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【 ORIGINAL ARTICLE 】

Association between the Suita Score and Stroke Recurrence in Patients with First-ever Ischemic Stroke: A Prospective Cohort Study

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Abstract:

Objective The Suita score is used to predict the 10-year prognosis of developing coronary heart disease (CHD). This study examined the association between the Suita score and stroke recurrence within one year in Japanese patients who experienced first-ever ischemic stroke.

Methods This prospective cohort study at a stroke center in Japan included patients who experienced first-ever acute ischemic stroke (AIS) or a transient ischemic attack (TIA). During hospitalization, the Suita score was measured as the main exposure. Patients with a ≥5% predicted CHD risk were classified into the high-risk group. The primary outcome was stroke recurrence within one year of the stroke onset. A multivariate Cox regression analysis was conducted and adjusted for confounding and prognostic factors.

Results Among the 1,204 patients evaluated, 937 (78%) were classified as having a high risk of developing CHD. Stroke recurrence was observed in 66 patients during the follow-up period. In the multivariate analysis, after adjusting for confounding and prognostic factors, such as non-small vessel occlusion and prescription of lipid-lowering agents at the time of discharge, a ≥5% predicted CHD risk was associated with the 1-year stroke recurrence after the initial onset [adjusted hazard ratio (HR)=2.20, 95% confidence interval (CI)=1.00-4.91, p=0.049; adjusted HR=2.00, 95% CI=1.01-4.14, p=0.048; adjusted HR=0.42, 95% CI=0.24-0.73, p=0.002].

Conclusion The Suita score, adapted for use in ischemic stroke with the same mechanism, correlated with the short-term recurrence within one year. Our findings suggest that the Suita score may be useful for predicting the long-term prognosis of developing CHD as well as the short-term recurrence for patients with first-ever AIS and TIA.

Key words: ischemic stroke, coronary heart disease risk, stroke secondary prevention, cohort study

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Introduction

Stroke recurrence and cardiovascular events are major concerns for stroke survivors. A previous study revealed that recurrent stroke and cardiovascular events accounted for approximately one-third of deaths within five years after stroke among patients who experienced a first-ever stroke (1). Preventing these events after stroke is critical for both patients and medical professionals (2). The American Heart Association (AHA)/American Stroke Association (ASA) recommends implementation of non-invasive risk assessment tools, including the Framingham Risk Score (FRS) and diagnostic test of carotid disease (combined and individually), to prevent the development of coronary heart disease (CHD) following stroke (3).

Furthermore, risk assessments for both CHD and stroke recurrence may be equally important among stroke survivors due to their high-risk of stroke recurrence. In Australia and Japan, the stroke recurrence rates at 1, 5, and 10 years after

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the initial onset were reported to be 10%, 30%, and 50%, respectively (4, 5). Therefore, preventing stroke recurrence is considered a major strategy for reducing the risk of CHD, as stated in the AHA/ASA statement.

We based our hypothesis on the assumption that risk factors of stroke recurrence are similar to the FRS components, the most commonly used CHD risk algorithm worldwide (3, 6, 7). If existing CHD risk algorithms can also predict stroke recurrence in post-stroke patients, we can concurrently evaluate the risks of CHD and stroke recurrence. However, because the present study was conducted in Japan, we utilized the Suita score, a CHD risk evaluation algorithm developed using data from the general Japanese population that adds chronic kidney disease (CKD) to the FRS (8). The Suita score has been used previously to assess the 10-year CHD risk in Japan and is considered a more practical method for assessing CHD risk in Japanese patients with a better predictive ability than the FRS (8).

Despite several studies having been conducted, whether or not the predictive score for CHD is associated with stroke recurrence is unclear. Therefore, we assessed the CHD risk using the Suita score in Japanese patients who experienced first-ever ischemic stroke and investigated whether or not the Suita score was associated with stroke recurrence within one year.

Materials and Methods

Design and setting

This was a prospective cohort study conducted at the Brain Attack Center Ota Memorial Hospital in Japan between April 13, 2016, and June 30, 2018. The hospital is located in a suburban area in west Japan and treats over 1,000 stroke patients per year. This study was registered under the University Medical Hospital Information Network (UMIN) Registry (identifier UMIN000040720).

