Impact of white matter hyperintensity on the long-term outcome in stroke patients with large artery atherosclerosis

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Impact of white matter hyperintensity on the long-term outcome in stroke patients with large artery atherosclerosis

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ABSTRACT

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Background: The presence of white matter hyperintensity (WMH) is related with poor long-term outcomes. Previous studies showed that the highest mortality rates were reported in patients with large atherosclerosis (LAA) or cardioembolism, and the lowest with lacunar strokes. However long-term outcome is unknown in patients with LAA and WMH. We investigated the impact of WMH on the long-term outcome in patients with LAA.

Methods : From May 1999 to June 2007, consecutive patients with acute ischemic stroke were included. They were followed for a median of 7.7 years (interquartile range, 5.5–9.9). Long-term mortality and causes of death were identified using death certificates or telephone interviews. Degree of WMH was

assessed by Fazekas grade on fluid-attenuated inversion recovery image. Severe WMH was defined as Fazekas grade ≥2.

Results: Among 2913 patients, the stroke subtype was LAA in 753 patients (25.8%). After excluding patients with unavailable FLAIR images, data of 556 patients were analyzed. Mean age was 65.6 ± 10.3 years and 66.9% were men. Severe WMHs were found in 286 patients (51.4%). During follow-up, 208 patients (37.4%) died. The Kaplan-Meier survival analysis showed that old age, diabetes, initial national institutes of health stroke scale, and severe WMH were associated with long-term mortality. The Cox regression analysis showed that severe WMH was an independent predictor for long-term mortality. LAA patients with severe WMH showed 1.57-fold (95% CI, 1.17-2.11) higher mortality rate compared to those without.

Conclusion: The degree of WMH might be one of surrogate markers for long-term outcome in patients with LAA. Atherosclerotic burdens in both small and large arteries might impact on long-term prognosis in ischemic stroke patients.

Key words: large artery atherosclerosis; white matter hyperintesity; mortality; brain infarction

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I. INTRODUCTION

Cerebral small vessel disease (SVD) encompasses all the pathological processes that affect not only the small vessels of the brain, but also capillaries and small veins.[1] SVD is thought to be the one of the most frequent pathological neurological process and has a crucial role in aging, stroke and other diverse diseases.[1-3] Although SVD is mainly associated with microvascular pathogenesis such as endothelial dysfunction and leakage of the blood-brain barrier, macrovascular diseases such as atherosclerosis and hypertension also have been associated with SVD.[1,4] SVD includes small subcortical infarcts, lacunes, prominent perivascular spaces, cerebral microbleeds, and white matter hyperintensity (WMH).[5]

WMH is a well known one of SVD and also called leukoaraiosis[6]. WMH is defined as patchy or confluent periventricular and subcortical areas of higher signal intensity on magnetic resonance imaging (MRI).[7-10] WMH is associated

with increasing age, hypertension, and other cerebrovascular risk factors.[11,12] Although WMH is strongly associated with vascular risk factors, it is also known as an independent predictor for the risk of symptomatic stroke,[13] stroke recurrence,[14] post stroke dementia,[15] and poor functional outcome at 3 months.[16] Furthermore, WMH increases the risk of long-term mortality in the general population,[17] young patients with ischemic stroke,[18] patients with lacunar infarction[19] and patients with atherosclerotic diseases.[20]

Stroke is the third most common cause of death worldwide.[21] The predictors of stroke prognosis include increasing age, SVD burden, a history of previous symptomatic atherothrombosis, smoking, cardiac failure, atrial fibrillation, pre-stroke functional status, and stroke severity. In the acute phase of stroke, one of the most important predictors is stroke severity, whereas, during follow-up, one of the most robust predictors of long-term mortality is increasing age.[22-24]

Among stroke subtypes, stroke of incomplete evaluation showed the highest mortality, followed by cardioembolism, large artery atherosclerosis (LAA), and lacunar infarction (LAC).[25] In LAA stroke subtype, major pathomechanism is artery to artery thromboembolism from atherosclerosis of major artery. However the main pathomechanism of the LAC is occlusion of asingle deep perforating intracerebral artery due to lipohyalinosis and microatheromatosis.[26,27] Among stroke subtypes, WMH is strongly linked to LAC as they share common small artery pathologies.[4,26,28] However, little is known about the impact of WMH on the long-term outcome in stroke patients of LAA subtype.

