



The Added Prognostic Value of Intracranial Artery Morphology to Predict Non-Cardioembolic Ischemic Stroke

두개내 동맥의 형태학적 특성이 비심인성 색전 뇌경색 발생 위험에 미치는 추가적 예후 가치

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Purpose: To assess the added prognostic value of the morphologic characteristics of intracranial arteries in the risk modeling of a future non-cardioembolic stroke.

Materials and Methods: This retrospective study included 86 patients without acute ischemic stroke who first underwent magnetic resonance imaging (MRI) including the time-of-flight magnetic resonance angiography (TOF-MRA) at 3T. Diffusion-weighted imaging (DWI) was performed for the follow-up imaging of these patients > 120 days after the initial MRI. The TOF-MRA result was used to analyze three morphological characteristics: dilatation, stenosis, and tortuosity. The presence of acute ischemic stroke was assessed using the follow-up DWI data. We built two prognostic models: model 1 includes the conventional stroke-risk factors, while model 2 includes the conventional risk factors and the morphologic characteristics of the intracranial arteries. We used the likelihood-ratio test to compare these two models. The models' performances were evaluated using Harrell's concordance index.

Results: Fourteen patients suffered non-cardioembolic strokes. The performances of the two models differed significantly regarding the future-risk modeling of the non-cardioembolic stroke ($p = 0.031$). The Harrell's concordance index of model 2 (0.78 ± 0.05) exceeded that of model 1 (0.72 ± 0.07).

Conclusion: In addition to the conventional stroke-risk factors, the morphologic characteristics of the intracranial arteries were useful in the modeling of the future risk of the non-cardioembolic ischemic stroke.

Index terms

Cerebral Arteries
Morphology
MRI Angiography
Brain Infarction
Intracranial Arteriosclerosis

Received May 24, 2017

Revised August 8, 2017

Accepted October 21, 2017

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INTRODUCTION

Time-of-flight magnetic resonance angiography (TOF-MRA) is one of the most commonly used magnetic resonance imaging (MRI) for assessing intracranial arterial disease. TOF-MRA is useful to detect and diagnose localized arterial disease, such as steno-occlusive lesions or aneurysms. In addition, given its relatively large field of view and high spatial resolution, TOF-MRA provides a general overview of the morphological characteristics of imaged vasculature (1, 2). Information regarding morphological characteristic, such as tortuosity and dilatation,

are well-known morphological characteristics of intracranial arteries (2-6). Previous studies have suggested that these morphological characteristics are important imaging phenotypes that reflect the atherosclerotic changes and aging of intracranial arteries (1-3, 5, 7).

Atherosclerotic changes in intracranial arteries are important causes of acute ischemic stroke. Therefore, previous studies have suggested that there is an association between the morphological characteristics of intracranial arteries and acute ischemic stroke (3, 4, 8, 9). However, previous reports have only suggested that there is an association between them using cross

sectional studies (3, 4, 8-11). There has been limited assessment of causality. One study suggested the prognostic value of the morphological characteristics of the vasculature (12). However, this study only focused on young patients with connective tissue disease; therefore, it is difficult to generalize their results to the general population. In this study, we evaluated the morphological characteristics of intracranial arteries using TOF-MRA at 3T. In a retrospective cohort, we then assessed the added prognostic value of the morphological characteristics of intracranial arteries to predict future ischemic stroke in addition to conventional stroke risk factors.

MATERIALS AND METHODS

Study Population

We systemically reviewed our radiology database to create a retrospective cohort (Fig. 1). We identified patients according

to the following inclusion criteria: 1) patients who first underwent MRI, including TOF-MRA on 3T; 2) no acute ischemic stroke on initial MRI; 3) follow-up MRI with diffusion-weighted imaging (DWI); and 4) follow-up interval ≥ 120 days. We identified 29466 patients (41173 MRIs) who underwent brain MRI between January 2011 and September 2015. A total of 22774 patients were excluded because they underwent MRI without imaging follow-up and 2900 because they had MRI for brain neoplastic lesions, endovascular surgery, or epilepsy. Finally, we identified 3878 patients who underwent two or more MRI. Among these patients, we excluded the following: 1) patients who underwent first MRI at 1.5T ($n = 1284$) because better image quality and spatial resolution of MRA at 3T than 1.5T, those were critical for diameter measurement and morphological evaluation; 2) patients who did not first undergo TOF-MRA ($n = 882$); 3) those without DWI on follow-up MRI ($n = 264$); and 4) those in whom the interval between the initial TOF-MRA and