Patients and ethical considerations

We included patients with new-onset acute ischemic stroke (AIS) or transient ischemic attack (TIA) who were admitted to and treated at the stroke center during the study period. We excluded patients if 1) their Suita score could not be evaluated during admission, 2) they died before discharge, 3) they died [modified Rankin Scale (mRS) score of 6] within three months after discharge, or 4) they had undergone carotid endarterectomy within one year of the AIS or TIA onset.

AIS was defined as follows: 1) a new symptomatic neurological deterioration that persisted for ≥24 hours, not attributable to a nonischemic cause, or 2) a new symptomatic neurological deterioration, not attributable to a non-ischemic cause and accompanied by evidence of a new brain infarction, according to neuroimaging data. Based on the neuroimaging data, TIA was defined as the development of new neurological symptoms or deficits that persisted for <24 hours with no evidence of new infarction.

This study was approved by the ethics committee of the Brain Attack Center Ota Memorial Hospital and followed the tenets of the Declaration of Helsinki and ethical standards of the responsible committee on human experimentation. All personal identifiers were removed and replaced with a code in the final compiled dataset. Written informed consent was obtained from each patient during admission.

Variables

Outcome measurements

In our hospital, patients admitted due to stroke are usually followed up regularly after discharge (once a year), and their outcomes are measured annually, even if they are being treated at another hospital. In the current study, the primary outcome was stroke recurrence within one year from the initial onset. Recurrent stroke was defined as ischemic stroke, cerebral hemorrhaging, or TIA. Cerebral hemorrhaging was defined as acute extravasation of blood into the brain parenchyma based on neuroimaging data. According to neuroimaging data, TIA was defined as the development of new neurological symptoms or deficits lasting <24 hours with no evidence of new infarction.

Exposure: the Suita score

The Suita score is a coronary prediction algorithm developed for the Japanese population (3). It differs from the FRS by including an additional assessment of the CKD stage and includes the following factors: age, sex, current smoking status, presence of diabetes mellitus (DM), blood pressure (BP), low-density lipoprotein-cholesterol (LDL-C) levels, high-density lipoprotein-cholesterol (HDL-C) levels, and the CKD stage (Fig. 1).

The demographic and lifestyle components of the Suita score, including the age, sex, and current smoking habits, were measured by clinical nurses at the time of hospitalization. Patients were considered current smokers if they smoked ≥1 cigarette per day before the onset of stroke symptoms. The presence of DM, CKD stage, BP, and LDL-C and HDL-C levels were assessed through blood tests and using BP monitors at the time of hospitalization. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. The eGFR of each participant was calculated using the creatine (Cre) value, their age, and the equations below (9).

Men: eGFR (mL/min/1.73 m^2)=$194\times(Cre)^{-1.094}\times Age^{-0.287}$

Women: eGFR (mL/min/1.73 m^2)=$194\times Cre^{-1.094}\times Age^{-0.287}\times 0.739$

The CKD stage was defined by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guidelines (10). CKD was categorized into stages based on the eGFR: Stage 3 (eGFR=30-60 mL/min/1.73 m^2) and Stage 4 or 5 (eGFR <30 mL/min/1.73 m^2).

Furthermore, the Suita score was calculated at the time of hospitalization. Patients were categorized into 9 groups based on the predicted risk of developing CHD within the next 10 years, as follows: <1%, 1%, 2%, 3%, 5%, 9%, 14%,

Risk Factor

Variable	Score
Age	
35-44	30
45-54	38
55-64	45
65-69	51
≥ 70	53
Female	-7
Current Smoker	5
DM	6
Blood pressure	
Optimal blood pressure	-7
Normal and high normal	0
Stage 1 hypertension	4
Stage 2 hypertension	6
LDL (mg/dl)	
< 100	0
100-139	5
140-159	7
160-179	10
≥ 180	11
HDL (mg/dl)	
< 40	0
40-59	-5
≥ 60	-6
CKD	
eGFR>60	0
Stage 3	3
Stage 4 or 5	14

