Impacts of internal carotid artery stenosis degree on the outcomes of ischemic stroke patients

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Impacts of internal carotid artery stenosis degree on the outcomes of ischemic stroke patients

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ABSTRACT

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Background

Atherosclerosis of internal carotid artery (ICA) is a well-recognized cause of cerebral infarction. However, previous studies were not systematically analyzed the impacts of the ICA stenosis degree on the outcome of ischemic stroke patients. The objective of this study was to clarify the relationship between infarction patterns and prognosis according to the degree of ICA stenosis.

Methods

From the Yonsei Stroke Registry, 3686 consecutive stroke patients were recruited from January 2004 to December 2009. According to the criteria, finally 264 patients with ICA stenosis only were enrolled. Infarction patterns were determined using diffusion weighted MRI images (DWI). DWI patterns

were categorized into five categories: (1) subcortical (2) territorial (3) confluent infarction with additional lesion (4) disseminated, and (5) borderzone infarctions. Univariate and multivariate analyses were performed to evaluate the association between the degree of ICA stenosis and various factors including initial stroke severity, functional outcomes at discharge and at 3 months.

Results

Subcortical infarction was observed in 61.5% of the patients with <50% ICA stenosis. In the complete occlusion group, confluent infarction with additional lesions (41.3%) and territorial infarction (24.0%) were common. All patients with near occlusion group showed either disseminated pattern (70%) or confluent infarction with additional lesion (30%).

Initial stroke severity measured by NIHSS was associated with older age, ICA complete occlusion, territorial and confluent patterns. Poor outcome at discharge (mRS≥3) was independently associated with initial NIHSS score and early neurological deterioration (END) after adjustment with ICA stenosis and DWI patterns. Older age is also the predictive factor of poor outcome at 3 months.

Comparing with <50% stenosis group, complete ICA occlusion group had 7.53-fold (CI 3.88-14.62) higher initial stroke severity measured by NIHSS score, 7.45-fold (CI 3.83-14.52) higher mRS at discharge and 5.95-fold (CI 3.10-11.40) higher mRS at 3 months. Likewise, comparing with 50-99%

stenosis group, complete ICA occlusion group showed a 6.14-fold (CI 2.98-12.65) higher initial NIHSS score, 5.88-fold (CI 2.85-12.12) higher mRS at discharge, 5.67-fold (CI 2.74-11.73) higher mRS at 3 months. Compared with near occlusion group, initial NIHSS score is 4.96-fold (CI 1.18-20.86) higher in complete occlusion group but mRS at discharge and mRS at 3 months were not different.

Conclusions

we demonstrated that infarction patterns were highly different depending on the degree of ICA stenosis and the patients with complete ICA occlusion showed significantly poor outcomes comparing with other degree of stenosis. Different infarction pattern according to degree of ICA stenosis might be associated with outcome in patients with carotid diseases.

Key words: internal carotid artery, outcomes, stroke, magnetic resonance imaging, diffusion-weighted

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I. INTRODUCTION

Atherosclerosis of internal carotid artery (ICA) is a well-recognized cause of cerebral infarction. Significant atherosclerotic stenoses of the proximal ICAs on ipsilateral side are found in 20% to 30%.[1, 2]

Understanding of stroke mechanism is important to find high risk patients and to determine the best therapeutic strategies. A stroke in patients with ICA steno-occlusive lesion is developed from either embolism or hemodynamic compromise.[3] Currently, both hypoperfusion and embolism is thought to be occurred simultaneously and typically make a borderzone area infarction in patients with ICA disease.[4] Patients with an impaired perfusion may have more risk of artery-to-artery embolism due to a static flow. The areas with marginal perfusion may be more vulnerable to the emboli because of impairment in washout mechanism.[4, 5]

Few studies conducted for the infarction patterns according to the degree of ICA stenosis using diffusion-weighted imaging (DWI).[6-8] Moreover, little is known about the association between the degree of ICA stenosis and the variable short-term. In patients with symptomatic ICA stenosis, the risk of stroke may be increased according to the severity of the stenosis,[9] and we assumed that the degree of ICA stenosis is also associated with infarction pattern and clinical outcomes in patients with stroke.

The purpose of the present study was to analyze the infarction patterns and various outcomes according to the degree of ICA stenosis in patients with acute ischemic stroke.

II. MATERIALS AND METHODS

1. Patients and Evaluation

All patients in this study were selected from the Yonsei Stroke Registry over 6-year period (January 2004 – December 2009). The Yonsei Stroke Registry is a prospective hospital-based registry for the patients with acute cerebral infarction or transient ischemic attack within 7 days after symptom onset.[10] During admission, all patients were thoroughly investigated for clinical symptoms, past medical history, and vascular risk factors. Registered patients underwent brain imaging studies with MR or brain computed tomography (CT). An angiographic study was also performed using CT angiography, magnetic resonance angiography, or digital subtraction angiography. Initial stroke severity was determined by National Institute of Health stroke Scale (NIHSS) scores and short-term functional outcomes were determined by Modified Rankin Scores (mRS) at discharge and at 3 months. Poor outcome was defined as mRS$\geq$3. In hospital worsening was determined using early neurological deterioration (END) . The END was defined as any increase in the NIHSS score by one or more points or stroke related death from admission to the third hospital day.

2. Stroke subtype classification

The Trial of ORG 10172 in Acute stroke Treatment (TOAST) classification had been widely used in various studies.[11] In the TOAST classification, large artery atherosclerosis is defined when there is significant (≥ 50%) stenosis of the large artery relevant to the acute infarction. Cardioembolism (CE) is defined when there is at least one potential cardiac source of embolism, which is defined in the TOAST classification. A patient with a lacunar infarction should have one of the classic clinical lacunar syndrome and a relevant subcortical hemispheric or brain stem lesion with a diameter <1.5 cm. Stroke of other determined etiology includes patients with a rare cause of stroke, such as nonatherosclerotic vasculopathy, hypercoagulable state, and hematologic disorder. Stroke of undetermined etiology is defined when the mechanism of stroke cannot be determined and is further subdivided into undetermined etiology because of multiple causes identified, undetermined etiology attributable to negative evaluation despite extensive work-up, and undetermined etiology attributable to incomplete evaluation.[11]

The YES classification (Yonsei Etiopathologic Stroke classification) was made to overcome limitations of TOAST classification. [12] In the YES classification, patients with atherothrombosis (AT) should have atherosclerosis of an intra- or extracranial artery, which is relevant to the patient's symptoms and signs and which has been shown on imaging studies. Presences of systemic atherosclerosis were included atherosclerosis in one or more non-relevant arteries, aortic atheroma demonstrated by transesophageal echocardiography, angiographically documented coronary artery occlusive disease, and angiographically documented peripheral artery occlusive disease. An Atherothrombosis with Significant stenosis of Larger Artery (ASLA) is a specific group in patients with AT. When the patients have either a significant stenosis of more than 50% or occlusion of the relevant major cerebral artery, those patients are classified as ASLA. CE is defined when there is at least one potential cardiac source of embolism, which is defined in the TOAST classification. When the patient has a single ischemic lesion occurring in a single perforating arterial territory, he/she is considered as a small artery disease (SAD). In the patients with SAD, angiographic studies of the relevant arteries should be normal. Patients who have rare cause of a stroke classified into stroke of other determined etiology (SOD). Stroke of undetermined etiology (SUD) has three subtypes; SUD of more than two caused identified (SUDm), SUD of incomplete evaluation (SUDi), and SUD of uncertain determination (SUDu).[12]

By definition, the TOAST classification has limitation for less than 50% stenosis in cerebral arteries. Therefore, in this study, we used AT and ASLA in the YES classification for patients selection. When a patient was admitted more than twice because of recurrent strokes, each data was analyzed as a different event.