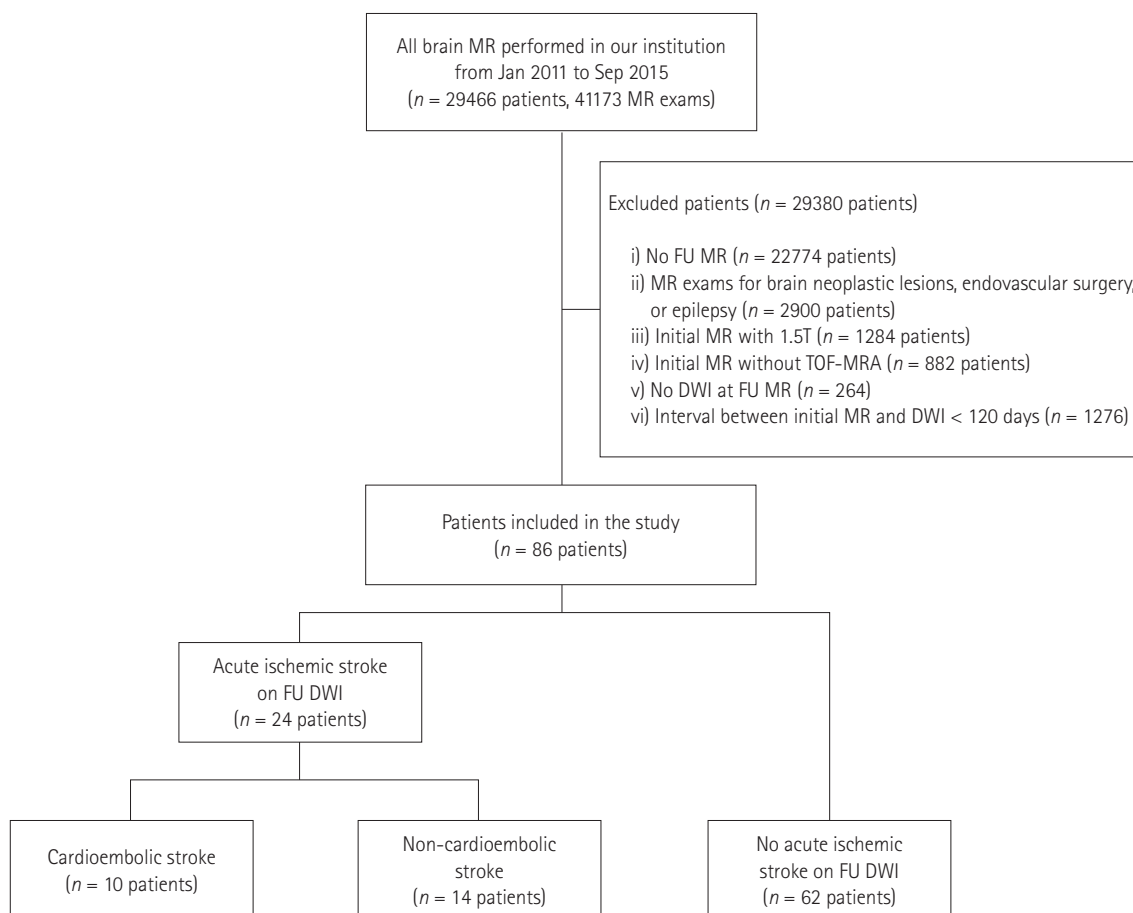


Fig. 1. Patient selection flow chart. After systematic evaluation of the radiology database, 86 patients were included in this study. Among them, 14 patients had acute non-cardioembolic ischemic strokes.

DWI = diffusion-weighted imaging, FU = follow-up, MR = magnetic resonance, TOF-MRA = time-of-flight magnetic resonance angiography

DWI was < 120 days ($n = 1276$). A total of 86 patients (40 males and 46 females, age 69.9 ± 10.9 years old) were included. This study was approved by the Institutional Review Board (KC15RISI0558). Informed consent was waived for this retrospective study. The reasons for first MRI was suspected stroke or transient ischemic attack ($n = 27$), headache ($n = 26$), dizziness or syncope ($n = 17$), known arterial stenosis ($n = 5$), regular follow-up after previous stroke ($n = 7$), others such as traumatic brain injury ($n = 4$). Reasons for second MRI was suspected stroke or transient ischemic attack ($n = 49$), headache ($n = 3$), dizziness or syncope ($n = 28$), known arterial stenosis ($n = 2$), others such as traumatic brain injury ($n = 4$).