Predicted Probability of CHD in 10 years

Total Score	Probabilty(%)
≤35	<1
36-40	1
41-45	2
46-50	3
51-55	5
56-60	9
61-65	14
66-70	22
≥71	>28

DM: diabetes mellitus, LDL-C: low density lipoprotein cholesterol,
HDL-C: high density lipoprotein cholesterol, CKD: chronic kidney disease,
Blood pressure[mmHg]: Optimal (SBP <120, DBP <80), Normal (SBP <130, DBP <85),
High normal (SBP <140, DBP <90), Stage 1 hypertension (SBP <160, DBP <100),
Stage 2 hypertension (SBP ≥160, DBP ≥100)
CKD: Stage 1 or 2 (eGFR 60 mL/min/1.73 m^2), Stage 3 (eGFR 30-60 mL/min/1.73 m^2),
Stage 4 or 5 (eGFR <30 mL/min/1.73 m^2)

Figure 1. The calculation of the Suita score.

22%, and >28%. The risk of developing CHD was determined using the method described by Nishimura et al. (8). According to that study, patients with a ≥5% predicted risk were classified into the high-risk group. The 10-year risk of developing CHD in the Japanese population calculated using a Suita score ≥5% was equivalent to ≥20% using the FRS (8).

Covariates

We collected the following variables from electronic health records: dyslipidemia, atrial fibrillation (AF), CHD, heart failure, alcohol consumption, obesity, the National Institutes of Health Stroke Scale (NIHSS) score, stroke subtype, length of stay (LOS, in days), the mRS score at the time of discharge, prescription of antithrombotic agents, and prescription of oral lipid-lowering agents at discharge (11-14).

Dyslipidemia was defined as using lipid-lowering agents or a total cholesterol level ≥220 mg/dL, triglyceride level ≥150 mg/dL, LDL-C level ≥140 mg/dL, or HDL-C level <40 mg/dL. AF was defined based on a previous diagnosis of AF or electrocardiogram results acquired during hospitalization. Heart failure was defined by a brain natriuretic peptide level ≥80 pg/mL at the time of admission. Patients were considered alcohol drinkers if they drank, on average, >48.6 g of pure alcohol per day (equivalent to >2 servings of Japanese rice wine). Obesity was defined by a body mass index ≥25 kg/m^2. In terms of stroke subtypes, AIS and TIA were categorized according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (15). The TOAST criteria were also used to define pathophysiological subtypes of ischemic stroke, which were classified into five major mechanistic categories as follows: large-artery atherosclerosis, cardioembolism, small vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology. All patients were evaluated by neurologists.

Statistical analyses

The baseline patient data are presented as the frequencies and percentages (%) for categorical variables and as medi-

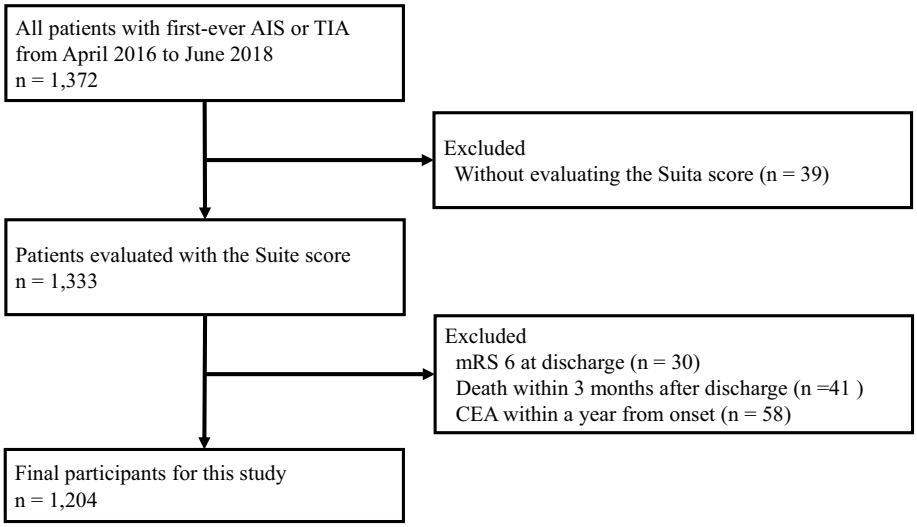

Figure 2. Patient flowchart. AIS: acute ischemic stroke, TIA: transient ischemic attack, mRS: modified Rankin Scale, CEA: carotid endarterectomy

