

ABCD3 and ABCD3-I Scores Are Superior to ABCD2 Score in the Prediction of Short- and Long-Term Risks of Stroke After Transient Ischemic Attack

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ABCD3 and ABCD3-I scores are superior to ABCD2 score in the prediction of short- and long-term risk of stroke after TIA

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Abstract

Background and Purpose: Several risk scores have been developed to predict the stroke risk after transient ischemic attack (TIA). However, the validation of these scores in different cohorts is still limited. The objective of this study was to elucidate whether these scores were able to predict short-term and long-term risk of stroke in patients with TIA.

Methods: From the Fukuoka Stroke Registry, 693 patients with TIA were followed up for 3 years. Multivariable-adjusted Cox proportional hazards model was used to assess the hazard ratio of risk factors for stroke. The discriminatory ability of each risk score for incident stroke was estimated by using C-statistics and continuous net reclassification improvement (NRI).

Results: The multivariable-adjusted Cox proportional hazards model revealed that dual TIA and carotid stenosis were both significant predictors for stroke after TIA, whereas abnormal diffusion weighted image was not. ABCD3 (C-statistics 0.61) and ABCD3-I (C-statistics 0.66) scores improved the short-term predictive ability for stroke (at 7 days) compared with the ABCD2 score (C-statistics 0.54). Addition of intracranial arterial stenosis (at 3 years, NRI 30.5%, $P < 0.01$) and exclusion of abnormal diffusion weighted imaging (at 3 years, NRI 24.0%, $P < 0.05$) further improved the predictive ability for stroke risk until 3 years after TIA.

Conclusions: The present study demonstrates that ABCD3 and ABCD3-I scores are superior to the ABCD2 score for the prediction of subsequent stroke in patients with TIA.

Addition of neuroimaging in the ABCD3 score may enable prediction of long-term stroke risk after TIA.

Introduction

In patients with transient ischemic attack (TIA), subsequent stroke often occurs early after the first symptoms.^{1,2} Therefore, early diagnosis and prompt treatment are required to prevent subsequent stroke in patients presenting with TIA.^{3,4}

To predict early occurrence of stroke after TIA, several risk scores have been developed and widely used in clinical practice. In 2005, the ABCD score was developed by Rothwell *et al.* to predict the risk of stroke after TIA; the original ABCD score consisted of four components, namely, age, blood pressure, clinical features of TIA, and duration of symptoms.⁵ In 2007, Johnston *et al.* proposed a new risk score, ABCD2, in which the presence of diabetes mellitus was added as another component to the original ABCD score.⁶ In 2010, Merwick *et al.* proposed two novel scores to predict early risk of stroke after TIA, namely, the ABCD3 and ABCD3-I scores.⁷ In the ABCD3 score, dual TIA (the presence of 2 or more TIA symptoms within 7 days) is added to the ABCD2 score. In the ABCD3-I score, the presence of abnormal findings on neuroimaging (i.e., carotid stenosis or abnormal acute diffusion weighted image (DWI) on brain magnetic resonance imaging (MRI)) was further added to the ABCD3 score.⁷ Moreover, recent studies have shown that intracranial arterial stenosis was associated with recurrent stroke after TIA.^{8,9} Although the predictive abilities of ABCD and ABCD2 have been investigated by many studies, the results are still conflicting.¹⁰⁻¹⁸ Moreover, those of the ABCD3 and ABCD3-I scores have not yet been validated, and the ability of these scores

to predict stroke after TIA over the long term is unknown.

The aims of the present study were to elucidate whether the ABCD2, ABCD3, and ABCD3-I, with or without addition of intracranial arterial stenosis, scores are associated with short-term and long-term risk of stroke after TIA, and to determine whether the ABCD3 and ABCD3-I scores are superior to the ABCD2 score for the prediction of stroke after TIA, using the data from a prospective multicenter study in Japan.

Methods

Study population

The Fukuoka Stroke Registry (FSR) is a multicenter, hospital-based database of patients with acute stroke or TIA, and seven stroke centers in Fukuoka, Japan participate in the registry (see Appendix).^{19,20} From June 2007 to August 2012, a total of 6246 patients with acute stroke or TIA who were hospitalized within 7 days after onset were registered in the FSR database. In the present study, 693 patients with definite TIA who did not receive thrombolytic therapy were analyzed.

