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【 ORIGINAL ARTICLE 】

Validation of the R_2CHADS_2 and $CHADS_2$ Scores for Predicting Post-stroke Cognitive Impairment

Kazuo Washida[1], Hisatomo Kowa[1], Hirotoshi Hamaguchi[2], Fumio Kanda[1] and Tatsushi Toda[1]

Abstract:
Objective Post-stroke cognitive impairment often afflicts stroke survivors and is a major obstacle both for cognitive and physical rehabilitation. Stroke risk scores ["Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke" ($CHADS_2$) and "$CHADS_2$ + creatinine clearance <60 mL/min" (R_2CHADS_2)] are used to assess the future risk of cardioembolic stroke in patients with atrial fibrillation (AF). However, congestive heart failure, hypertension, aging, diabetes mellitus, stroke, and renal dysfunction are also risk factors for cognitive impairment.
Methods Sixty-two patients with nonvalvular AF-induced cardioembolic stroke underwent cognitive testing, including the Japanese version of the Montreal Cognitive Assessment (MoCA-J), Mini-Mental State Examination (MMSE), and Apathy Scale. The correlations between the MoCA-J/MMSE/Apathy Scale scores and stroke risk scores were examined.
Results The average $CHADS_2$ and R_2CHADS_2 scores were 4.1±1.0 and 5.6±1.6, respectively. The average MoCA-J, MMSE, and Apathy Scale scores were 17.4±6.2, 22.0±5.3, and 20.0±8.9, respectively. The $CHADS_2$ and R_2CHADS_2 scores were negatively correlated with the MoCA-J/MMSE and positively correlated with the Apathy Scale. The R_2CHADS_2 score was more sensitive to poststroke cognitive impairment than the $CHADS_2$ score. This correlation was stronger for MoCA-J than for MMSE, as the MMSE scores were skewed toward the higher end of the range. The results for individual MoCA-J and MMSE subtests indicated that the visuoexecutive, calculation, abstraction, and remote recall functions were significantly decreased after cardioembolic stroke.
Conclusion These results suggest that the R_2CHADS_2 and $CHADS_2$ scores are useful for predicting post-stroke cognitive impairment.

Key words: R_2CHADS_2 score, $CHADS_2$ score, Montreal Cognitive Assessment, Apathy Scale, post-stroke cognitive impairment

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Introduction

Atrial fibrillation (AF) increases the risk of cardioembolic stroke as well as the burden of cognitive impairment (1). AF-induced cardioembolic stroke often causes a cognitive decline in stroke survivors, initiating a viscious cycle leading to a poor prognosis (2). However, the burden of cardioembolic stroke stemming from its effect on cognition has long been underestimated. Anticoagulation therapy is strongly recommended for preventing cardioembolic stroke in patients with nonvalvular AF. Unfortunately, patients after AF-induced cerebral embolism tend to be cognitively impaired, and their drug non-compliance can seriously threaten their survival. Thus, the cognitive assessments of patients with AF-induced cardioembolic stroke should be carefully performed to ensure the prevention and treatment of post-stroke cognitive impairment (PSCI).

The "Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke" ($CHADS_2$) score can assess

[1]Division of Neurology, Graduate School of Medicine, Kobe University, Japan and [2]Department of Neurology, Kita-harima Medical Center, Japan
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Correspondence to Dr. Kazuo Washida, washida@med.kobe-u.ac.jp

Table 1. The R_2CHADS_2 and $CHADS_2$ Scores.

Risk factor	R_2CHADS_2 (Maximum score, 8) Points	$CHADS_2$ (Maximum score, 6) Points
Renal dysfunction	2	N/A
Congestive heart failure	1	1
Age ≥75	1	1
Hypertension	1	1
Diabetes	1	1
Previous stroke/TIA	2	2

TIA: transient ischemic attack, N/A: not applicable

the future risk of cardioembolic stroke in patients with AF (3, 4). Recently, the R_2CHADS_2 score, which supplements the $CHADS_2$ score with an additional 2 points for creatinine clearance <60 mL/min, was proposed as a new tool for predicting cerebral embolism, as renal dysfunction is a powerful predictor of cardioembolic stroke (5). The R_2CHADS_2 and $CHADS_2$ scores are well-validated for assessing the future risk of cerebral embolism. However, risk factors for cognitive impairment such as renal dysfunction (6), congestive heart failure, hypertension, aging, diabetes mellitus, and stroke can also be gathered and graded using the R_2CHADS_2 and $CHADS_2$ scores.