ans with interquartile ranges (IQR) for continuous variables. A χ^2 test was performed to compare categorical variables. Student's *t*-test and the Mann-Whitney U test were performed to compare normally distributed or continuous and non-normally distributed or non-continuous variables, respectively. The reference standard for the Suita score was <5%. The time-to-recurrence was assessed using a Kaplan-Meier curve of cumulative incidence rates and compared between groups by log-rank test. For the primary analysis, we estimated the adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) using Cox regression models to evaluate the association between the Suita score and stroke recurrence within one year. A multivariate Cox regression analysis was conducted and adjusted for the following confounding and prognostic factors: AF, CHD, non-small-vessel occlusion, the prescription of antithrombotic agents, and prescription of lipid-lowering agents at the time of discharge (16).

All statistical analyses were performed using the IBM SPSS Statistics for Windows, version 24.0 (IBM, Armonk, USA) and STATA version 16.0 (Stata, College Station, USA) software programs. p values <0.05 were considered statistically significant, and all p values were two-tailed.

Results

Patient selection

A total of 1,372 patients with first-ever AIS or TIA were admitted to our hospital between April 13, 2016, and June 30, 2018. We evaluated the Suita score for 1,333 of the patients admitted during the study period, excluding those for whom the Suita score was not evaluated during admission (Fig. 2), those who died (mRS 6) before discharge (n=30), those who died within 3 months after discharge (n=41), and those who underwent carotid endarterectomy (n=58) within 1 year from the AIS or TIA onset. Ultimately, 1,204 patients were included in the final analyses (Fig. 2).

Patient characteristics

According to the Suita score, a total of 937 (78%) patients were classified as being at high risk (risk of developing CHD ≥5%; Table 1). The median (IQR) age was 75 (66-83) years old, 56% of the patients were men, and the median baseline NIHSS score was three points. Furthermore, 46% of the patients were prescribed or administered oral lipid-lowering agents at the time of discharge. Compared to the low-risk group, patients in the high-risk group were more likely to be older, men, obese, current smokers and drinkers, and diagnosed with hypertension, DM, dyslipidemia, and CKD (Table 1). However, the age, sex, hypertension, DM, dyslipidemia, and CKD were factors associated with the Suita score (Fig. 1). On dividing ischemic stroke into subtypes, large-artery atherosclerosis was the most prevalent subtype in the high-risk group. The rates of AF, CHD, and heart failure as well as the median NIHSS score at the time of admission, median LOS, mRS score at discharge, and prescription rate of antithrombotic agents at discharge did not differ markedly between the groups (Table 1).

Stroke recurrence

Stroke recurrence was observed in 66 cases during the follow-up period [TIA (n=3), ischemic stroke (n=52), and cerebral hemorrhaging (n=11)]. Patients with a ≥5% risk had a higher recurrence rate than those with a <5% risk, except for the 14% category (Fig. 3).

Association between the Suita score and one-year stroke recurrence

Kaplan-Meier curves showed that the 1-year stroke recurrence tended to be higher in the high-risk group than in the low-risk group (risk of developing CHD <5%); however, the difference was not statistically significant (6.1% vs. 3.4%,

Table 1. Patient Characteristics at Baseline.