3. Assessment of stroke risk factors

Hypertension was defined by using antihypertensive medication before admission or a resting systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥ 90 mmHg on repeated check. Diabetes mellitus was diagnosed when a patient had a fasting plasma glucose value ≥ 126 mg/dL or had been treated with an oral hypoglycemic agent or insulin. Hyperlipidemia was defined as a fasting serum total cholesterol level ≥6.2 mmol/L or a history of treatment. A current smoker was defined as an individual who smoked at the time of stroke or had quit smoking within 1 year.

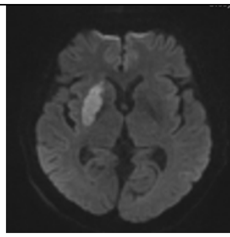
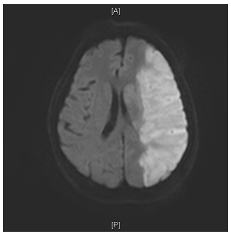
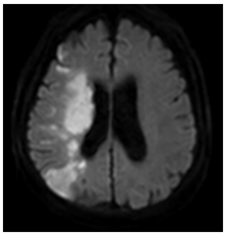
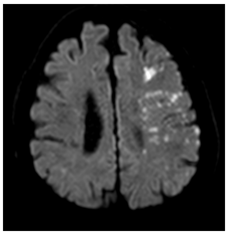
4. Neuroimaging analysis

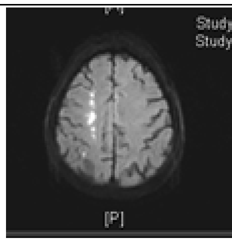
The degree of ICA stenosis was measured by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.[13] The ICA stenosis was grouped as follows; <50%, 50-99%, near occlusion, and total occlusion. A near occlusion was defined by the following criteria: (1) very severe stenosis at the site of the residual lumen, (2) delayed flow of angiographic contrast material, and (3) reduced arterial caliber secondary to artery collapse,[13] (4) intracranial collaterals seen as cross-filing of contralateral vessels or ipsilateral contrast dilution.[14] Contralateral carotid disease was classified as <50% stenosis, 50-99% stenosis, and total occlusion.

The patterns of the ischemic lesions were divided into five categories using DWI considering lesion size, distribution and location.[6, 15] A subcortical infarction is defined as a lesion in the territory of deep perforating branches originating from the distal ICA or the middle cerebral artery (MCA) trunk. A territorial infarction is defined as a large ischemic lesion involving the cerebral cortex and subcortical structures in one or more major cerebral artery territories.

A confluent infarction with additional lesion represents a large ischemic lesion, as in territorial infarction, with additional smaller lesions either in cortical or in subcortical regions, probably due to partial fragmentation of the embolus. A disseminated pattern is defined as small lesions involving mainly cortical regions in random fashion on the distal territory of the cerebral arteries. A borderzone infarction denotes lesions either completely or predominantly located in regions considered to be one of the hemodynamic risk zones between major cerebral arteries: the superficial or cortical borderzones wedged between the anterior cerebral artery (ACA) and MCA or between the MCA and posterior cerebral artery (PCA), and the deep or subcortical borderzone located in the vascular territory between deep and superficial arterial systems. Representative examples of infarction patterns are shown in the Table 1.

Table 1. Classification of infarction patterns

Infarction patterns	Description	Imaging examples of DWI
Subcortical infarction	A territory of deep perforating branches originating from the distal ICA or the MCA trunk	
Territorial infarction	A large ischemic lesion involving the cerebral cortex and subcortical structures in one or more major cerebral artery territories	
Confluent infarction with additional lesion	A large ischemic lesion, with additional lesions either in cortical or in subcortical regions, probably due to partial fragmentation of the embolus.	
Disseminated infarction	Small lesions are sprinkled in random fashion	

Borderzone infarction	One of the hemodynamic risk zones between major cerebrovascular territories	

5. Statistical Analysis

The SPSS for Windows (version 18.0; SPSS, Chicago, IL) and the R package version 2.15.0 (http://www.R-project.org) were used for statistical analysis. The Pearson χ^2 test was used for comparisons between the baseline categorical variables and one-way ANOVA was used for continuous variables.

The univariate analysis for initial stroke severity, occurrence of END, and poor outcome at discharge or at 3 months were conducted. Variables with $P < 0.1$ in univariate analysis were entered into the multivariate model. The multiple linear regression analysis was applied to determine independent factors of initial stroke severity and the logistic regression analyses were used for occurrence of END, and poor outcome at discharge or at 3 months. A value of $P < 0.05$ was considered statistically significant.

III. RESULTS

1. Study Patients

During the study period, 3683 patients with acute ischemic stroke were registered in the Yonsei Stroke Registry. Among them, the patients with transient ischemic attack (n=323) and who received thrombolytic therapy or ICA angioplasty and stent (n=322) were excluded. Among the remaining patients, 1875 of other etiologies besides AT or ASLA in the YES classification were excluded.[12] The patients with posterior circulation lesions (n=475) and missing data (n=36) were also excluded. The remaining 632 patients were divided into the patients with ICA stenosis alone (n=264) and tandem intracranial stenosis along with relevant ICA disease (n=368). Finally, 264 patients with ICA stenosis only were further analyzed (Figure 1).