The Montreal Cognitive Assessment (MoCA) is more sensitive than the Mini-Mental State Examination (MMSE) for detecting PSCI (7). The MoCA is a well-established cognitive screening tool with a good sensitivity and specificity in detecting PSCI and, unlike the MMSE, includes executive tasks (8). The five-word recall MoCA subtest can also detect memory impairment. Additionally, post-stoke apathy (PSA), a troublesome neuropsychiatric sequela, often afflicts stroke survivors and is an important obstacle both for cognitive and physical rehabilitation. PSA is a disturbance of motivation evidenced by low self-activation or emotional indifference, and the Apathy Scale has been validated in many clinical studies (9). The clinical value of the R_2CHADS_2 and $CHADS_2$ scores will be enhanced if the cardioembolic stroke risk evaluation is found to be predictive for PSCI and/or PSA.

The main aim of this study was to evaluate the additive value of the R_2CHADS_2 and $CHADS_2$ scores in assessing the cognitive impairment of patients with cardioembolic stroke compared to the MoCA, MMSE, and Apathy Scale. Our results indicate that the R_2CHADS_2 and $CHADS_2$ scores can predict cognitive decline in stroke survivors.

Materials and Methods

Participants

Sixty-two patients with first-ever cardioembolic stroke due to nonvalvular AF were enrolled in this study more than three months after admission to the Kobe University Neurology Clinic. AF was diagnosed according to a standardized procedure that included the documented medical histories and electorocardiograms. Patients taking part in the study gave their written informed consent, as approved by the Committee of Medical Ethics within our faculty. All procedures were performed in accordance with the guidelines for the clinical study from the ethics committee of Kobe University.

Patients with infratentorial infarction were excluded. Patients with strategic single-infract dementia involving areas such as the hippocampus, thalamus, and basal forebrain, were excluded in accordance with National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (10). Patients who had problems that interfered with cognitive testing, such as aphasia, severe dysarthria, inability to use the dominant arm, and poor vision, were also excluded because they were unable to complete the tests (11). The existence of pre-stroke cognitive impairment, including mild cognitive impairment, was denied based on family interviews. Patients with other dementing illnesses, including Alzheimer's disease and Lewy body dementia, were not enrolled in this study to exclude the possibility of nonvascular causes of neurodegenerative cognitive impairment.

R_2CHADS_2 and $CHADS_2$ scoring

Sixty-two consecutive patients with cardioembolic stroke were scored with the R_2CHADS_2 and $CHADS_2$ when they were admitted to the hospital. All cardioembolic strokes were confirmed by magnetic resonance imaging. The clinical diagnosis of cardioembolic stroke was made according to the conventional Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (12). The R_2CHADS_2 and $CHADS_2$ scoring paradigms are described in Table 1. The R_2CHADS_2 score was determined by assigning 1 point each for the presence of congestive heart failure (C), hypertension (H), age ≥75 years (A), and diabetes mellitus (D) and by assigning 2 points for renal dysfunction (R_2; creatinine clearance <60 mL/min, calculated with the Cockcroft-Gault formula) and for a history of stroke or transient ischemic attack (S_2). The maximum R_2CHADS_2 score is 8 points (5). The $CHADS_2$ score was calculated by assigning 1 point each for the presence of congestive heart failure (C), hypertension

Table 2. Patient Clinical Features and Demographics.

Variable	Value
Mean age, year (range)	76.3±9.0 (50-89)
Gender (M:F)	42:20
Education, year (range)	11.3 (6-16)
NIHSS±SD (range)	2.3±1.8 (0-9)
Modified Rankin Scale, mean±SD (range)	1.87±1.1 (0-4)
Hypertension, n (%)	46 (74.2)
Diabetes mellitus, n (%)	22 (35.5)
Dyslipidemia, n (%)	31 (50.0)
Cigarette smoking, n (%)	26 (41.9)
R_2CHADS_2 score±SD (range)	5.6±1.6 (2-8)
$CHADS_2$ score±SD (range)	4.1±1.0 (2-6)
MoCA-J±SD (range)	17.4±6.2 (4-30)
MMSE±SD (range)	22.0±5.3 (5-30)
Apathy Scale±SD (range)	20.0±8.9 (0-42)

NIHSS: National Institute of Health stroke scale, MoCA-J: the Japanese version of Montreal cognitive assessment, MMSE: mini-mental state examination, SD: standard deviation

(H), age ≥75 years (A), and diabetes mellitus (D) and by assigning 2 points for a history of stroke or transient ischemic attack (S_2). The maximum $CHADS_2$ score is 6 points (3).