	Total (N=1,204)	Suita score		p value
		<5% (n=267)	≥5% (n=937)	
Age -yr, median (IQR)	75(66-83)	72(53-83)	75(68-83)	<0.001
Male sex, n (%)	675(56)	96(36)	579(62)	<0.001
Medical history, n (%)				
Hypertension	889(74)	175(66)	714(76)	<0.001
Diabetes mellitus	407(34)	35(13)	372(40)	<0.001
Dyslipidemia	737(61)	134(50)	603(64)	<0.001
Atrial fibrillation	236(20)	60(23)	176(19)	0.180
Coronary heart disease	81(7)	15(6)	66(7)	0.412
Heart failure	329(27)	74(28)	255(27)	0.871
Chronic kidney disease	479(40)	70(26)	409(44)	<0.001
Current smoking, n (%)	252(21)	33(12)	219(23)	<0.001
Drinking habit, n (%)	118(10)	14(5)	104(11)	0.005
Obesity, n (%)	308(26)	53(20)	255(27)	0.015
NIHSS at admission, mdean (IQR)	3(1-6)	2(1-6)	3(1-6)	0.272
LDL-cho (mg/dL), median (IQR)	120(98-142)	101(88-125)	124(104-147)	<0.001
HDL-cho (mg/dL), median (IQR)	50(42-60)	55(46-64)	49(40-58)	<0.001
Subtype of stroke, n (%)				0.063
TIA	47(4)	12(5)	35(4)	
Large-artery atherosclerosis	229(19)	53(20)	176(19)	
Cardioembolism	277(23)	47(18)	230(25)	
Small-vessel occlusion	237(20)	57(21)	180(19)	
Stroke of other determined etiology	165(14)	48(18)	117(13)	
Stroke of undetermined etiology	249(21)	50(19)	199(21)	
Length of hospital stay (days), median (IQR)	14(11-19)	14(11-19)	14(10-19)	
Modified Rankin Scale at discharge, n (%)				0.230
0-1	688(57)	162(61)	526(56)	
2-3	245(20)	55(21)	190(20)	
4-5	271(23)	50(19)	221(24)	
Prescription drugs at discharge, n (%)				
Antithrombotic agents	1164(97)	254(95)	910(97)	0.110
Oral lipid lowering agents	552(46)	91(34)	461(49)	<0.001

Data are presented as the median (IQR) or number (%) of patients. Heart failure was defined as BNP (brain natriuretic peptide) ≥80 pg/mL at baseline. Current smoking was defined as smoking ≥1 cigarette per day before the onset. Drinkng habit was defined as drinking regularly an estimated amount of >48.6g of pure alcohol per day. Obesity was defined as BMI (body mass index) ≥25 at baseline. IQR: inter-quartile range, NIHSS: National Institutes of Health Stroke Scale, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, TIA: transit ischemic attack

log-rank p=0.095; Fig. 4). In the multivariate analysis, after adjusting for confounding and prognostic factors, such as non-small-vessel occlusion and the prescription of lipid-lowering agents at the time of discharge, a ≥5% predicted CHD risk was associated with the 1-year stroke recurrence rate after the initial onset (adjusted HR=2.20, 95% CI=1.00-4.91, p=0.049; adjusted HR=2.00, 95% CI=1.01-4.14, p=0.048; adjusted HR=0.42, 95% CI=0.24-0.73, p=0.002; Table 2).

Discussion

Using the Suita score, we evaluated the 10-year risk of CHD in Japanese patients who had experienced their first-ever AIS or TIA. We found that, according to the Suita score, 78% of patients could be classified as high risk (≥5% risk). After adjusting for confounders, the one-year stroke recurrence tended to be higher in the high-risk group than in the low-risk group.

The Suita score was likely associated with one-year stroke recurrence in first-ever AIS and TIA patients because the factors included in the Suita score (such as hypertension, DM, dyslipidemia, smoking status, and CKD) are similar to the risk factors of stroke recurrence (hypertension, DM, dyslipidemia, and smoking). As previously reported, hypertension is independently associated with an increased risk of recurrent stroke in the long-term follow-up of elderly stroke patients (17). Furthermore, in young ischemic stroke patients, a high acute-phase BP was independently associated with a high risk of recurrent stroke (18). The Suita score includes the CKD stage in its evaluation, rather than considering the history of cardiovascular disease, such as prior CHD, stroke, and peripheral artery disease, which is used in the FRS for risk assessment. The Suita score also helps evaluate