We hypothesized that stroke patients with LAA and WMH might have poor outcome because they have both large and small artery pathology together. Therefore, we investigated whether WMH is an independent predictor of poor

long-term outcome in stroke patients with LAA.

II. MATERIALS AND METHODS

1. Patients and evaluation

Subjects for this study were drawn from consecutive patients with acute ischemic stroke who had been registered in the Yonsei Stroke Registry from May 1999 to June 2007. The Yonsei Stroke Registry is a prospective hospital-based registry for patients with cerebral infarction or transient ischemic attack within 7 days after symptom onset.[29]

During admission, all patients were thoroughly investigated for medical history, clinical manifestations, and the presence of vascular risk factors. All registered patients underwent brain imaging studies including brain computed tomography (CT) or magnetic resonance imaging (MRI). An angiographic study using CT angiography, MR angiography or digital subtraction angiography was the standard evaluation tool. Every patient was evaluated with 12-lead electrocardiography, chest x-ray, lipid profile, and standard blood tests. Transesophageal echocardiography (TEE) was a part of the standard evaluation, except in patients with decreased consciousness, impending brain herniation, poor systemic conditions, inability to accept an esophageal transducer due to swallowing difficulty or tracheal intubation or lack of informed consent. Transthoracic echocardiography (TTE), heart CT, and Holter monitoring were performed in the selected patients.[30-32] A stroke unit was opened in the study hospital on December 2002. Since then, most patients have been admitted to the stroke unit and were monitored continuously with ECG during their stay in the stroke unit. Since July 2006, heart CT using multislice computed tomography

had been performed for the evaluation of the coronary artery, aorta, and heart. Patients were indicated for heart CT when they had at least one of the following: (1) presence of atherosclerosis in the intracranial or extracranial cerebral artery, (2) presence of ≥2 risk factors for coronary artery disease such as hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, and central obesity, and (3) old age (men >45 years, women >55 years).[33]

Among the consecutive patients who had been registered in the prospective stroke registry, those with transient ischemic attack were excluded. When a patient was admitted more than twice due to recurrent strokes, only data for the first admission was used for this study. Initial stroke severity was determined by National Institute of Health Stroke Scale (NIHSS) scores and score tertiles were used for the analysis. This study was approved by the Severance Hospital Institutional Review Board, Yonsei University Health System.

2. Stroke subtype classification and clinical variables

The stroke subtype was determined according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.[34] Large artery atherosclerosis is defined when there is significant (≥50%) stenosis of the large artery relevant to the acute infarction. [34] Stroke classification was determined at weekly stroke conferences on the basis of a consensus among stroke specialists, and was prospectively entered into the computerized database.[29]

3. Risk factors

Hypertension was defined when a patient had a resting systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on repeated measurements during hospitalization or had been taking antihypertensive medication. Diabetes mellitus was diagnosed when a patient had a fasting plasma glucose

value ≥7 mmol/L or had been treated with an oral hypoglycemic agent or insulin. Hyperlipidemia was diagnosed when a patient had a fasting serum total cholesterol level ≥6.2 mmol/L, low density lipoprotein-cholesterol ≥4.1 mmol/L or had been taking a lipid-lowering drug after the diagnosis of hyperlipidemia. A current smoker was defined as an individual who smoked at the time of stroke or had quit smoking within one year.

4. Assessment of white matter hyperintensity

WMH was defined as supratentorial hyperintense lesions on FLAIR imaging according to the standards for reporting vascular changes on neuroimaging criteria.[5] When patients had multiple imaging studies, the first MRI was used for white matter grading.