Neuropsychological examination

All subjects underwent a general physical and neurologic examination and a neuropsychological assessment, including the Japanese version of the MoCA (MoCA-J), MMSE, and Apathy Scale, more than three months after cardioembolic stroke. A MoCA-J<24 was regarded as evidence of cognitive decline, and Apathy scale ≥16 was regarded as evidence of apathy in this study. Two neurologists were involved in the neuropsychological assessment; if they did not agree, the patients were re-examined for a final evaluation.

Statistical analyses

The correlations of the individual cognitive function with the MoCA-J, MMSE, and Apathy Scale scores were calculated using the Pearson correlation analysis. To examine the related factors of the R_2CHADS_2 score, a multiple regression analysis was performed using the following variables: age, education, National Institute of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), and the MoCA-J, MMSE, and Apathy Scale scores. Subtests of the MoCA-J and MMSE were evaluated by dividing the mean subtest score by its standard deviation. A lower Z-score indicates greater discrimination between subjects. Differences with $p < 0.05$ were considered statistically significant in all statistical analyses performed.

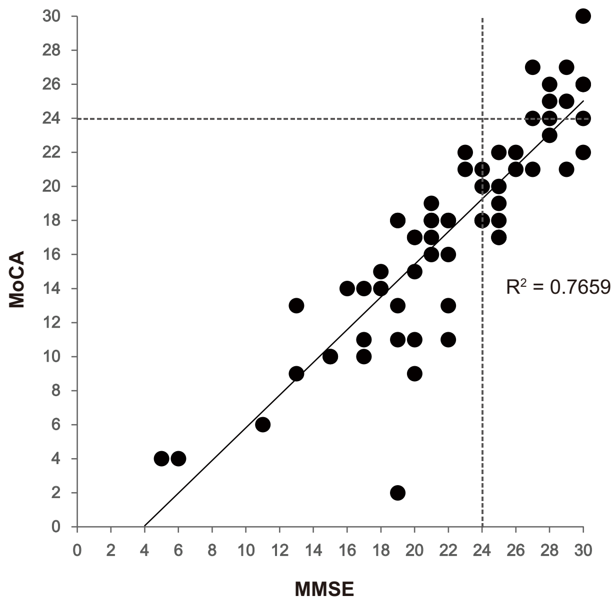

Figure 1. The distributions of the MoCA-J and MMSE scores of patients after cardioembolic stroke. A significant relationship was found between the MoCA-J and MMSE scores (R^2=0.77; $p<0.05$). The MoCA-J scores are normally distributed, whereas the MMSE scores are skewed toward the higher end of the range.

Results

Patient demographics

The clinical features and demographic data of patients are summarized in Table 2. All patients had at least one risk factor for ischemic cerebrovascular disease, such as hypertension, diabetes mellitus, dyslipidemia, or cigarette smoking. In this study, patinets who had problems that interfered with cognitive testing, such as aphasia, severe dysarthria, inability to use the dominant arm, and poor vision, were excluded because they were unable to complete the testing. As a result, patients with severe stroke were not enrolled [the mean NIHSS was 2.3±1.8 (range, 0-9) and the mean mRS was 1.87±1.1 (range, 0-4)]. These patient's clinical histories and radiological features excluded the possibility of coexisting single-strategic infarct dementia.

Relationship between MoCA-J and MMSE

There was a significant relationship between MoCA-J and MMSE (R^2=0.77; $p<0.05$) (Fig. 1). The MoCA-J scores were normally distributed, whereas the MMSE scores were skewed toward the higher end of the range. Of the 51 patients with an impaired MoCA-J score (<24), only 35 (69%) had an impaired MMSE score (<24), whereas all 35 patients with an impaired MMSE had an impaired MoCA-J score.

