* 2017; 15(1):11. <https://doi.org/10.1186/s12916-017-0779-7>
28. Cotroneo AM, Castagna A, Putignano S, Lacava R, Fanto F, Monteleone F, *et al.* Effectiveness and safety of citicoline in mild vascular cognitive impairment: the IDEALE study. *Clin Interv Aging* 2013; 8:131-7. <https://doi.org/10.2147/CIA.S38420>