TIA was defined as a focal cerebral ischemic event with neurological symptoms lasting less than 24 hours regardless of brain lesions detected by brain imaging tests, including computed tomography (CT) and magnetic resonance imaging (MRI), and was diagnosed on admission by more than one stroke neurologist in the hospital. Patients received antiplatelet or anticoagulant therapy depending on the etiologies of TIA.

Treatments for risk factors were done based on the Japanese guidelines for the management of stroke. The medical information was collected using a case report form and medical record and inserted into the database with an aid of expert research nurses.

Risk factors

Blood pressure was measured in the chronic stage after TIA, and hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or a previous history of hypertension. Diabetes mellitus was determined by either the diagnostic criteria of the Japan Diabetes Society²¹ in the chronic stage or a medical history of diabetes. Dyslipidemia was defined as either a serum low-density lipoprotein-cholesterol ≥ 3.26 mmol/L, high-density lipoprotein-cholesterol < 1.03 mmol/L, triglycerides ≥ 1.69 mmol/L or a history of antihyperlipidemic medication. Atrial fibrillation was diagnosed based on electrocardiographic findings on admission or during hospitalization, or a previous history of atrial fibrillation. Estimated glomerular filtration rate (eGFR) was determined using the equation proposed by the Japanese Society of Nephrology as follows: $eGFR (\text{mL}/\text{min}/1.73 \text{ m}^2) = 194 \times [\text{serum creatinine (mg/dL)}]^{1.094} \times [\text{age (year)}]^{-0.287} \times 0.739$ (if female).²² Chronic kidney disease (CKD) was defined as a low eGFR ($< 60 \text{ mL}/\text{min}/1.73 \text{ m}^2$). Smoking was defined as a previous or current smoking habit before the onset of TIA. Coronary heart disease was defined as a previous history of angina pectoris, myocardial infarction, and percutaneous coronary intervention or

coronary artery bypass graft surgery. Dual TIA was defined as the occurrence of at least two TIAs (i.e., the index TIA and one other TIA) within 7 days.

Neuroimaging findings

Carotid stenosis was defined as more than 50% narrowing in the lumen of the internal carotid artery which was responsible for the neurological symptoms detected by carotid ultrasonography, magnetic resonance angiography (MRA), computerized tomographic angiography (CTA) or conventional angiographic examination. Intracranial arterial stenosis was defined as more than 50% narrowing in the lumen of the arteries which were responsible for the neurological symptoms detected by intracranial MRA, CTA or angiography. The presence of these vascular lesions was evaluated by carotid ultrasonography in 660 patients (95.2%), intracranial MRA in 672 patients (97.0%), extracranial MRA in 254 patients (37.0%), CTA in 158 patients (22.8%), and conventional angiography in 57 patients (8.2%).

CT imaging was performed in 402 patients (58.0%) predominantly to exclude hemorrhagic stroke or evaluation for arterial lesions. DWI findings on MRI upon admission or during hospitalization were considered abnormal if there was at least one hyperintense area that was consistent with the presence of an infarcted lesion. The abnormal DWI findings were diagnosed by stroke neurologists and neuroradiologists. DWI on brain MRI was performed in 675 patients (97.4%). Among them, 345 patients

underwent MRI within 24 hours of the TIA symptoms, and 615 patients underwent MRI within 3 days. For 18 patients, MRI was not performed due to contraindications, including 15 pacemaker implantations, one aorta stent, one cerebral artery clip, and one patient with claustrophobia.

Risk assessment of stroke events

The risk assessment of subsequent stroke events for individual patients was conducted by means of ABCD2, ABCD3, and ABCD3-I scores in the same manner as in the previous studies.⁵⁻⁷ We modified the original ABCD3-I score based on the findings from the multivariable analyses in this study. We constituted new scores with a combination of DWI abnormalities (d), and carotid stenosis or $\geq 50\%$ stenosis of intracranial arterial stenosis (c/i) (Table 1). The ABCD3-I(d,c/i) score was designated by adding an intracranial artery to original ABCD3-I, and the ABCD3-I(c/i) score was defined as the ABCD3-I(d,c/i) score with the abnormal DWI excluded (Table 1).