Overall and subscale cognitive test results

The mean cognitive scores were 17.4±6.2 (MoCA-J), 22.0

Table 3. Cognitive Test Results: Average Subtest Scores.

MoCA-J	Visuoexecutive/5	Naming/3	Attention/6	Language/3	Abstraction/2	Recall/5	Orientation/6
Average (SD)	2.8 (1.4)	2.5 (0.9)	4.1 (1.7)	1.3 (0.9)	1.0 (0.8)	0.4 (1.0)	4.4 (1.9)
Z-score	1.9	2.7	2.3	1.4	1.2	0.5	2.4

MMSE	Orientation/10	Registration/3	Attention/calculation/5	Recall/3	Naming/2	Language/6	Drawing/1
Average (SD)	7.9 (2.5)	2.9 (0.4)	2.2 (1.7)	1.0 (1.1)	1.9 (0.3)	5.2 (1.2)	0.8 (0.4)
Z-score	3.2	8.3	1.3	0.9	6.4	4.5	1.9

MoCA-J: the Japanese version of Montreal cognitive assessment, MMSE: mini-mental state examination, SD: standard deviation

±5.3 (MMSE), and 20.0±8.9 (Apathy Scale) (Table 2). The MoCA-J and MMSE subtest results are summarized in Table 3. Coefficients of variation >3 were found in four MMSE subtests (orientation, registration, naming, and language) but in no MoCA-J subtests. The individual MoCA-J and MMSE subtest results indicated that the cognitive function for visuoexecutive, calculation, abstraction, and remote recall significantly declined after cardioembolic stroke.

Relationship between the R_2CHADS_2, $CHADS_2$ scores, and cognitive function tests

The average R_2CHADS_2 and $CHADS_2$ scores were 5.6±1.6 and 4.1±1.0, respectively (Table 2). In patients with cardioembolic stroke, there was a significant correlation between the R_2CHADS_2 and MoCA-J scores (R^2=0.52; p<0.05) (Fig. 2A). There was also a significant correlation between the R_2CHADS_2 and MMSE scores (R^2=0.42; p<0.05) (Fig. 2B). In addition, significant correlations were found between the MoCA-J and the $CHADS_2$ score (R^2=0.41; p<0.05) (Fig. 3A). The MMSE was also significantly correlated with $CHADS_2$ score (R^2=0.34; p<0.05) (Fig. 3B). The R_2CHADS_2 score was more sensitive to cognitive decline after cardioembolic stroke than the $CHADS_2$ score. Compared with MoCA-J scores, the MMSE scores were skewed toward the higher end of the range (ceiling effect), and the MoCA-J exhibited greater sensitivity to cognitive decline in stroke survivors, the same tendency as observed in our previous study (13).

Relationship between the R_2CHADS_2, $CHADS_2$ scores and apathetic symptoms

The average Apathy Scale score was 20.0±8.9 (Table 2). Overall, 69% of patients with cardioembolic stroke tended to be apathetic (Apathy scale ≥16). There was a significant correlation between the R_2CHADS_2 score and the Apathy Scale score (R^2=0.54; p<0.05) (Fig. 2C). The Apathy Scale score was also significantly correlated with the $CHADS_2$ score (R^2=0.40; p<0.05) (Fig. 3C).

Related factors of the R_2CHADS_2 score

A multiple regression analysis in all subjects was performed using the following variables: age, education, NIHSS, mRS, MoCA-J, MMSE, and Apathy Scale scores. Among the variables examined, the NIHSS, mRS, MoCA-J, and Apathy Scale scores were selected as independent correlates of the R_2CHADS_2 score in patients with cardioembolic stroke (Table 4).

Discussion

We showed that the R_2CHADS_2 and $CHADS_2$ scores were significantly correlated with those of the MoCA-J and MMSE. Notably, the R_2CHADS_2 score was more sensitive to cognitive decline after cardioembolic stroke than the $CHADS_2$ score, and the MoCA-J was more sensitive than the MMSE. The individual subtests of the MoCA-J and MMSE indicate that the cognitive function for visuoexecutive, calculation, abstraction, and remote recall are significantly affected following cardioembolic stroke. Furtheremore, apathetic symptoms as assessed by the Apathy Scale were positively correlated with the R_2CHADS_2 and $CHADS_2$ scores.