We assessed the following patient characteristics from the medical records at the time of first MRI: 1) age; 2) sex; 3) hypertension; 4) type 2 diabetes; 5) dyslipidemia; 6) smoking history; 7) previous coronary artery disease; 8) previous ischemic stroke history; and 9) the degree of proximal internal carotid artery (ICA) stenosis. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or current treatment with antihypertensive drugs. Patients taking medications for diabetes (insulin or oral hypoglycemic) were considered to have diabetes mellitus. Dyslipidemia was diagnosed if the patient had any of the following: low-density lipoprotein cholesterol level ≥ 140 mg/dL, high-density lipoprotein cholesterol level ≤ 40 mg/dL, triglyceride level ≥ 150 mg/dL, or treatment with lipid-lowering medications (13). Patients were considered to have a history of coronary artery disease if they had previous angina pectoris, myocardial infarction, or coronary artery bypass.

MRI Protocols




All initial MRIs were performed in a 3T machine (MAGNETOM Verio, Siemens AG Healthcare Sector, Erlangen, Germany) with a 16-channel head and neck coil. Initial MRI included three-dimensional (3D) TOF-MRA and T2-weighted images of the brain, and 3D TOF-MRA of the neck. Other sequences, such as fluid attenuation inversion recovery (FLAIR) images or T1-weighted images were performed according to the clinical circumstances. 3D TOF-MRA of the brain was performed with 6 slabs, each including 40 axial slices of 0.5-mm thickness and no interslice gaps using the following parameters: repetition time/echo time/flip angle = 22 ms/3.6 ms/18°, 384×331 for the fre-

quency/phase encoding matrix, a number of excitation 1, and a bandwidth of 186 Hz/pixel. A $0.4 \times 0.4 \times 0.5$ mm voxel was acquired after interpolation. A saturation band 40 mm thick was applied for venous flow suppression. The generalized autocalibrating partially parallel acquisitions parameters were set to an acceleration factor of 2 in the phase encoding direction with 24 reference k-space lines for calibration. The total acquisition time was 7 min and 28 s. Other MRIs were acquired by vendor-standard parameters. Follow-up DWI imaging was performed in three different MR units [MAGNETOM Verio, Signa excite HD (GE Medical Systems, Milwaukee, WI, USA), or Achieva (Philips Healthcare, Best, the Netherlands)] according to the clinical circumstances, using standard $b = 1000$ s/mm².

Evaluation of the Morphological Characteristics of Intracranial Arteries on TOF-MRA

Two radiologists who were blinded to the clinical parameters evaluated the morphological characteristics of the initial TOF-MRA. On the vertical and horizontal rotation maximal intensity projection images of the initial TOF-MRA, the reviewer analyzed three morphological characteristics of the intracranial arteries (Table 1). These included dilatation, stenosis, and tortuosity. In order to assess intracranial artery dilatation, we measured the maximal diameter of the basilar artery (BA), and the terminal segments of both distal ICAs. The mean of these three maximal diameters were used as dilatation measurements of the intracranial arteries. The stenosis score was determined by the number of stenotic segments among seven pre-defined segments [terminal segments of both distal ICA, M1 segments of both middle cerebral artery (MCA), and the V4 segments of the vertebral artery (VA) and BA]. Stenotic segments were defined as those with $\geq 50\%$ stenosis based on the Warfarin-Aspirin Symptomatic Intracranial Disease criteria (14). Tortuosity was assessed in three segments of the intracranial arteries, including M1 segments of both MCA and BA, on a three-point scale. Zero indicates linear shape, 1 curved shape, and 2 sigmoid shape (1). The summation of these three segment scores was used to calculate the tortuosity score. The other four segments (terminal segments of both distal ICA and V4 segments of the VA) were not evaluated for tortuosity given their natural tortuosity.

Table 1. Evaluation of Morphological Characteristics on TOF-MRA

Category	Definition
Dilatation	The mean maximal diameter of BA and terminal segments of both distal ICAs
Stenosis	The number of stenotic segments* among the terminal segments of both distal ICAs, M1 segments of both MCA, V4 segments of VA, and BA
Tortuosity	Summation of three segment scores (M1 segments of both MCAs and BA)
	<div style="display: flex; justify-content: space-around; align-items: flex-end;"> <div style="text-align: center;"> <p>0 for linear shape</p>  </div> <div style="text-align: center;"> <p>1 for curved shape</p>  </div> <div style="text-align: center;"> <p>2 for sigmoid shape</p>  </div> </div>

*Stenotic segments; $\geq 50\%$ stenosis using WASID.