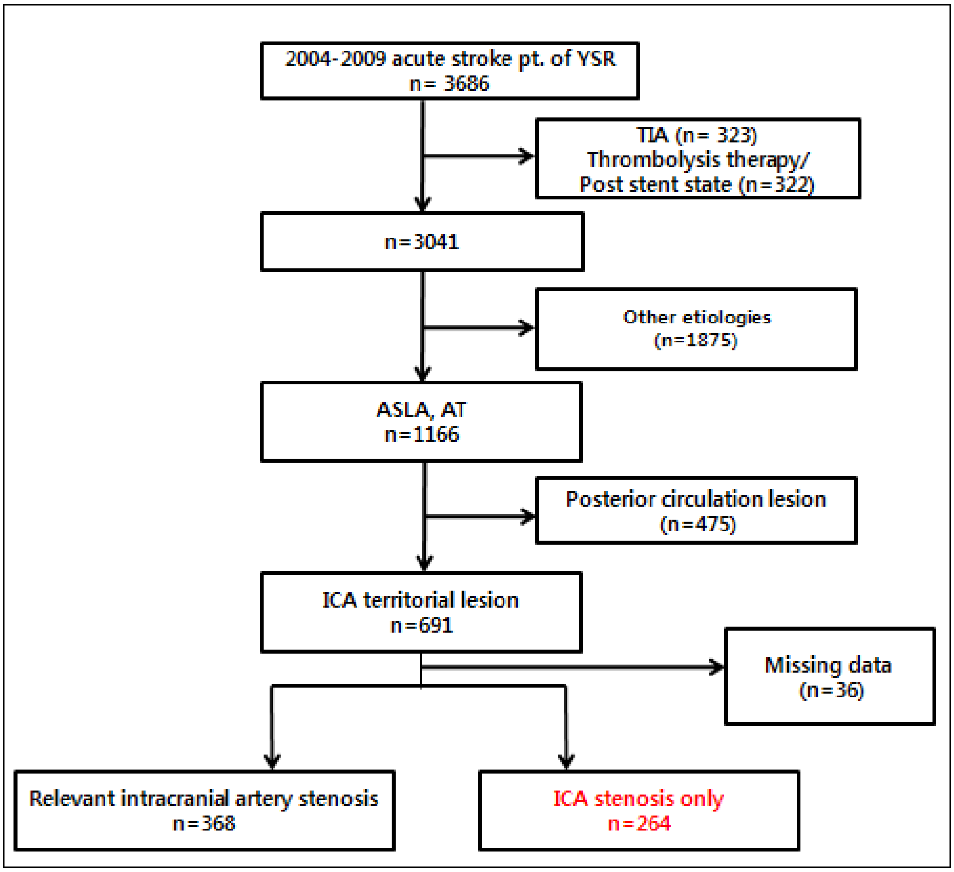


Figure 1. Patients selection

YSR=Yonsei Stroke Registry, TIA=transient ischemic attack, AT= atherothrombosis, ASLA= atherothrombosis with significant stenosis of a large artery, ICA=internal carotid artery

2. Comparisons between ICA stenosis only versus coexisting tandem intracranial stenosis

Comparisons between the patients with ICA stenosis only (n=264) and tandem intracranial stenosis along with relevant ICA disease (n=368) were conducted. Male was more likely to have an isolated ICA stenosis rather than tandem intracranial stenosis (68.2% vs. 54.1%, $p<0.001$). Current smokers were also more frequently observed in the ICA stenosis only group (34.1%) compared with tandem intracranial stenosis group (26.6%) ($p=0.043$). Presence of contralateral ICA stenosis was more common in patients with ICA stenosis only group ($p<0.001$). Whereas, occurrence of END was more common in patients with tandem intracranial artery stenosis (15.8% vs. 9.8%, $p=0.014$) (Table 2).

Table 2. Comparison of characteristics between pure ICA stenosis and coexisting tandem intracranial artery stenosis

	ICA stenosis only (n=264)	Tandem intracranial artery stenosis (n=368)	*p*
Age			
mean ± SD	67.5 ± 10.0	67.2 ± 11.1	0.084
Median	68 (24-90)	68 (33-92)	
Male	180 (68.2)	199 (54.1)	<0.001
Hypertension	218 (82.6)	301 (81.8)	0.8
DM	111 (42.0)	137 (37.2)	0.221
Hyperlipidemia	40 (15.2)	58 (15.8)	0.835
Smoking	90 (34.1)	98 (26.6)	0.043
Preceding TIA history	20 (7.6)	27 (7.3)	0.91
Initial glucose	150.1 ± 69.2	143.37 ± 59.9	0.195
Initial SBP	155 ± 29.6	159.9 ± 29.2	0.789
Affected side			
Left	139 (52.7)	217 (59.0)	0.114
Right	125 (47.3)	151 (41.0)	
Contralateral ICA stenosis			
No stenosis	112 (42.4)	221 (60.1)	<0.001
<50%	110 (41.7)	110 (29.9)	
50-99%	34 (12.9)	32 (8.7)	
Occlusion	8 (3.0)	5 (1.4)	

TOAST			
LAA	148 (56.1)	219 (59.5)	0.631
LAC	27 (10.2)	29 (7.9)	
UM	7 (2.7)	14 (3.8)	
UN	82 (31.1)	106 (28.8)	
YES			
ASLA	155 (58.7)	206 (56.0)	0.066
AT	109 (41.3)	162 (44.0)	
END	26 (9.8)	58 (15.8)	0.014
Initial NIHSS score			
mean ± SD	5.90 ± 5.99	5.37 ± 5.10	0.231
median (IQR)	3 (2-6.75)	4 (2-7)	
Poor outcome at discharge (mRS≥3)	92 (34.8)	133 (36.1)	0.738
Poor outcome at 3 months (mRS≥3)	91 (34.5)	134 (36.4)	0.615

Data are expressed as a number (%).

DM: diabetes mellitus, TIA: transient ischemic attack, SBP: systolic blood pressure, ICA: internal carotid artery, TOAST: Trial of Org 10172 in Acute Stroke Treatment, LAA: large artery atherosclerosis, LAC: lacune, UM: stroke of undetermined etiology due to multiple causes, UN: stroke of undetermined etiology due to negative evaluation, AT: atherothrombosis, ASLA: atherothrombosis with significant stenosis of a large artery, END: early neurological deterioration, NIHSS: National Institute of Health Stroke Scale, mRS: modified Rankin Scale.

3. Demographic characteristics of patients with ICA stenosis alone

Among the 264 patients with ICA stenosis alone, the mean age was 67.5 ± 9.9 years old and 68.2% were male. Presence of cerebral artery atherosclerosis was determined using digital subtraction angiography in 113 patients (42.8%) and with MR angiography in 151 patients (57.2%). Degree of ICA steno-occlusive lesions were <50% of stenosis in 109 patients (41.3%), complete ICA occlusion in 75 patients (28.4%), and 50-99% of stenosis in 79 patients (26.5%). Near occlusion in ICA was the least frequently found in 10 patients (3.8%).

The most frequent stroke subtype of TOAST classification was large artery atherosclerosis (56.1%) followed by multiple causes (31.1%), lacunar infarction (10.2%) and negative evaluation (2.7%).

About half of the patients with complete ICA occlusion were current smokers. Preceding TIAs were more frequent in patients with 50-99% stenosis group compared with those with the other degrees of stenosis (p=0.001) (Table 3).