The $CHADS_2$ score has been validated for predicting future cardioembolic stroke and is widely used in daily clinical practice (3, 4). The Japanese Circulation Society's treatment guidelines for AF recommend that patients with ≥1 point on the $CHADS_2$ score should be prescribed anticoagulation treatment (14, 15). However, several clinical studies have shown that half of all cardioembolic strokes occur in low-risk patients with 0 or 1 points on the $CHADS_2$ score (4). The discriminatory power of the $CHADS_2$ score for predicting cardioembolic stroke is limited, and the R_2CHADS_2 score was therefore proposed based on compelling evidence that renal dysfunction is a strong predictor of cardioembolic stroke (5). While risk factors for dementia, such as congestive heart failure, hypertension, aging, diabetes mellitus, and stroke, can be gathered and graded using the $CHADS_2$ score, additional risk factor for cognitive impairment, such as renal dysfunction (6), can also be evaluated by the R_2CHADS_2 score. This is likely why the R_2CHADS_2 score was more sensitive to cognitive decline after cardioembolic stroke than the $CHADS_2$ score in this study.

Recently, novel oral anticoagulants (NOACs) have been found to be more effective and safer than conventional warfarin therapy. Unlike warfarin, NOACs do not require frequent monitoring of blood test results, and they are easy to take. The European Society of Cardiology strongly recom-

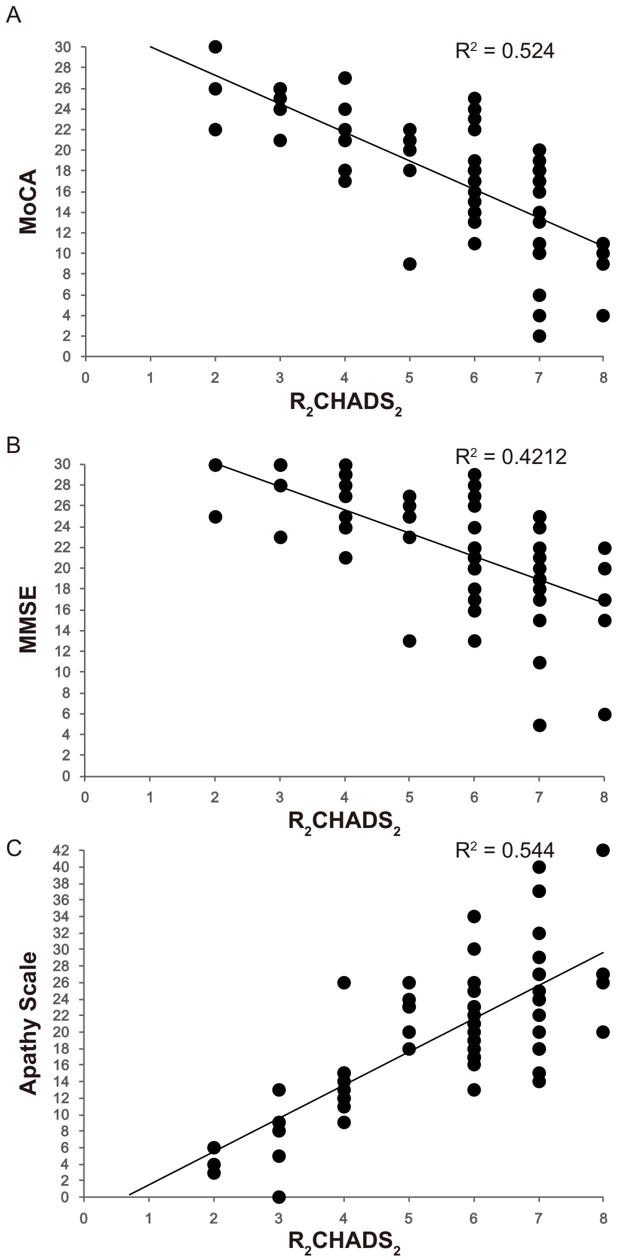

Figure 2. The distributions of the R_2CHADS_2, MoCA-J, MMSE, and Apathy Scale scores of patients after cardioembolic stroke. There was a significant relationship between the MoCA-J and R_2CHADS_2 scores (R^2=0.52; p<0.05) (A). There was also a significant relationship between the MMSE and R_2CHADS_2 scores (R^2=0.42; p<0.05) (B). Apathetic state also significantly correlated with the R_2CHADS_2 score (R^2=0.54; p<0.05) (C).