Stroke occurrence

The main outcome of this study was a stroke (either ischemic or hemorrhagic) after TIA. Stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours. Stroke events were identified by trained research nurses who were blinded to the clinical data through telephone interviews using a standardized

interview form. Patients were followed up at 3, 6, and 12 months after onset, and yearly thereafter. All information was reviewed by the event committee members, who were masked to the clinical background. When the committee members could not be convinced of stroke event, detailed information on subsequent stroke was also sought from general practitioners or hospital records. All patients were followed up prospectively during hospitalization and after discharge for a median of 392 days. During the follow-up period, 113 subjects experienced subsequent stroke events.

Statistical analysis

The incidence of stroke after TIA was calculated by the Kaplan-Meier method and compared by using a Cox proportional hazards model. The hazard ratios (HRs) and their 95% confidence intervals (CIs) for the development of stroke at 7 days, 90 days, and 3 years after TIA were estimated by using a multivariable-adjusted Cox proportional hazards model. We constituted multivariable models which included factors of ABCD2, ABCD3, and ABCD3-I scores, and/or intracranial arterial stenosis. To assess the accuracy of the risk assessment of incident stroke for each risk score, C-statistics were calculated, and the difference in the C-statistics were tested using the DeLong method.²³ To investigate the extent to which each risk score improved the risk assessment of incident stroke in comparison to the ABCD2 score, the continuous net reclassification improvement (NRI) was calculated,²⁴ with the predicted probabilities of incident stroke

being determined for each participant using the relevant Cox model. Statistical analyses were performed using the JMP version 9 software program (SAS Institute Inc., Cary, NC). Two-sided values of $p < 0.05$ were considered statistically significant in all analyses.

Ethical considerations

The ethics committee of each hospital approved this study. Written informed consent was obtained from all participants.

Results

Demographics of the patients

Table 2 shows the characteristics of the 693 patients. The distribution of the patients is shown according to the scores in Table 2. Antithrombotics had been administered in 243 patients before onset (antiplatelets in 210 patients, anticoagulants in 50 patients, and both in 17 patients). At discharge, antithrombotics were prescribed in 687 patients. Carotid endarterectomy and carotid artery stenting were performed during hospitalization in 20 and 7 patients, respectively.

Validity of ABCD2, ABCD3, and ABCD3-I scores

The overall incidence of stroke was 6.9% at 7 days, 10.4% at 90 days, and 21.6% at 3 years after onset of TIA. During the follow up period, 38 patients died in this cohort.

Figure 1 shows the incidence of stroke over the 3 years after TIA in patients with ABCD2, ABCD3, and ABCD3-I scores. When stratified by the ABCD2 score, the stroke incidence was significantly higher at 90 days and 3 years after TIA in the high-risk group than in the low-risk group (Figure 1A). When analyzed using the ABCD3 score, the stroke risk at each time point over the 3 years after TIA was significantly higher in the moderate- and high-risk groups than in the low-risk group (Figure 1B). When stratified by the ABCD3-I score, the risk of subsequent stroke was higher in the high-risk group than in the low- and moderate-risk groups (Figure 1C).

Components of the ABCD3-I scores and risk of stroke after TIA

Table 3 shows the results of a Cox proportional hazard model analysis performed to elucidate risk factors associated with stroke incidence in the short and long term. In multivariable model 1, dual TIA, DWI abnormalities (d), and carotid stenosis (c) were included in addition to variables in the ABCD2 score. In model 2, carotid and/or intracranial arterial stenosis (c/i) was included instead of carotid stenosis as in model 1. As shown in model 1, carotid stenosis was a significant risk factor for stroke at each time point from 7 days to 3 years after TIA. As shown in model 2, dual TIA and the combined carotid and/or intracranial arterial stenosis were significant risk factors for stroke at each time point over the 3 years after TIA. HRs for these factors in the short term tended to be higher than those in the long term. On the contrary, abnormal DWI was not a significant

risk factor for stroke in either model. Based on these findings, we constituted ABCD3-I(d,c/i) and ABCD3-I(c/i) scores with a modification of the original ABCD3-I score (Table 1).