BA = basilar artery, ICA = internal carotid artery, MCA = middle cerebral artery, TOF-MRA = time-of-flight magnetic resonance angiography, VA = vertebral artery, WASID = Warfarin-Aspirin Symptomatic Intracranial Disease

Evaluation of Brain MRI and Outcome Definitions

Previous ischemic stroke lesions (territorial or lacunar infarcts) and white matter hyperintensities were assessed on T2-weighted and FLAIR images from the first series of images. The presence of white matter hyperintensities was graded according to the visual rating scale proposed by Fazekas and Schmidt, with scores ranging from 0 to 3 (15). The degree of ICA stenosis was measured according to the North American Symptomatic Carotid Endarterectomy Trial criteria on TOF-MRA of the neck area (16).

Acute ischemic stroke was defined via follow-up DWI. If the patients had diffusion-restriction lesions on follow-up DWI, the patients were considered as having had acute ischemic strokes. If the patients had no diffusion-restriction lesions on follow-up DWI, the patients were considered as not having acute ischemic stroke at that time. An experienced stroke neurologist reviewed the medical records and MR of the patients with acute ischemic stroke. This neurologist identified cardioembolic strokes by the following characteristics: the presence of a medium-sized (maximal diameter of the lesion, 15 to 30 mm) or large (> 30 mm) cerebral infarction; cerebral cortex involvement; stroke onset during ordinary daily activities; duration of focal neurological deficit > 24 hours; and identification of a commonly accepted cardioembolic source in the absence of confirmatory clinical (ipsilateral carotid bruit) or investigative results (Doppler ultrasonography, carotid angiography or MRA) of the lesions in the ipsilateral supra-aortic trunks (17, 18).

Statistical Analysis

To investigate the added value of the morphological characteristics of the intracranial arteries to future non-cardioembolic stroke risk, two prognostic models for future non-cardioembol-

ic stroke were compared in order using the following method.

First, we performed univariate analysis using Cox proportional hazard analysis for future non-cardioembolic stroke risk with conventional stroke risk factors and the three morphological characteristics of intracranial arteries (dilatation, stenosis, and tortuosity). Multivariate analysis was then performed using the Cox regression model with the significant factors from univariate analysis ($p < 0.2$) to build two multivariate models. Model 1 only included conventional risk factors, while model 2 included conventional risk factors and additional morphological characteristics of the intracranial arteries. Before comparison of two models, multicollinearity was confirmed by calculating the variable inflation factor of each variable included in the models. A variable inflation factor > 2 was considered multicollinearity, which influenced the estimated power. The likelihood-ratio test was used to compare the two models, with and without the morphological characteristics. In addition, the performance of models 1 and 2 was evaluated using the Harrell concordance index (C-index). A C-index value of 0.5 indicates random prediction, while 1.0 indicates perfect prediction. We also performed the same analysis for all acute ischemic strokes (non-cardioembolic and cardioembolic strokes) to evaluate whether there was prognostic value for modeling of all acute ischemic stroke surrogates. All analyses were performed with R (version 3.2.2, R Foundation, Vienna, Austria; www.R-project.org) statistical packages.

RESULTS

Patient Characteristics

Twenty-four of 86 patients experienced acute ischemic stroke

Table 2. Patient Characteristics (*n* = 86)

Variable	No Stroke (<i>n</i> = 62)	Non-Cardioembolic Stroke (<i>n</i> = 14)	Cardioembolic Stroke (<i>n</i> = 10)	<i>p</i> -Value
Age (year)	69.5 (64, 77)	67.5 (63, 73)	80 (67, 82)	0.114
Sex (%)				0.939
Female	33 (53.2)	8 (57.1)	5 (50.0)	
Male	29 (46.8)	6 (42.9)	5 (50.0)	
Hypertension (%)	36 (58.1)	13 (92.9)	9 (90.0)	0.012
Diabetes (%)	20 (32.3)	3 (21.4)	4 (40.0)	0.603
Dyslipidemia (%)	15 (24.2)	5 (35.7)	5 (50.0)	0.208
Coronary artery disease (%)	9 (14.5)	3 (21.4)	4 (40.0)	0.151
Previous territorial infarction (%)	10 (16.1)	5 (35.7)	3 (30.0)	0.201
White matter hyperintensity (%)				0.919
None	31 (50.0)	8 (57.1)	4 (40.0)	
Mild	19 (30.6)	3 (21.4)	3 (30.0)	
Moderate	7 (11.3)	1 (7.1)	2 (20.0)	
Severe	5 (8.1)	2 (14.3)	1 (10.0)	
Lacune (%)	24 (38.7)	7 (50.0)	6 (60.0)	0.382
ICA stenosis (NASCET method, %)	0 (0, 0)	0 (0, 0)	0 (0, 32)	0.117
Mean diameter (cm)	2.8 (2.5, 2.9)	3.1 (3, 3.3)	2.8 (2.6, 3.4)	0.005
Tortuosity score	3 (2, 4)	3 (2, 4)	2 (2, 4)	0.35
Stenosis score (%)				0.726
0	54 (85.5)	11 (78.6)	9 (90)	
1	7 (11.3)	2 (14.3)	0 (0)	
2	2 (3.2)	0 (0)	1 (10)	
3	0 (0)	1 (7.1)	0 (0)	
Observation duration (days)	611.05 ± 376.75	683.14 ± 360.54	660.80 ± 391.06	0.778