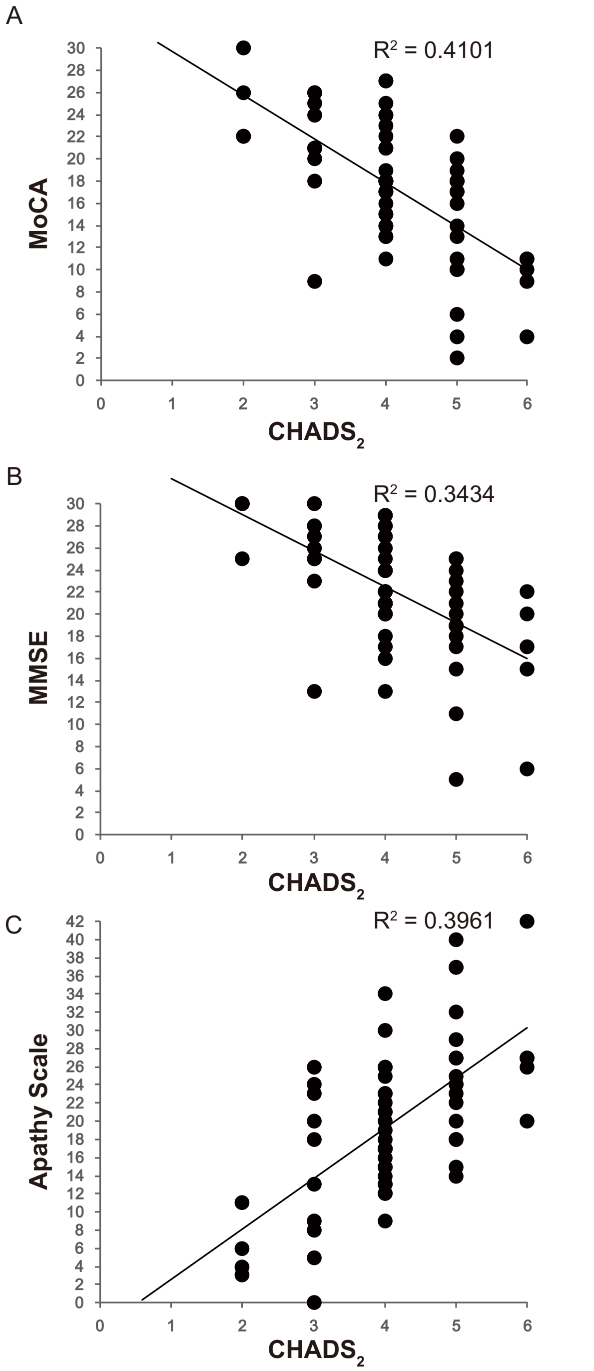

Figure 3. The distributions of the $CHADS_2$, MoCA-J, MMSE, and Apathy Scale scores of patients after cardioembolic stroke. There was a significant relationship between the MoCA-J and $CHADS_2$ scores (R^2=0.41; p<0.05) (A). There was a significant relationship between the MMSE and $CHADS_2$ scores (R^2=0.34; p<0.05) (B). Apathetic state also significantly correlated with the CHADS2 score (R^2=0.40; p<0.05) (C).

mends NOACs as the first choice for preventing cardioembolic stroke (16). Anticoagulant compliance is receiving increased focus as an avenue for preventing future cerebral embolism. However, patients who have experienced a cardioembolic stroke tend to be cognitively impaired and have difficulty taking NOACs or warfarin as directed. Such treatment noncompliance is a serious threat to stroke survivors. Clinicians should exercise caution concerning this risk in cognitively impaired patients, and the cognitive function of stroke survivors after cardioembolic stroke should be monitored rigorously. In this study, the R_2CHADS_2 and $CHADS_2$ scores were significantly correlated with cognitive impairment due to cerebral embolism. Our findings therefore demonstrate the increased clinical value of the R_2CHADS_2 and $CHADS_2$ scores. Patients with high scores should be carefully monitored with regard to drug compliance. In addition,

Table 4. Result of Stepwise Multiple Regression Analysis.