Comparisons of predictive abilities among several risk scores

C-statistics of the ABCD3, ABCD3-I, and ABCD3-I(d,c/i) scores were significantly higher than those of the ABCD2 score at 7 days, but not at 90 days and 3 years (Table 4). On the other hand, the C-statistics of ABCD3-I(c/i) showed significantly greater values than those of the ABCD2 score at all time points tested between 7 days and 3 years. The analyses using continuous NRI revealed that the ABCD3-I(d,c/i) and ABCD3-I(c/i) scores improved the risk classification of stroke events for 3 years after TIA (Table 5).

Discussion

The major findings of this study were as follows: (1) the ABCD3 and ABCD3-I scores were superior to the ABCD2 score for predicting subsequent stroke in patients with definite TIA; (2) the inclusion of neuroimaging findings in the scoring improved the predictive ability for not only short-term but also long-term occurrence of stroke after TIA; and (3) dual TIA and stenotic vascular lesions were significant predictors for stroke, whereas abnormal DWI was not.

Predictivity of the ABCD2 score

The ABCD and ABCD2 scores were first developed to triage patients with high risk for stroke among those who were likely to have TIA diagnosed by a primary care physician. Some studies have indicated that the ABCD2 score is useful for predicting stroke after TIA,^{6,7,10-12} whereas other studies have suggested it is not useful for such prediction.^{13-15,25} One possible explanation for this discrepancy is that the usefulness of these scores may differ among study populations, i.e., population-based study or hospital-based study, TIA diagnosed by non-expert physicians or by stroke specialists, inpatients or outpatients, and definite TIA or possible TIA.^{16,17} We found that the ABCD2 score was not useful to predict stroke after TIA in our cohort of patients with TIA. In this study, we included patients who were diagnosed as having definite TIA by stroke neurologists and underwent optimal treatment during hospitalization. In addition, carotid stenosis (18.6%) or both carotid stenosis and/or intracranial arterial stenosis (32.3%) were more prevalent in the subpopulation of the low-risk group than in the low-risk group in the previous study.⁷ These factors could have led to a failure of the score to predict future stroke.¹⁸

Dual TIA

This study revealed that a TIA event within 7 days prior to TIA (dual TIA) was a useful factor to predict short-term and long-term stroke and that dual TIA significantly improved the performance of the ABCD2 score (Table 4 and 5). The previous studies showed

conflicting results in regard to whether or not dual TIA can predict future stroke, with some studies suggesting TIA had such a predictive ability^{7,13,25} and others suggesting it did not.^{26,27} The difference may have been related to a difference among the physicians making the diagnoses, i.e., in some studies the diagnoses were made by stroke specialists,^{7,13,25} and in others they were made by general practitioners or emergency physician at clinics and emergency departments.^{26,27} The accuracy of TIA determines the usefulness of dual TIA, since the impact of dual TIA may be underestimated if patients with symptoms mimicking TIA are included as having TIA. Further validation studies will be needed to elucidate whether dual TIA is predictive of stroke after TIA.

Carotid stenosis and intracranial arterial stenosis

Recent studies have demonstrated that carotid stenosis^{14,28} or intracranial arterial stenosis^{8,9} were associated with recurrent stroke. The rate of procedures for carotid lesions was low in this study, which may have lead to enhanced risk of this factor for future stroke. Carotid disease is less common, and carotid endarterectomy or carotid artery stenting is less frequently performed in Japan. In contrast, intracranial atherosclerotic stenosis is more prevalent in Asian population including Japanese.^{29,30} Large artery intracranial atherosclerotic stenosis has emerged as the most common stroke subtype worldwide and is associated with a high risk of recurrent stroke.^{29, 30} Therefore, we constituted a novel score, ABCD-I(d,c/i), by adding intracranial arterial stenosis to the ABCD3-I score and

validated its usefulness. Carotid stenosis and/or intracranial arterial stenosis was significantly associated with stroke in not only the short but also the long term for up to 3 years. Addition of intracranial arterial stenosis resulted in an improvement of the conventional scores to predict future stroke until 3 years after TIA (Table 5).

Abnormal DWI

It has been shown that abnormal DWI was a risk factor for short-term recurrence of stroke after TIA.^{31,32} In contrast, the present analysis did not show statistical significance of abnormal DWI as a risk factor for recurrent stroke. In this study, the rates of stroke occurrence after TIA in patients with normal and abnormal DWI were 5.9% and 8.8% within 7 days, and 10.2% and 11.3% within 90 days, respectively. The incidence in the abnormal DWI group was similar to that reported in the previous studies; however, that in the normal DWI group was 5 to 7 times higher than in the previous study.³² This is probably because we included only patients with definite TIA in this study, leading to a high risk of stroke even in patients with normal DWI. If we enroll patients with probable TIA or possible TIA, TIA mimics would be included, leading to a lowered risk of stroke in the normal DWI group relative to that in the abnormal group. However, the larger number of cases could produce the difference, since the risk of stroke in the abnormal DWI group tended to be high in the short term.