Table 3. Demographic characteristics of the patients with ICA stenosis only

	Stenosis group					
	<50%	50-99%	Near occlusion	Complete occlusion	Total	*p*
	109 (41.3)	70 (26.5)	10 (3.8)	75 (28.4)	264 (100.0)	
Age						
mean ± SD	67.18 ± 9.1	68.96 ± 9.4	67.30 ± 11.9	66.51 ± 11.3	67.47 ± 9.9	0.829
median	68 (46-86)	71 (35-90)	67 (50-89)	68 (24-86)		
Male	73(67.0)	48 (68.6)	5 (50.0)	54 (72.0)	180 (68.2)	0.551
Hypertension	97 (89.0)	55 (78.6)	9 (90.0)	57 (76.0)	218 (82.6)	0.088
DM	42 (38.5)	34 (48.6)	5 (50.0)	30 (40.0)	111 (42.0)	0.539
Hyperlipidemia	14 (12.8)	8 (11.4)	2 (20.0)	16 (21.3)	40 (15.2)	0.306
Old stroke history	26 (23.9)	23 (32.9)	3 (30.0)	14 (18.7)	66 (25.0)	0.249
Smoking	31 (28.4)	21 (30.0)	1 (10.0)	37 (49.3)	90 (34.1)	0.006
Preceding TIA history	4 (3.7)	13 (18.6)	0 (0.0)	3 (4.0)	20 (7.6)	0.001

MRA	82 (75.2)	22 (31.4)	3 (30.0)	44 (58.7)	151 (57.2)	<0.001
DSA	27 (24.8)	48 (68.6)	7 (70.0)	31 (41.3)	113 (42.8)	
Initial glucose (mean ± SD)	147.28 ± 66.48	158.46 ± 70.72	151.30 ± 105.78	150.1 ± 69.2		0.931
Initial SBP (mean ± SD)	157.66 ± 29.39	151.19 ± 34.86	171.20 ± 25.17	155 ± 29.6		0.085
Initial DBP (mean ± SD)	87.44 ± 15.09	83.46 ± 16.63	87.10 ± 14.77	84.24 ± 14.86		0.808
Affected side						
Left	55 (50.5)	45 (64.3)	3 (30.0)	36 (48.0)	139 (52.7)	0.081
Right	54 (49.5)	25 (35.7)	7 (70.0)	39 (52.0)	125 (47.3)	
Contralateral ICA stenosis						
No stenosis	50 (45.9)	29 (41.4)	4 (40.0)	29 (38.7)	112 (42.4)	0.329
<50%	50 (45.9)	26 (37.1)	2 (20.0)	30 (40.0)	110 (41.7)	
50-99%	7 (6.4)	11 (15.7)	2	14 (18.7)	34 (12.9)	
Occlusion	2 (1.8)	4 (5.7)	0 (0.0)	2 (2.7)	8 (3.0)	
TOAST						
LAA	0 (0.0)	66 (94.3)	10 (100.0)	72 (96.0)	148 (56.1)	<0.001

LAC	27 (24.8)	0 (0.0)	0 (0.0)	0 (0.0)	27 (10.2)	
UN	0 (0.0)	4 (5.7)	0	3 (4.0)	7 (2.7)	
UM	82 (75.2)	0 (0.0)	0 (0.0)	0 (0.0)	82 (31.1)	
YES						
ASLA	0 (0.0)	70 (100.0)	10 (100.0)	75 (100.0)	155 (58.7)	<0.001
AT	109 (100.0)	0	0	0	109 (41.3)	

Data are expressed as a number (%).

DM: diabetes mellitus, TIA: transient ischemic attack, SBP: systolic blood pressure, DBP: diastolic blood pressure, ICA: internal carotid artery, TOAST: Trial of Org 10172 in Acute Stroke Treatment, LAA: large artery atherosclerosis, LAC: lacune, UM: stroke of undetermined etiology due to multiple causes, UN: stroke of undetermined etiology due to negative evaluation, MRA: magnetic resonance angiography, DSA: digital subtraction angiography, AT: atherothrombosis, ASLA: atherothrombosis with significant stenosis of a large artery, END: early neurological deterioration, NIHSS: National Institute of Health Stroke Scale, mRS: modified Rankin Scale.

4. DWI Patterns according to degree of ICA stenosis

The DWI patterns were quite different according to degree of ICA stenosis ($p<0.001$). Among all the study patients, subcortical lesion (34.5%) was the most common followed by disseminated lesion (24.6%), confluent infarction with additional lesion (22.3%), and territorial lesion (9.5%). Whereas, borderzone involvement was the least frequent (9.1%).

According to degree of ICA steno-occlusive lesions, subcortical lesion was the most frequent in patients with <50% ICA stenosis (61.5%). Disseminated lesion (38.6%) and borderzone lesion (21.4%) were frequent in patients with 50-99% stenosis. In contrast, complete ICA occlusion group frequently showed confluent infarction with additional lesions (41.3%) or territorial lesions (24.0%). All patients in near occlusion group showed only two patterns either disseminated lesion (70.0%) or confluent infarction with additional lesion (30.0%) (Table 4) (Figure 2).

Table 4. DWI lesion pattern according to degree of ICA stenosis

	Stenosis group					
	<50%	**50-99%**	**Near occlusion**	**Complete occlusion**	**Total**	***p***
DWI patterns						
Subcortical	67 (61.5)	13 (18.6)	0 (0.0)	11 (14.7)	91 (34.5)	<0.001
Territorial	6 (5.5)	1 (1.4)	0 (0.0)	18 (24.0)	25 (9.5)	<0.001
Confluent with additional lesion	11 (10.1)	14 (20.0)	3 (30.0)	31 (41.3)	59 (22.3)	<0.001
Disseminated	21 (19.3)	27 (38.6)	7 (70.0)	10 (13.3)	65 (24.6)	<0.001
Borderzone	4 (3.7)	15 (21.4)	0 (0.0)	5 (6.7)	24 (9.1)	<0.001

Data are expressed as a number (%).
DWI: diffusion weighted MRI images.

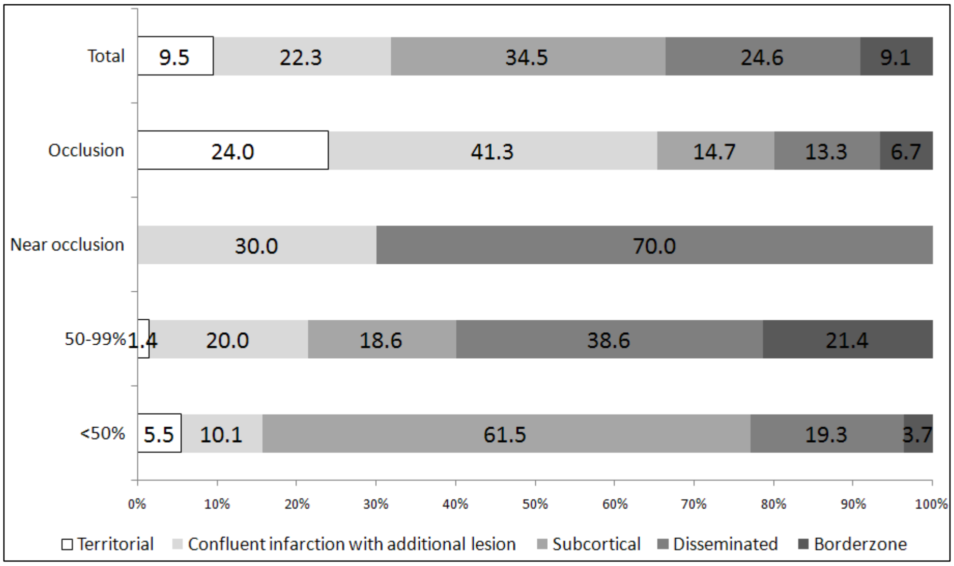


Figure 2. Cumulative frequency distribution of DWI patterns in patients with different degrees of ICA stenosis.