p-values were calculated using the chi-square or Mann-Whitney U test. Values are median with interquartile range in parentheses or number of patients with percentages in parentheses.

ICA = internal carotid artery, NASCET = North American Symptomatic Carotid Endarterectomy Trial

Table 3. Univariate Analysis Result for HRs for Ischemic Strokes (*n* = 86)

Variable	HR (95% CI) for Non-Cardioembolic Ischemic Stroke (<i>n</i> = 14)	<i>p</i> -Value	HR (95% CI) for Acute Ischemic Stroke (<i>n</i> = 24)	<i>p</i> -Value
ICA stenosis	1.04 (1.01–1.07)	0.01*	1.04 (1.01–1.06)	< 0.001*
Hypertension	4.12 (0.54–31.8)	0.14 [†]	3.57 (0.83–15.3)	0.07 [†]
Diabetes mellitus	0.66 (0.18–2.40)	0.52	1.02 (0.42–2.47)	0.97
Dyslipidemia	1.35 (0.44–4.15)	0.59	1.89 (0.81–4.38)	0.13 [†]
Coronary artery disease	1.67 (0.45–6.17)	0.44	2.76 (1.10–6.92)	0.02*
Previous territorial infarction	2.84 (0.92–8.74)	0.06 [†]	2.53 (1.06–6.06)	0.03*
Lacune	1.27 (0.44–3.62)	0.66	1.54 (0.69–3.45)	0.29
White matter hyperintensity		0.75		0.69
Mild	1.10 (0.28–4.40)		1.52 (0.54–4.29)	
Moderate	0.37 (0.05–2.97)		0.79 (0.22–2.83)	
Severe	0.60 (0.08–4.84)		0.60 (0.12–2.91)	
Mean diameter	3.27 (1.10–9.74)	0.04*	2.31 (0.89–6.02)	0.11 [†]
Tortuosity score	1.35 (0.88–2.07)	0.17 [†]	1.25 (0.89–1.73)	0.20 [†]
Stenosis score	1.99 (0.91–4.34)	0.07 [†]	1.70 (0.88–3.24)	0.15 [†]

**p* < 0.05.

[†]*p* < 0.2.

CI = confidence interval, HR = hazard ratio, ICA = internal carotid artery

on follow-up DWI. Among them, fourteen patients had non-cardioembolic strokes. Hypertension was more frequent in the patients in the stroke group ($p = 0.012$) than it was in the non-stroke group. The mean diameters were larger in patients with strokes than in those without stroke ($p = 0.025$). The clinical characteristics of the patient population according to the occurrence of ischemic stroke and its type are listed in Table 2.

Univariate Analysis of Future Stroke Risk

Univariate analysis (Table 3) revealed that both the degree of ICA stenosis and the mean diameter of the intracranial arteries were significantly associated with future non-cardioembolic ischemic stroke risk ($p < 0.05$). Hypertension, previous territorial infarcts, the tortuosity score, and stenosis score were also marginally associated with future ischemic stroke ($p < 0.2$). For all ischemic strokes, the degree of ICA stenosis, history of coronary artery disease, and previous territorial infarction were significantly associated with future ischemic stroke risk. Hypertension, dyslipidemia, the mean diameter of the intracranial arteries, tortuosity score, and stenosis scores were marginally associated with future ischemic stroke ($p < 0.2$).

Multivariate Analysis of Future Stroke Risk

The multivariate analysis results are presented in Table 4.

Among the three morphological characteristics, the mean diameter of the intracranial arteries was significantly associated with future non-cardioembolic strokes [hazard ratio (HR) 9.45, 95% confidence interval (CI) 1.41–63.55, $p = 0.02$] (Fig. 2). The stenosis score was marginally associated with future non-cardio-

embolic strokes (HR 2.26, 95% CI 0.84–6.07, $p = 0.11$). In contrast, tortuosity was not associated with future non-cardioembolic strokes (HR 0.97, 95% CI 0.57–1.63, $p = 0.9$).