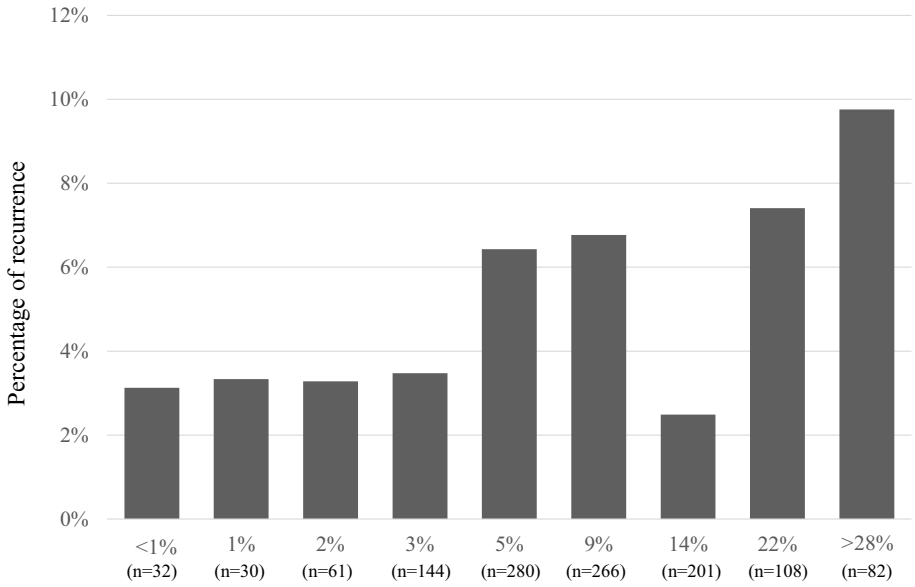

Figure 3. **One-year stroke recurrence rate by the Suita score.**

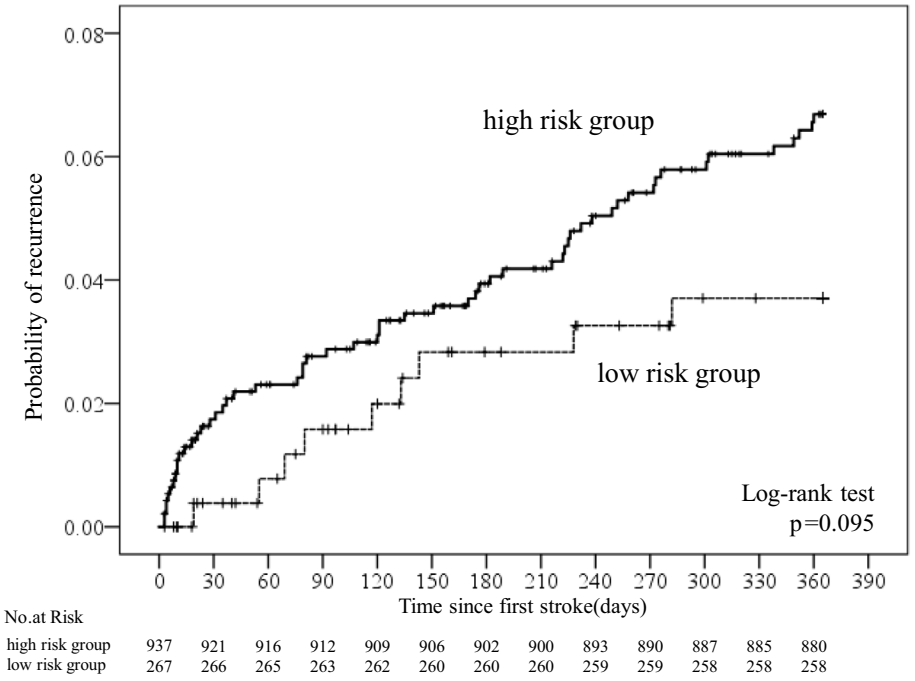

Figure 4. **Kaplan-Meier survival curves for stroke recurrence within one year according to the Suita score.**

lipid abnormalities using the LDL-C level instead of the total cholesterol level. The CKD stage is a relatively novel biomarker that can predict the risk of developing CHD (19-21). The present study results also suggested that the CKD stage can predict the risk of stroke recurrence. In Japan, the CKD stage is independently associated with acute recurrent cerebral infarction with AF (22). Previous studies that have assessed risk factors associated with stroke recurrence showed that lowering the LDL-C levels was able to prevent stroke recurrence (23-25). Therefore, the Suita score, which includes the CKD stage and LDL-C level, was associated with stroke recurrence in patients with AIS and TIA.