Frequency of each pattern is shown in percentages. The graph was aligned in the order of territorial, confluent, subcortical, disseminated, and borderzone.

5. Clinical outcomes according to the degree of ICA stenosis

According to the degree of ICA stenosis, clinical outcomes were quite different. All the parameters including initial NIHSS score, NIHSS score at 3 days of admission, mRS at discharge and mRS at 3months were worst in the patients with ICA complete occlusion (Table 5).

Comparing with <50% stenosis group, complete ICA occlusion group had 7.53-fold (CI 3.88-14.62) higher initial stroke severity measured by NIHSS score, 7.45-fold (CI 3.83-14.52) higher mRS at discharge and 5.95-fold (CI 3.10-11.40) higher mRS at 3 months. Comparing with 50-99% stenosis group, complete ICA occlusion group showed a 6.14-fold (CI 2.98-12.65) higher initial NIHSS score, 5.88-fold (CI 2.85-12.12) higher mRS at discharge, 5.67-fold (CI 2.74-11.73) higher mRS at 3 months. Compared with near occlusion group, initial NIHSS score is 4.96-fold (CI 1.18-20.86) higher in complete occlusion group but mRS at discharge and mRS at 3 months showed no statistical differences.

Table 5. Short-term outcomes according to degree of ICA stenosis

Outcome No. (%)	Stenosis group				*p*
	<50%	50-99%	Near occlusion	Complete occlusion	
Total	109 (41.3)	70 (26.5)	10 (3.8)	75 (28.4)	
Initial NIHSS score					
mean ± SD	4.19 ± 4.89	3.90 ± 4.09	4.00 ± 2.67	10.49 ± 6.78	<0.001
0-5	85 (78.0)	52 (74.3)	7 (70.0)	24 (32.0)	<0.001
≥6	24 (22.0)	18 (25.7)	3 (30.0)	51 (68.0)	
3days NIHSS score					
median (IQR)	2 (1-3)	2 (0.75-4)	2 (0.75-3.50)	9 (4-15)	
0-5	91 (83.5)	60 (85.7)	9 (90.0)	28 (37.3)	<0.001
≥6	18 (16.5)	10 (14.3)	1 (10.0)	47 (62.7)	
END	8 (7.3)	4 (5.7)	1 (10.0)	13 (17.3)	0.077
mRS at discharge					
mean ± SD	1.56 ± 1.40	1.53 ± 1.35	2.40 ± 1.35	3.33 ± 1.60	<0.001
median (IQR)	1 (1-2)	1 (0-2.25)	2 (1.75-4)	4 (2-5)	
poor (mRS ≥ 3)	22 (20.2)	17 (24.3)	4 (40.0)	49 (65.3)	<0.001
mRS at 3months					
mean ± SD	1.61 ± 1.57	1.59 ± 1.59	2.30 ± 1.42	3.31 ± 1.66	<0.001
median (IQR)	1 (1-2)	1 (0-2)	2 (1-4)	4 (2-5)	
poor (mRS ≥ 3)	24 (22.0)	16 (22.9)	4 (40.0)	47 (62.7)	<0.001

Data are expressed as a number (%).

END: early neurological deterioration, NIHSS: National Institute of Health Stroke Scale, mRS: modified Rankin Scale.

6. Determinant of initial stroke severity

Univariate analysis for initial stroke severity demonstrated that older age, complete ICA occlusion, hyperlipidemia, infarction pattern of territorial and confluent infarction with additional lesion were associated with higher initial NIHSS score. Multiple linear regression analyses using three different models revealed that independent factors for initial stroke severity were older age, complete ICA occlusion and infarction pattern of territorial and confluent infarction with additional lesion (Table 6).

Table 6. Univariate and multivariate analysis for initial stroke severity

	Univariate		Multivariate Model 1		Multivariate Model 2		Multivariate Model 3	
	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p
Age	0.071 (0.037)	0.055	0.093 (0.033)	0.008	0.085 (2.124)	0.007	0.095 (0.030)	0.002
Male	0.112 (0.793)	0.888						
ICA stenosis								
<50%	ref		ref				ref	
55-99%	-2.719 (0.819)	0.001	-0.486 (0.802)	0.545			-0.256 (0.803)	0.749
Near occlusion	-1.972 (1.930)	0.308	-0.516 (1.713)	0.763			-0.156 (1.637)	0.924
Occlusion	6.419 (0.716)	< 0.001	6.068 (0.788)	< 0.001			3.774 (0.822)	<0.001
Hypertension	1.035 (0.971)	0.288						
Diabetes	-0.274 (0.748)	0.714						
Smoking	0.475 (0.778)	0.611						
Hyperlipidemia	2.920 (1.014)	0.004	2.103 (0.901)	0.02	1.241 (0.873)	0.157	1.103 (0.835)	0.188

Initial glucose	0.004 (0.005)	0.509						
Initial SBP	0.008 (0.013)	0.521						
Diffusion patterns								
Subcortical	ref				ref		ref	
Territorial	8.596 (1.144)	<0.001			9.402 (1.148)	<0.001	7.083 (1.191)	<0.001
Confluent infarction with additional lesion	4.039 (0.850)	<0.001			4.642 (0.833)	<0.001	3.179 (0.885)	<0.001
Disseminated	-3.436 (0.830)	<0.001			-1.047 (0.822)	0.204	-1.139 (0.851)	0.182
Borderzone	-3.436 (0.830)	<0.001			-0.183 (1.154)	0.874	-0.421(1.184)	0.722
Contralateral stenosis								
No stenosis	ref		ref		ref		ref	
< 50%	-0.152 (0.749)	0.839	-0.178 (0.703)	0.801	-0.637 (0.691)	0.358	-0.542 (0.662)	0.413
50-99%	2.177 (1.094)	0.048	0.954 (1.032)	0.356	1343 (0.983)	0.173	0.983 (0.942)	0.298
Total occlusion	-1.955 (2.153)	0.625	-1.205 (1.914)	0.53	-1.774 (1.841)	0.336	-1.515 (1.760)	0.39

Model 1: including ICA stenosis, excluding DWI patterns
Model 2: including DWI patterns, excluding ICA stenosis
Model 3: including both

7. Factors associated with poor outcome at discharge

According to degree of ICA stenosis poor outcome at discharge were found in 20.2% of <50% stenosis group, 24.3% of 50-99% stenosis group, 40.0% of near occlusion group, whereas, 65.3% of complete ICA occlusion group showed poor outcome at discharge (Figure 3).