The performance of models 1 (conventional risk factors only) and 2 (conventional risk factors and morphological findings) were significantly different with regard to modeling future non-cardioembolic stroke risk ($p = 0.031$). Harrell's C-index of model 2 (0.75, 95% CI 0.571–0.929) was higher than that of model 1 (0.678, 95% CI 0.467–0.889). In contrast, models 1 and 2 did not differ in modeling the future risk of all ischemic strokes ($p = 0.367$). The C-index of model 1 (0.717, 95% CI 0.560–0.874) was similar to that of model 2 (0.736, 95% CI 0.587–0.885). We did not identify multicollinearity of the included variables in any of the models.

DISCUSSION

The association between imaging characteristics of the intracranial arteries, atherosclerotic changes and aging has been previously reported. The presence of a stenotic segment is a well-known manifestation of atherosclerotic changes (1, 19, 20). Furthermore, tortuous and dilated intracranial arteries, aging and hypertension have also been reported as important atherosclerosis risk factors (3, 5, 7, 21). We investigated three morphological characteristics of the intracranial arteries. Our result suggested that three morphological characteristics of intracranial arteries may be imaging phenotypes and surrogates for atherosclerotic changes. We think that the prognostic value of a high burden of intracranial atherosclerotic changes may be associat-

Table 4. Multivariate Analysis Result for HRs for Ischemic Stroke ($n = 86$)

Variable	Non-Cardioembolic Stroke				All Ischemic Stroke			
	Model 1 HR (95% CI)	p -Value	Model 2 HR (95% CI)	p -Value	Model 1 HR (95% CI)	p -Value	Model 2 HR (95% CI)	p -Value
Hypertension	3.64 (0.46–28.59)	0.22	3.95 (0.44–35.28)	0.22	2.71 (0.60–12.29)	0.20	2.41 (0.51–11.34)	0.27
Previous territorial infarction	3.49 (1.03–11.87)	0.04	3.55 (1.03–12.20)	0.04	4.14 (1.39–12.31)	0.01	4.04 (1.28–12.77)	0.02
ICA stenosis	1.04 (1.01–1.08)	0.009	1.04 (1.00–1.08)	0.061	1.04 (1.02–1.07)	0.002	1.04 (1.02–1.07)	0.002
Coronary artery disease	NA		NA		2.54 (0.87–7.43)	0.09	2.24 (0.77–6.48)	0.14
Dyslipidemia	NA		NA		0.98 (0.33–2.91)	0.97	1.02 (0.33–3.13)	0.98
Mean diameter	NA		9.45 (1.41–63.55)	0.02	NA		2.01 (0.66–6.10)	0.22
Tortuosity score	NA		0.97 (0.57–1.63)	0.90	NA		0.95 (0.66–1.39)	0.80
Stenosis score	NA		2.26 (0.84–6.07)	0.11	NA		1.65 (0.74–3.66)	0.22

Model 1: Analysis with conventional risk factors, Model 2: Analysis with conventional risk factors and morphological characteristics of the intracranial arteries.

CI = confidence interval, HR = hazard ratio, ICA = internal carotid artery, NA = not available

ed with future non-cardioembolic stroke. An interesting finding is that the dilatation of intracranial artery was more important than other morphologic characteristics, including stenosis or tortuosity. One study suggested that the non-stenotic intracranial arteries of patients with acute ischemic stroke patients showed the tendency of positive remodeling (11). Also, increased intracranial arterial diameter was suggested as a possible marker of chronic vascular insufficiency of the brain and was associated with vascular risk factors (3, 4).