Short- and long-term recurrence

The ABCD2 score was originally shown to predict short-term recurrence after TIA. The score may be useful to predict long-term risk of stroke after TIA, although its usefulness has not been established.^{33,34} Our study showed that there were statistically significant differences at 90 days and 3 years in the risk of stroke between the ABCD2 low-risk and high-risk groups. In contrast, there has been no study concerning the usefulness of the ABCD3 and ABCD3-I scores to predict future stroke after TIA. In this study, we demonstrated striking findings that the stroke incidence after TIA was statistically different until 3 years according to the ABCD3 and ABCD3-I scores. The ABCD3-I(d,c/i) score and ABCD3-I(c/i) score maintained significantly improved predictive power up to 3 years after TIA (Table 5). Since the C-statistics for long-term recurrence tended to be higher when abnormal DWI was excluded from the model, abnormal DWI may not be useful to predict long-term recurrence. The predictive power of these scores decayed as the follow up period was prolonged (Table 4). To predict long-term recurrence after TIA, further improvement of the risk score is needed.

Strengths and limitations

This study had some important strengths. The diagnosis of patients was accurate and the imaging evaluation was done in all patients without contraindication. As a Japanese nationwide survey reported that MRI was used for the diagnosis of TIA in 93% of patients,

TIA is often diagnosed based on MRI in Japan.³⁵ The frequency of the neuroimaging and follow up rates were remarkably high. Finally, the results of this study should be of particular relevance because a validation of these scores in Asian populations is currently lacking. On the other hand, there were also limitations in this study. Subjects were inpatients hospitalized in the FSR, which could have caused a selection bias. However, most of patients with definite TIA may have been included in this study, since admission to the hospitals was advised for all patients who were suspected to have TIA to identify the onset mechanism and start urgent treatment according to the Japanese guidelines.³⁶ The information about the treatment after discharge was unavailable. However, the treatments after discharge were done by each practitioner, which reflects medical practice in real-world setting. All stroke events after TIA were not confirmed by neuroimaging. Although we adopted observational points and risk categories similar to those in the previous study,⁷ the fitness of each risk group was poor due to the different HR among risk factors. Finally, we cannot generalize an addition of intracranial arterial stenosis to the ABCD3-I score across ethnic groups, because intracranial arterial stenosis is less frequent in a non-Asian population and MRA is not commonly used worldwide.

In conclusion, the ABCD3 or ABCD3-I score, which includes dual TIA or carotid stenosis and DWI abnormality, improved the performance of the ABCD2 score to predict stroke recurrence in a cohort of patients with definite TIA. The consideration of

intracranial arterial stenosis may have intensified the predictive ability of the score for recurrent stroke until 3 years after TIA. In patients with definite TIA, stroke recurrence was probably high even in the absence of abnormal DWI.

Since the C-statistics of each score were not high, ranging between 0.6 and 0.7, an improvement of the scores is needed. Further studies will be needed to elucidate the validity of the scores in a subpopulation of patients with normal DWI, if the diagnosis of TIA changes from a time-based diagnosis to a tissue-based one in the future.

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Conflict of interests: None

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Figure legend**Figure 1. Stroke incidence after TIA**

The incidence of stroke at different time points after TIA is shown according to the risk categories of ABCD2 score (A), ABCD3 score (B), and ABCD3-I score (C). The different columns indicate stroke incidence in low- (open column), moderate- (shaded column), and high-risk patients (closed column). * $p < 0.05$ vs. low-risk; † $p < 0.05$ vs. moderate-risk.