Univariate analysis showed that older age, hyperlipidemia, higher initial NIHSS scores, occurrence of END, infarction pattern of territorial and confluent infarction with additional lesions, and complete ICA occlusion were related with poor outcome at discharge.

In multivariate analysis, initial NIHSS score and occurrence of END were associated with poor outcome at discharge after adjustment for both degree of ICA stenosis and DWI patterns. Complete ICA occlusion were related to poor outcome at discharge (OR 2.68; CI 1.00-7.17; p=0.046, model 1) in the model excluding DWI patterns (Table 7).

Table 7. Univariate and multivariate analysis for poor outcome at discharge (mRS score 3-6)

	Univariate		Multivariate Model 1		Multivariate Model 2		Multivariate Model 3	
	OR(95%, CI)	*p*	OR(95%, CI)	*p*	OR(95%, CI)	*p*	OR(95%, CI)	*p*
Age	1.03 (1.00-1.01)	0.049	1.03 (0.99-1.06)	0.204	1.03 (0.99-1.07)	0.191	1.03 (0.99-1.07)	0.139
Male	0.65 (0.38-1.11)	0.113						
ICA stenosis								
<50%	1		1				1	
55-99%	1.27 (0.62-2.60)	0.517	1.72 (0.67-4.39)	0.257			1.53 (0.53-4.45)	0.436
Near occlusion	2.64 (0.68-10.16)	0.159	3.67 (0.72-18.69)	0.117			4.54 (0.74-28.01)	0.103
Occlusion	7.45 (3.83-14.52)	<0.001	2.68 (1.00-7.17)	0.049			2.67 (0.88-8.11)	0.082
Hypertension	1.88 (0.91-3.91)	0.09	2.41 (0.82-7.11)	0.112	2.46 (0.83-7.28)	0.105	2.46 (0.83-7.34)	0.106
Diabetes	0.891 (0.53-1.49)	0.66						
Smoking	1.13 (0.66-1.92)	0.656						
Hyperlipidemia	2.11 (1.07-4.17)	0.031	0.98 (0.34-2.87)	0.975	1.22 (0.41-3.65)	0.719	1.11 (0.37-3.33)	0.855
Initial glucose	1.00 (0.99-1.01)	0.762						

Initial SBP	1.00 (1.00-1.01)	0.428						
Diffusion patterns								
Subcortical	1				1		1	
Territorial	8.57 (3.15-23.30)	< 0.001			0.68 (0.12-3.81)	0.658	0.44 (0.07-2.89)	0.395
Confluent infarction	4.23 (2.08-8.59)	< 0.001			1.82 (0.65-5.05)	0.254	1.12 (0.35-3.56)	0.849
Disseminated	0.83 (0.38-1.82)	0.647			1.08 (0.37-3.20)	0.889	0.67 (0.19-2.32)	0.523
Borderzone	1.37 (0.50-3.75)	0.537			3.28 (0.94-11.48)	0.064	22.42 (0.62-9.37)	0.202
Initial NIHSS scores	1.43 (1.31-1.56)	< 0.001	1.42 (1.29-1.57)	< 0.001	1.46 (1.31-1.63)	< 0.001	1.44 (1.29-1.60)	< 0.001
END	6.14 (2.47-15.23)	<0.001	9.24 (2.83-30.18)	< 0.001	12.97 (3.90-43.09)	< 0.001	11.45 (3.29-39.89)	< 0.001
Contralateral stenosis								
No stenosis	1							
< 50%	0.98 (0.58-1.63)	0.923						
50-99%	1.02 (0.48-2.17)	0.953						
Occlusion	1.91 (0.47-7.82)	0.369						

Model 1: including ICA stenosis, excluding DWI patterns

Model 2: including DWI patterns, excluding ICA stenosis

Model3: including both

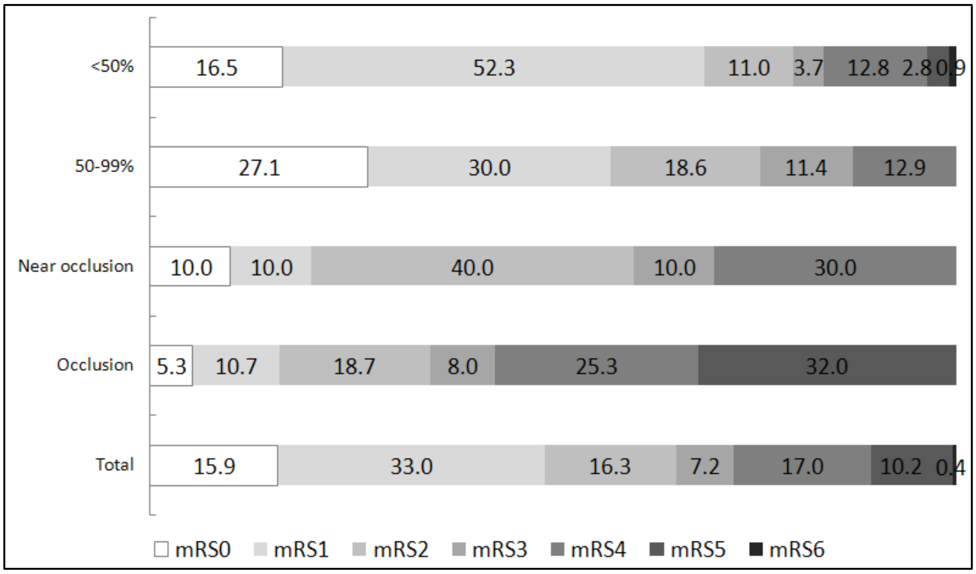


Figure 3. Cumulative frequency distribution of mRS at discharge in patients with different degrees of ICA stenosis.

The numbers are percentages of each patient.

8. Factors associated with poor outcome at 3 months

According to degree of ICA stenosis poor outcome at discharge were found in 21.9% of <50% stenosis group, 22.9% of 50-99% stenosis group, 40.0% of near occlusion group, whereas, 62.7% of complete ICA occlusion group showed poor outcome at discharge (Figure 4).

Univariate analysis showed that older age, hypertension, hyperlipidemia, initial higher NIHSS score, and occurrence of END were associated with poor outcome at 3 months. Along with these factors, infarction pattern of territorial and confluent infarction with additional lesion, and complete ICA occlusion were associated with poor outcome at 3 months. Patients with ICA occlusion showed a 5.95-fold higher poor outcome at 3 months compared with those with <50% ICA stenosis. Among the DWI patterns, the odds ratio for poor outcome at 3 months was highest in patients with territorial infarction (OR 9.13; CI 3.34-24.92) followed by confluent infarction with additional lesions (OR 3.93; CI 1.93-9.01).