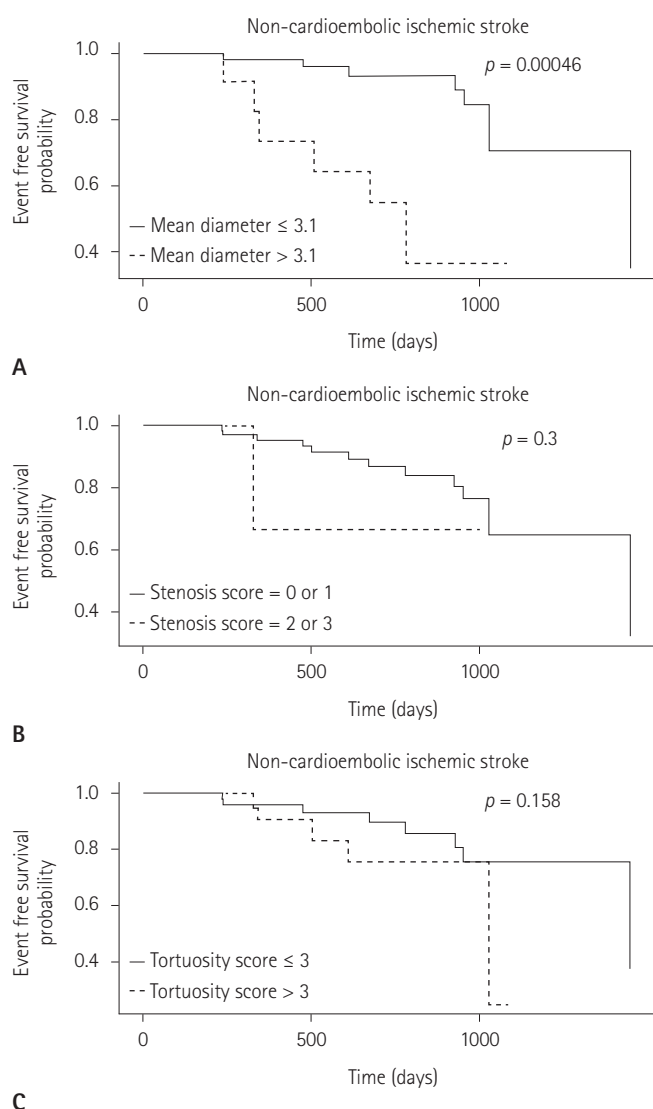


Fig. 2. Survival curves of non-cardioembolic strokes according to three morphological characteristics. Three survival curves for non-cardioembolic stroke according to the intracranial arterial diameter (**A**), stenosis score (**B**) and tortuosity score (**C**). A mean intracranial arterial diameter > 3.1 was associated with significant risk for future non-cardioembolic stroke ($p < 0.001$). Tortuous intracranial arteries were also associated with a tendency toward a high probability of future non-cardioembolic stroke ($p = 0.158$).

In our study, the imaging surrogates of intracranial atherosclerosis had added value for future non-cardioembolic stroke risk modeling. Because there is an association between the morphological characteristics of intracranial arteries and some stroke risk factors, one might argue that there was a multicollinearity effect between the risk factors and morphological characteristics. However, our results suggested the lack of multicollinearity between known stenotic risk factors and morphological characteristics. In addition, the mean diameters of intracranial arteries were independently associated with future non-cardioembolic stroke in model 2. The lack of multicollinearity might be explained by the unique value of imaging surrogates (22). There may be individual variability of imaging phenotypes among patients with the same risk factors and demographics. This was due to different susceptibility of individual risk factors. For this reason, imaging surrogates have different clinical significance from the risk factors. Different imaging phenotypes might result from variation in susceptibility to stroke and atherosclerotic risk factors. The morphologic characteristics of intracranial arteries were thought to be imaging the phenotypes of intracranial arterial atherosclerosis, with additional clinical significance.

Acute ischemic stroke is a collection of heterogeneous diseases causing brain tissue ischemia. The Trial of ORG 10172 in Acute Stroke Treatment classification is one example that highlights the heterogeneous nature of ischemic stroke (23). Cardioembolic stroke, which accounts for approximately one in four ischemic strokes, has a relatively different pathophysiology and treatment strategy than does other types of ischemic stroke (23-25). Embolism from the heart to the brain results from one of the following mechanisms: structural heart abnormalities (e.g., left ventricular aneurysm), cardiac valvular disease, right-to-left shunts (paradoxical embolism), and rhythm disturbance (6). Dilatation, tortuosity and stenotic segments of the intracranial arteries are associated with atherosclerotic changes. However, these characteristics were not closely linked to the mechanism of cardioembolic stroke. This finding explains why the morphological characteristics of intracranial arteries do not add value to the prediction of all types of ischemic stroke. One clinical study found that atrial fibrillation and the sudden onset of symptoms were independently associated with cardioembolic stroke; in contrast, hypertension, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia and age were all

significantly associated with atherothrombotic infarctions (26). In our study, hypertension was significantly more frequent in the non-cardioembolic stroke group than it was in the cardioembolic stroke group.

We performed a systematic, retrospective review to determine future stroke risk based on conventional ischemic stroke risk factors, in addition to the morphologies of intracranial arteries. We found that the risk of future ischemic strokes is influenced by coronary artery disease, hypertension, stenosis of the proximal ICA, and imaging evidence of prior ischemic strokes. These findings are concordant with those of previous reports (27-29). This concordance also suggests that our retrospective cohort was relevant to assess future ischemic stroke risk. A history of coronary artery disease particularly increases the risk of future ischemic stroke, although it does not affect the risk of future non-cardioembolic stroke.