Table 1. Point score of ABCD2, ABCD3, and ABCD3-I score

	ABCD2 score	ABCD3 score	ABCD3-I score	ABCD3-I(d, c/i) score	ABCD3-I(c/i) score
Age \geq 60years	1	1	1	1	1
Blood pressure \geq 140/90mmHg	1	1	1	1	1
Clinical feature					
Speech impairment without weakness	1	1	1	1	1
Unilateral weakness	2	2	2	2	2
Duration 10-59min	1	1	1	1	1
\geq 60min	2	2	2	2	2
Diabetes mellitus present	1	1	1	1	1
Dual TIA	NA	2	2	2	2
Imaging					
Ipsilateral \geq 50% stenosis of internal carotid artery	NA	NA	2	NA	NA
Ipsilateral \geq 50% stenosis of internal carotid artery and/or cerebral major artery	NA	NA	NA	2	2
Acute diffusion-weighted imaging hyperintensity	NA	NA	2	2	NA
Total	0-7	0-9	0-13	0-13	0-11

NA : not applicable, (d) : diffusion weighted image, (c) : carotid stenosis, (i) : intracranial arterial stenosis.

Dual TIA was defined as TIA prompting medical attention plus at least one other TIA in the preceding 7 days.

Table 2. Patient characteristics

Age, y, mean±SD	69±13
Male, n/N (%)	431 / 693 (62.2)
Risk factors, n/N (%)	
Hypertension	525 / 693 (75.8)
Dyslipidemia	389 / 692 (56.2)
Diabetes mellitus	163 / 693 (23.5)
Atrial fibrillation	127 / 693 (18.3)
Smoking	376 / 693 (54.3)
Chronic kidney disease, n/N (%)	224 / 693 (32.3)
Coronary heart disease, n/N (%)	122 / 693 (17.6)
Previous stroke, n/N (%)	141 / 693 (20.3)
Clinical feature, n/N (%)	
Speech impairment without weakness	78 / 693 (11.2)
Unilateral weakness	411 / 693 (59.3)
Duration of symptoms	
10-59min	248 / 693 (35.8)
≥60min	302 / 693 (43.6)
Dual TIA	132 / 693 (19.0)
Carotid stenosis, n/N (%)	151 / 693 (21.8)
Intracranial arterial stenosis, n/N (%)	154 / 689 (22.4)
Carotid and/or intracranial arterial stenosis, n/N (%)	264 / 693 (38.1)
Abnormal DWI, n/N (%)	285 / 675 (42.2)
Treatments, n/N (%)	
Antiplatelets	
Before onset	210 / 693 (30.3)
At discharge	569 / 693 (82.1)
Anticoagulants	
Before onset	50 / 693 (7.2)
At discharge	164 / 693 (23.7)
CEA or carotid artery stenting	27 / 693 (3.9)
ABCD2 score, median (interquartile range)	4 (3-5)
0-3:Low, n/N (%)	189 / 693 (27.2)
4-5:Moderate, n/N (%)	347 / 693 (50.0)
6-7:High, n/N (%)	157 / 693 (22.7)
ABCD3 score, median (interquartile range)	5 (4-6)
0-3:Low, n/N (%)	158 / 693 (22.8)
4-5:Moderate, n/N (%)	304 / 693 (43.9)
6-9:High, n/N (%)	231 / 693 (33.3)
ABCD3-I score, median (interquartile range)	6 (4-8)
0-3:Low, n/N (%)	93 / 675 (13.8)
4-7:Moderate, n/N (%)	407 / 675 (60.0)
8-13:High, n/N (%)	182 / 675 (25.9)

DWI : diffusion weighted image, CEA : carotid endarterectomy.

Dual TIA was defined as TIA prompting medical attention plus at least one other TIA in the preceding 7 days.

Table 3. Multivariable-adjusted hazard ratios for stroke after TIA at different time points of follow-up