Multivariate analysis revealed that older age, initial higher NIHSS score, occurrence of END was independent predictor of poor outcome at 3 months, whereas, complete ICA occlusion and DWI patterns were not independent predictors for poor prognosis at 3 months after adjustments (Table 8).

Table 8. Univariate and multivariate analysis for poor outcome at 3 months (mRS score 3-6)

	Univariate		Multivariate Model 1		Multivariate Model 2		Multivariate Model 3	
	OR(95%, CI)	*p*	OR(95%, CI)	*p*	OR(95%, CI)	*p*	OR(95%, CI)	*p*
Age	1.05 (1.02-1.08)	0.002	1.05 (1.00-1.10)	0.006	1.06 (1.01-1.10)	0.008	1.06 (1.02-1.10)	0.006
Male	0.68 (0.40-1.17)	0.162						
ICA stenosis								
<50%	1		1				1	
55-99%	1.05 (0.51-2.15)	0.895	1.19 (0.49-2.91)	0.696			0.95 (0.35-2.57)	0.915
Near occlusion	2.36 (0.62-9.05)	0.21	2.98 (0.58-15.24)	0.189			2.77 (0.47-16.51)	0.263
Occlusion	5.95 (3.10-11.40)	<0.001	2.12 (0.83-5.44)	0.116			1.89 (0.66-5.38)	0.234
Hypertension	2.13 (1.00-4.52)	0.049	2.61 (0.90-7.59)	0.079			2.73 (0.93-8.04)	0.069
Diabetes	0.80 (0.48-1.34)	0.393						
Smoking	1.00 (0.58-1.71)	0.995						
Hyperlipidemia	2.43 (1.23-4.81)	0.011	1.46 (0.54-3.94)	0.457			1.63 (0.58-4.55)	0.354
Initial glucose	1.00 (0.99-1.00)	0.747						

Initial SBP	1.01 (1.00-1.01)	0.23						
Diffusion patterns								
Subcortical	1				1		1	
Territorial	9.13 (3.34-24.92)	<0.001			0.866 (0.18-4.18)	0.857	0.66 (0.12-3.56)	0.631
Confluent	3.93 (1.93-9.01)	<0.001			1.70 (0.63-4.57)	0.298	1.31 (0.43-3.94)	0.637
Disseminated	1.07 (0.498-2.28)	0.871			1.37 (0.50-3.80)	0.541	1.12 (0.36-3.44)	0.848
Borderzone	1.46 (0.53-4.02)	0.461			3.08 (0.89-10.66)	0.076	2.88 (0.75-10.99)	0.122
Initial NIHSS scores	1.36 (1.26-1.47)	<0.001	1.35 (1.24-1.47)	<0.001	1.39 (1.26-1.53)	<0.001	1.37 (1.24-1.51)	<0.001
END	4.19 (1.78-9.83)	0.001	4.91 (1.59-15.22)	0.006	6.51 (2.09-20.31)	0.001	5.71 (1.99-18.39)	0.004
Contralateral stenosis								
no stenosis	1							
< 50%	1.08 (0.64-1.80)	0.776						
50-99%	1.21 (0.57-2.54)	0.621						
Total occlusion	1.94 (0.47-8.00)	0.356						

Model 1: including ICA stenosis, excluding DWI patterns
Model 2: including DWI patterns, excluding ICA stenosis
Model 3: including both

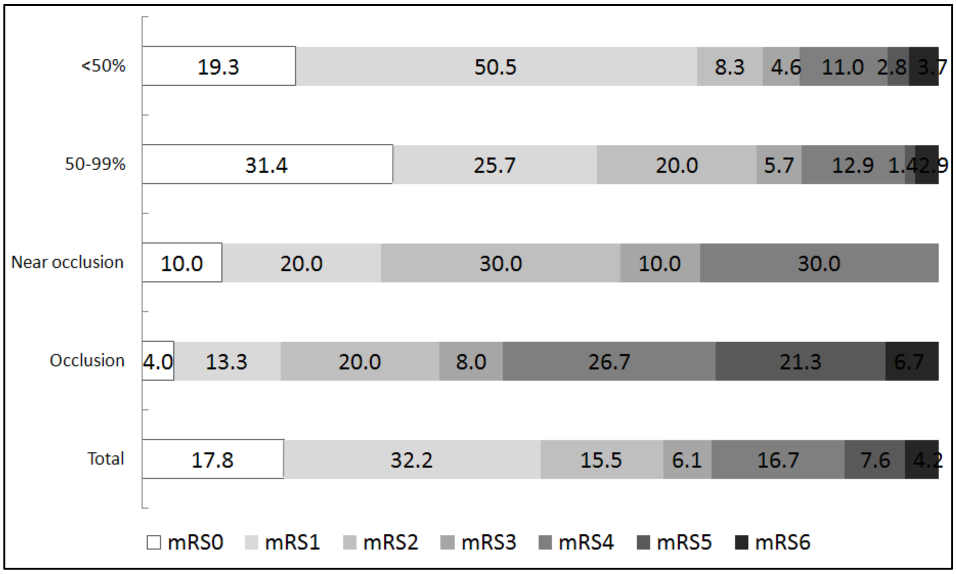


Figure 4. Cumulative frequency distribution of mRS at 3 months in patients with different degrees of ICA stenosis.

The numbers are percentages of each patient.

IV. DISCUSSION

The present study found two major findings regarding to the ischemic stroke from atherosclerotic ICA diseases. According to the degree of ICA stenosis, characteristic DWI patterns were found and it was associated with prognosis. This study also showed that the patients with complete ICA occlusion were higher likely to be poor outcomes including initial stroke severity, functional outcome at discharge and 3 months.

Among the five different infarction patterns from DWI, we found that each group showed different features according to degree of ICA stenosis. The patients with less than 50% stenosis were more likely to have subcortical infarction, whereas, borderzone and territorial patterns were less frequently found in the <50% stenosis group. Disseminated lesion and borderzone lesion were the most frequent in patients with 50-99% stenosis. Among the various stenosis groups, the patients with 50-99% stenosis more likely to have borderzone lesion comparing with other group. Infarction involving territorial blood supply (territorial infarction and confluent infarction with additional lesion) was main feature of the complete ICA occlusion group. All the patients with near occlusion showed confluent infarction with additional lesion (30%) or disseminated pattern (70%).

Different infarction pattern according to degree of ICA stenosis could be explained like below. First, 24.8% of the patients with <50% ICA stenosis were classified as lacunar infarction with the TOAST classification. Lower degree of stenosis may be associated with systemic atherosclerosis rather than embolic or hemodynamic mechanisms.