(Dependent variable: R_2CHADS_2)					
Predictors	R	R^2	Adjusted R^2	t value	p value
	0.844	0.712	0.675		
Age				1.420	0.161
Education				0.129	0.898
NIHSS				-2.786	<0.001
mRS				2.461	0.017
MoCA-J				-3.049	<0.001
MMSE				0.754	0.454
Apathy Scale				3.369	0.001

NIHSS: National Institute of Health stroke scale, mRS: modified Rankin scale, MoCA-J: the Japanese version of Montreal cognitive assessment, MMSE: mini-mental state examination

a multiple regression analysis showed that the NIHSS and mRS scores were independent correlates of the R_2CHADS_2 score in patients with cardioembolic stroke in this study. A prospective observational study reported that worse stroke severity scores independently contributed to the risk of developing cognitive impairment in stroke survivors (17). Therefore, patients with high NIHSS and mRS should also be carefully monitored with regard to drug compliance.

AF-induced cardioembolic stroke damages both the sensorimotor and cognitive functions of stroke survivors (1). Most patients who experience a cerebral embolism exhibit executive dysfunction when emboli damage white matter tracts. The white matter is the main component of frontal-subcortical circuits of the brain and is strongly associated with executive function (18). The MoCA is superior to the MMSE for detecting PSCI, especially executive functions such as visuoexecutive, abstraction, similarities, and conflicting instructions (19, 20). In addition to executive function, PSCI patients often exhibit memory impairment as a result of damage to the white matter that intimately connects to the hippocampus, which can also indirectly induce hippocampal atrophy via a remote effect (21). MoCA-J can also detect memory impairment through the 5-word recall subtest and seems the most suitable tool for detecting PSCI.

Patients who have suffered a stroke often experience mood changes. Apathy is a very troublesome sequela and can lead to caregiver exhaustion (9). PSA also acts as a barrier to meaningful participation in cognitive and physical rehabilitation (22). However, PSA has received little attention in daily clinical practice despite the fact that it is a serious reason for a poor post-stroke prognosis. Frontal lobe hypoactivity is hypothesized to contribute to the development of PSA (9). Stroke survivors with older age, poorer cognitive status, and frontal dysfunction tend to exhibit apathetic symptoms (9, 22). Cardioembolic stroke frequently damages the frontal-subcortical circuits of the brain, resulting in frontal lobe dysfunction (18). Notably, our results indicate that a poorer cognitive status can be predicted by the R_2CHADS_2 and $CHADS_2$ scores. This may explain why these scores were significantly correlated with the Apathy Scale score in this study. Early rehabilitation and drug treatment for PSA, including acetylcholinesterase inhibitors (23) and selective serotonin reuptake inhibitors (24), can improve the patient prognosis. Therefore, PSA should be carefully monitored to improve the prognosis of stroke survivors.

In this study, the cognitive scores of patients with R_2CHADS_2 scores 6-7 and $CHADS_2$ scores 4-5 were highly variable, and subtle cognitive declines could not be discriminated. We speculated that the vague criteria for the congestive heart failure (C) might be one of the reasons underlying this low discriminatory power. Clear-cut criteria for congestive heart failure might be more useful in predicting cognitive decline.

Several limitations associated with the present study warrant mention. First, we did not follow the 62 patients for an extended period of time. The temporal cognitive function profiles of patients with cardioembolic stroke should be explored over a longer time frame. Second, we included a relatively small number of patients. In the future, larger-scale clinical studies should be conducted to validate the clinical value of the R_2CHADS_2 and $CHADS_2$ scores for assessing PSCI. Third, we cannot completely deny the possibility that some patients had cognitive decline before cardioembolic stroke onset, although the existence of pre-stroke cognitive impairment was denied in the family interviews in this study. Patients with a high R_2CHADS_2 score have also many risk factors for dementia, and they tend to be cognitively impaired. In the future, prospective studies including pre-stroke cognitive scores should be conducted to exclude patients with pre-stroke cognitive impairment definitively.

Conclusion

In summary, these results suggest that the R_2CHADS_2 and $CHADS_2$ scores are useful for assessing cognitive decline in stroke survivors.

The authors state that they have no Conflict of Interest (COI).

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