Variables		7 days		90 days		3 years	
		HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Model 1							
ABCD2, moderate (4-5)	(vs. ABCD2, low)	1.04 (0.52, 2.22)	0.92	1.49 (0.81, 2.93)	0.20	1.32 (0.82, 2.19)	0.26
ABCD2, high (6-7)	(vs. ABCD2, low)	1.81 (0.83, 4.10)	0.14	2.13 (1.07, 4.39)	0.03	1.92 (1.12, 3.32)	0.02
Dual TIA	(yes vs. no)	2.88 (1.58, 5.13)	<0.001	2.06 (1.21, 3.38)	0.009	1.80 (1.17, 2.71)	0.008
Abnormal DWI	(yes vs. no)	1.55 (0.88, 2.74)	0.13	1.09 (0.68, 1.74)	0.72	1.20 (0.82, 1.73)	0.34
Carotid stenosis	(yes vs. no)	2.22 (1.23, 3.91)	0.009	1.73 (1.04, 2.82)	0.04	1.77 (1.17, 2.62)	0.007
Model 2							
ABCD2, moderate (4-5)	(vs. ABCD2, low)	1.00 (0.50, 2.15)	0.99	1.45 (0.79, 2.84)	0.24	1.30 (0.81, 2.15)	0.29
ABCD2, high (6-7)	(vs. ABCD2, low)	1.91 (0.87, 4.33)	0.11	2.16 (1.09, 4.46)	0.03	1.95 (1.14, 3.37)	0.01
Dual TIA	(yes vs. no)	2.81 (1.54, 5.04)	0.001	2.01 (1.18, 3.32)	0.01	1.77 (1.14, 2.66)	0.01
Abnormal DWI	(yes vs. no)	1.45 (0.82, 2.57)	0.20	1.04 (0.64, 1.66)	0.88	1.15 (0.79, 1.66)	0.47
Carotid stenosis and/or intracranial arterial stenosis	(yes vs. no)	2.43 (1.37, 4.41)	0.002	1.95 (1.22, 3.15)	0.005	1.62 (1.11, 2.35)	0.01

HR : hazard ratio, CI : confidence interval, DWI : diffusion weighted image.

HR in moderate or high risk ABCD2 scores was compared with that in low risk (0-3) of ABCD2 scores.

Table 4. C-statistics and improvement of ABCD3, and ABCD3-I scores in comparison to ABCD2 score

	7 days		90 days		3 years	
	C-statistics (95%CI)	P	C-statistics (95%CI)	P	C-statistics (95%CI)	P
ABCD2	0.54 (0.46, 0.62)		0.57 (0.50, 0.63)		0.57 (0.51, 0.62)	
ABCD3	0.61 (0.54, 0.68)	0.02	0.60 (0.54, 0.66)	0.10	0.59 (0.53, 0.64)	0.26
ABCD3-I	0.66 (0.57, 0.74)	0.004	0.61 (0.54, 0.68)	0.26	0.61 (0.55, 0.66)	0.17
ABCD3-I(d, c/i)	0.67 (0.59, 0.75)	0.003	0.63 (0.56, 0.69)	0.12	0.61 (0.56, 0.67)	0.13
ABCD3-I(c/i)	0.67 (0.59, 0.74)	0.002	0.64 (0.58, 0.71)	0.02	0.62 (0.56, 0.67)	0.047

CI : confidence interval, (d) : diffusion weighted image, (c) : carotid stenosis, (i) : intracranial arterial stenosis.
P values are calculated by the DeLong method, which compared each score with the ABCD2 score.

Table 5. Continuous NRI reclassification from ABCD2 score

	7 days		90 days		3 years	
	NRI (95%CI)	P	NRI (95%CI)	P	NRI (95%CI)	P
ABCD3, %	46.0 (17.9, 74.1)	0.001	28.2 (6.6, 50.0)	0.01	16.3 (-2.9, 35.5)	0.11
ABCD3-I, %	48.1 (19.1, 77.0)	0.001	12.9 (-11.1, 36.9)	0.30	14.9 (-4.9, 34.8)	0.15
ABCD3-I(d, c/i), %	52.3 (24.0, 80.5)	<0.001	36.8 (13.5, 60.2)	0.002	30.5 (11.5, 49.4)	0.002
ABCD3-I(c/i), %	59.9 (31.1, 88.7)	<0.001	39.5 (15.1, 63.9)	0.002	24.0 (3.9, 44.1)	0.02

CI : confidence interval, (d) : diffusion weighted image, (c) : carotid stenosis, (i) : intracranial arterial stenosis.
 Reclassification from the ABCD2 score.

Appendix

FSR Investigators

The participating Hospitals in the FSR were as follows: Kyushu University Hospital, National Hospital Organization Kyushu Medical Center, National Hospital Organization Fukuoka Higashi Medical Center, Fukuoka Red Cross Hospital, St. Mary's Hospital, Steel Memorial Yawata Hospital, Japan Labour Health and Welfare Organization Kyushu Rosai Hospital.

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