Second, the patients with 50-99% degree of stenosis showed typical stroke mechanism in patients with atherosclerotic ICA diseases. However, there exists debate about the mechanisms of stroke in patients with atherosclerotic ICA diseases. The main possible mechanisms are the artery-to-artery thromboembolism and hemodynamics compromise. Both mechanisms might be important but it is still unknown that which plays a major role in the individual patients. Borderzone infarcts are usually regarded as being caused by low cerebral blood flow distal to a severely narrowed or occluded ICA, whereas, artery-to-artery thromboembolism may be occurred from clots which related to high-shear stress of stenotic carotid artery. Increasing wall shear force in stenotic areas contributes to the detachment of thrombi.[16] In the postmortem arteriography and pathological study, massive infarcts involving two major cerebral artery territories were associated with distal ICA occlusion.[15] The borderzone infarcts were frequent in patients with ICA stenosis with poor circle of Willis collaterals,[15] or in patients with high-grade ICA stenosis.[17] And another study analyzing infarction pattern using DWI showed that a half of patients with high-grade stenosis had multiple lesions with hemodynamic alteration which could be appeared as borderzone infarction.[6] However, this association was denied in another larger study by showing many cases of borderzone infarcts occurred in patients with mild or moderate carotid disease.[18] The frequency of borderzone involvement (9.1%) in our study was low comparing with previous studies (17% to 32%).[6,17,18] Moreover, most borderzone area infarctions was seen in patients with 50-99% stenosis group rather than complete ICA occlusion or near occlusion. It means that severe carotid stenosis is not a prerequisite for borderzone infarction.

Third, cortical involvements were more common in patients with complete ICA occlusion than other groups. Among cortical involvement, multiple lesions were more common than single lesion in patients with complete ICA occlusion. The exact reason why multiple lesions are more prevalent than single lesion in patients complete ICA occlusion could not be determined because we excluded the patients with tandem intracranial occlusion. The stroke mechanisms in patients with complete ICA occlusion can be raised stump emboli from occlusion site, emboli travelling via collateral circulation, or hemodynamic insufficiency. If the size of emboli is smaller, small emboli could be disseminated in the relevant territory. If partial fragmentation of the embolus is larger, confluent with multiple additional lesion could be made. However, analysis including the patients with tandem intracranial occlusion might have another uncertainty because the thrombus may arise from proximal ICA or in situ thrombotic occlusion. Further prospective follow-up study for the patients with complete ICA occlusion might give the explanation.

Fourth, all patients with near occlusion showed confluent infarction with additional lesion and disseminated pattern. Neither borderzone, territorial, nor subcortical lesion was observed in patients with near occlusion. Many previous studies asserted that the patients with near occlusion showed favorable outcomes compared to other degree of ICA stenosis or occlusion due to their good collateral circulation.[14, 19] Our patients with near occlusion also showed less severe stroke than complete ICA occlusion.

This study also demonstrated the relationship between degree of ICA stenosis and short-term outcomes. The patients with complete ICA occlusion showed worst initial stroke severity and short-term functional outcomes at discharge or 3 months. Initial stroke severity is important factor for predicting later outcome.[20] In the multivariate analysis, older age, complete ICA occlusion and infarct patterns of territorial involvement and confluent infarction with additional lesion were associated with higher initial stroke severity. It can be assumed that larger infarction burdens with poor collateral by complete ICA occlusion are related with higher initial NIHSS scores.

Poor functional outcome at discharge and at 3 months were associated with older age, initial stroke severity, and occurrence of END. Complete ICA occlusion and DWI patterns were not independent factors of poor outcome. It might be associated with initial stroke severity and early recurrences are more important than degree of ICA stenosis or infarction patterns.[21] Collateral status or perfusion may also influence on the recovery after stroke.

This study has several limitations. First, this study was retrospectively conducted using prospective hospital based stroke registry. Therefore, heterogeneity of vascular imaging modality might influence the results. However, 42.8% of patients were evaluated with digital subtraction angiography, which can enable more accurate measurement of degree of ICA stenosis comparing with previous studies. Second, we could not certain whether ICA occlusion was acute or chronic. However, all patients should have relevant lesion corresponding carotid stenosis, and the false enrollment of chronic ICA steno-occlusive lesion might be small. Third, the perfusion imaging are not routine investigation in our stroke registry, we cannot measure the perfusion defect or collateral status. Previous study showed the higher prevalence of a complete circle of Willis had better outcome.[22] By contrast, others found no effect of different collateral flow patterns on clinical outcome in the patients with ICA occlusion.[6, 23] Further study including perfusion and collateral status can show more clear relationship between degree of ICA stenosis and functional outcomes.

V. CONCLUSION

In conclusion, we demonstrated that infarction patterns were highly different depending on the degree of ICA stenosis and the patients with complete ICA occlusion showed significantly poor outcomes comparing with other groups. Different infarction pattern according to degree of ICA stenosis might be associated with outcome in patients with carotid diseases.

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ABSTRACT (IN KOREAN)

뇌경색 환자에서 속목 동맥의 협착 정도가
환자 예후에 미치는 영향

<지도교수 남 효 석>

연세대학교 대학원 의학과

박 혜 영

속목 동맥의 동맥경화는 뇌경색의 잘 알려진 위험인자이다. 이 연구는 급성 뇌경색으로 입원한 환자들에서 속목 동맥 협착 정도에 따른 뇌 자기공명영상에서의 뇌경색의 양상을 확인하고, 예후와의 관계를 규명하고자 하였다.

연구는 2004 년 1 월부터 2009 년 12 월 사이에 급성 뇌경색으로 입원한 환자 중 순수하게 속목 동맥의 협착 또는 폐색이 뇌경색의 원인이 된 환자를 분석하였다. 확산강조 자기공명영상을 이용하여 뇌경색의 양상을 (1) 피질하성 (2) 영역성 (3) 융합성 (4) 파종성 (5) 경계성의 5 가지로 분류하였다.

속목 동맥의 협착 정도와 뇌경색의 양상 및 예후와 관계에 대하여 연구하였다. 피질하 경색은 50% 미만의 협착을 가진 환자들에서 61.5%를 차지하였다. 완전 폐색이 있는 환자들에서는 영역성

경색(24.0%)과 융합성 형태(41.3%)가 주요 양상이었다. 속목 동맥의 완전 폐색이 있는 환자들에서 초기 뇌경색의 중증도, 퇴원 시와 3 개월째의 예후가 다른 군에 비해서 나빴다.

초기 신경학적 중증도의 독립적인 인자는 고령, 속목 동맥의 완전 폐색, 영역성 및 융합성 경색이었다. 퇴원 시와 3 개월째의 나쁜 예후는 초기 신경학적 중증도와 입원 중 진행성 뇌경색을 보인 경우와 관계가 있었다.

결론적으로, 속목 동맥의 동맥경화 정도는 뇌경색 영상 소견에서 차이를 보였고, 완전 속목 동맥 폐색 환자의 나쁜 예후를 확인할 수 있었다. 속목 동맥의 동맥경화 정도에 따라서 뇌경색 영상 소견과 예후에서 차이를 보이는 것은 뇌경색 발생 기전이 다름을 반영하는 것으로 보여진다.

핵심 되는 말: 속목 동맥, 예후, 뇌경색, 확산강조 자기공명영상