Our study also showed that patients in the high-risk group, based on the Suita score, were more likely to be prescribed lipid-lowering agents at the time of discharge than those in the low-risk group; of note, <50% of patients in this study were prescribed these agents. Although guidelines indicate that lipid-lowering agents are the gold standard for managing dyslipidemia and reducing the recurrence of atherosclerotic cardiovascular diseases (26), these agents are prescribed at relatively low rates in Japan. For high-risk patients, increasing the use of lipid-lowering agents may reduce the risk of stroke recurrence. We used the Suita score

Table 2. Multivariate Cox Regression Analysis Associated with One-year Stroke Recurrence.

Variables	Adjusted model		
	HR	95%CI	p value
Suita score ≥5%	2.00	1.01 to 4.14	0.048
Atrial fibrillation	0.75	0.40 to 1.41	0.38
Non-small vessel occlusion	2.20	1.00 to 4.91	0.049
Coronary heart disease	0.72	0.23 to 2.30	0.58
Antithrombotic agent at discharge	0.68	0.24 to 2.51	0.68
Oral lipid lowering agents at discharge	0.42	0.24 to 0.73	0.002

The reference of the Suita score was under 5%. HR: hazard ratio, CI: confidence interval

in this study because the patients were Japanese. In Western populations, the FRS may provide a similar predictive value for one-year stroke recurrence. In the present study, whether or not the Suita score could predict stroke recurrence was unclear. The relationship of the Suita score with the long-term prognosis of stroke recurrence in patients with first-ever AIS and TIA should be explored in future studies.

Strengths and limitations

The major strength of the present study is that all patients were followed up at our hospital. We confirmed that all patients who needed to be hospitalized for stroke treatment were admitted to our hospital. Therefore, the primary outcome measurement was completed for all patients in this study. Furthermore, baseline data were measured the day after admission, with similar protocols used for all patients. Consequently, there were only a few missing exposures and no missing adjustment factors.

However, despite these strengths, several limitations should also be considered when interpreting the results of our study. First, recall bias may have affected several measurements for the adjusted factors, including smoking and drinking habits. However, to minimize the risk of bias, we collected data for these variables from patients and their families. Second, the Suita scores may have been overestimated because BP measurements were conducted at the time of admission, during the acute phase of AIS. Since the BP is generally higher at the onset of cerebral infarction than before onset, the Suita score would also be higher during the acute phase than in the post-acute phase. Third, since our study focused on the Japanese population, the generalizability of our findings may be limited. This study was conducted at a single center in Japan; therefore, the results may not be directly applicable to other hospitals in Japan or other countries. Furthermore, because our hospital handles a larger number of stroke patients than typical Japanese hospitals, the standard for stroke treatment may vary. Although we examined the patient characteristics according to the risk as determined by the Suita score, we were unable to determine why only the 14% group had a reduced rate of stroke recurrence. A possible explanation is that the median age of this group was 2 years younger than that of the 22% and >28% groups. We hope to assess this in a larger cohort in the future. Fourth, the uncertainty regarding the dosing status of all patients one year after AIS and TIA onset is also a potential limitation of this study. Finally, since we did not observe the patients continuously over the 10-year period of this analysis, whether or not the predicted risk is similar to the actual risk of developing CHD is unclear. Therefore, the observation period will need to be extended in future studies.

Conclusions

The Suita score is used to predict the 10-year prognosis of developing CHD. However, when adapted for ischemic stroke using the same mechanism, it correlated with short-term recurrence events within one year. These findings suggest that the Suita score may be useful for predicting the long-term prognosis of CHD development as well as short-term recurrence in patients with first-ever AIS and TIA.

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

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