In this study, we assessed the added prognostic value of the morphological characteristics of intracranial arteries to predict future ischemic stroke risk. When these morphological characteristics were combined with conventional risk factors, they were valuable in the prediction of future non-cardioembolic strokes. Among the three morphological characteristics that we included, the increased mean diameter or dilatation of the intracranial arteries was independently associated with future non-cardioembolic stroke risk. Stenosis of the intracranial arteries was also marginally associated with future risk of non-cardioembolic stroke.

This study has several limitations. First, the sample size of included patients was relatively small. Fortunately, however, we reviewed a large number of patients systematically. The prognostic values of known ischemic stroke risk factors were concordant with a previous large-scale study. Small sample size and small number of event might limit the statistical power of the result. Future study with large subject is required to validate our result. Due to small size of population, subgroup analysis according to a variety of stroke etiology cannot be done. Second limitation is that our retrospective approach involved a degree of selection bias. Patients who visited another hospital for stroke episode cannot be included. Furthermore, we could not include other known risk factors, such as smoking, heart disease (other than coronary artery disease), alcohol consumption, or family history, because this information was not available in

the medical records. Third limitation, which came using TOF-MRA, is that we could not detect some atherosclerotic changes. Because TOF-MRA only visualizes the lumen of the vessel, atherosclerotic plaques with positive remodeling cannot be detected (10, 11). Instead, we analyzed the diameter, degree of tortuosity and stenosis, all of which are well demonstrated on TOF-MRA. These characteristics are also associated with atherosclerotic changes. Additionally, the spatial resolution of the analyzed TOF-MRA might be not enough to quantify the degree of intracranial arterial stenosis, and measured value might be overestimating the true stenosis. Instead, we used the number of significantly stenotic segment, which might not be enough to represent the significance of stenosis degree of each segment. Although the number of stenotic segment showed marginal significance, future study is needed to validate this finding. Lastly, we used image-based definitions of acute ischemic stroke, rather than using medical records. Ischemic stroke was defined as only positive on DWI. Therefore, small lacunar infarcts or transient ischemic attack may have been missed. Also, because we defined stroke events based on diffusion-restriction lesion, we may miss subacute and chronic infarctions, or acute infarct patients those did not underwent DWI.

In conclusion, in combination with conventional stroke risk factors, assessment of the morphological characteristics of intracranial arteries adds value to predicting the risk of future non-cardioembolic ischemic stroke.

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두개내 동맥의 형태학적 특성이 비심인성 색전 뇌경색 발생 위험에 미치는 추가적 예후 가치

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목적: 두개내 동맥의 형태학적 특성이 비심인성 색전 뇌경색 발생 위험에 미치는 추가적 예후 가치를 분석하고자 하였다.

대상과 방법: 후향적 연구를 시행하였으며, 급성 뇌경색이 없으면서 유체 속도 강조 자기공명 혈관조영술(time-of-flight magnetic resonance angiography; 이하 TOF-MRA)을 포함한 3T 자기공명영상을 시행한 86명의 환자가 등록되었다. 환자들은 첫 자기공명영상 시행 이후 > 120일 뒤에 확산강조영상(diffusion-weighted imaging; 이하 DWI)을 포함한 추적검사를 시행하였다. TOF-MRA에서 두개내 동맥의 확장, 협착, 사행의 세 가지 형태학적 특성을 분석하고 추적 DWI에서 급성 허혈성 뇌경색 여부를 평가하여 두 가지 예측 모형을 만들었다. 모형 1은 전통적 뇌경색 위험인자를, 모형 2는 이와 두개내 동맥의 형태학적 특성을 포함하였다. 두 모형 비교에 우도비 검정(likelihood-ratio)을 사용하였고, 모형의 성능은 Harrell의 일치 지수로 평가하였다.

결과: 14명의 환자가 비심인성 색전 뇌경색으로 진단되었고, 두 모형의 성능은 비심인성 색전 뇌경색 발생 위험 예측에 있어서 유의한 차이를 보였다($p = 0.031$). Harrell의 일치 지수는 모형 2 (0.78 ± 0.05)가 모형 1 (0.72 ± 0.07)보다 높았다.

결론: 전통적 뇌경색 위험인자와 더불어, 두개내 동맥의 형태학적 특성은 비심인성 색전 뇌경색 발생 위험 예측에 있어서 유용하다.

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