The degrees of both periventricular white matter hyperintensity (PVWMH) and deep white matter hyperintensity (DWMH) were assessed using a 4-level ordinal scale (none, mild, moderate, or severe) based on the methodology of Fazekas. PVWMH was graded as 0 = absence, 1 = “caps” or pencil-thin lining, 2 = smooth “halo”, 3 = irregular WMH extending into the deep white matter. Separate DWMH signals were rated as 0 = absence, 1 = punctuate foci, 2= beginning confluence of foci, 3 = large confluent areas.[35] Severe WMH was defined as grades ≥2 in the Fazekas scale in either periventricular or deep white matter and others were defined as mild or no WMH.[36]

Two neurologists who were blinded to the clinical findings performed analysis of hyperintensity separately. Inter-rater reliability in terms of determining the degree of WMH was calculated. The kappa values for the Fazekas scale of PVWMH, DWMH, and final WMH burden were 0.799, 0.754, and 0.838, respectively.

5. Short term functional outcome and long-term mortality

Short-term functional outcomes at 3 months were determined based on the modified Rankin scale (mRS). Poor outcome was defined as a mRS score >2. Long-term mortality and causes of death were identified using death certificates from the Korean National Statistical Office. In Korea, by law, all deaths of Koreans must be reported to the National Statistical Office. The physician who examined the decedent certified deaths during the hospitalization or within 48 hours after discharge from a hospital. For deaths not certified by physicians, any vague or missing item on the death certificate is clarified by the National Statistical Office via telephone.[37] Deaths among subjects from May 1999 to December 31, 2007 were confirmed by matching the information in the death records and identification numbers assigned to subjects at birth.[38]

6. Statistical analysis

SPSS for Windows (version 21.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The Pearson chi-square test was used to compare frequencies. For continuous variables, data distributions were examined for normality using the Kolmogorov-Smirnov test. Provided that the data did not deviate from a normal distribution, the mean and standard deviation (SD) were calculated and independent sample t-tests were used for comparisons. For data that were not normally distributed, we reported descriptive statistics as the median and interquartile range (IQR) and compared them using the Kruskal-Wallis test. . Independent predictors for poor outcome at 3 months were determined using the logistic regression analysis. Variables with $p < 0.1$ in univariable analysis and sex were entered into the multivariable model. To compare the long-term mortality according to presence of severe WMH, a Kaplan-Meier analysis was used to estimate survival conditions and the

log-rank test was used to compare rate estimates. The Cox proportional hazard regression analysis was performed to calculate crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). For univariable Cox analyses, the presence of severe WMH and possible confounding factors including age, sex, hypertension, diabetes, current smoking, hyperlipidemia, and initial NIHSS scores were compared. Variables with $p < 0.1$ in the univariable analyses and sex were entered into the multivariable Cox regression model to identify independent predictors of long-term mortality.

III. RESULTS

1. Study population

During the study period, 2193 patients of acute ischemic stroke patients were admitted and registered in the Yonsei stroke registry. Among the 2193 patients, 753 patients were categorized into stroke of LAA subtype. After excluding 197 patients with unavailable FLAIR imaging, 556 patients were finally included in this study. Patients were followed for a median of 7.7 years (IQR, 5.5–9.9).

The median age of the patients was 66.5 years (IQR, 59.0-73.0) and 66.9% of the patients were men. Overall, 46.4% were younger than 60 years and 2.0% were older than 80 years. The initial median NIHSS score was 4 (IQR, 2–9) (Table 1). Severe WMH was found in 286 patients (51.4%) and no WMH was found in 4 patients (0.7%) (Table 2).

Deep WMH and periventricular WMH were influenced by each other ($p < 0.001$, linear by linear association). When comparing with patients with mild or no WMH, those with severe WMH were older ($p < 0.001$), more frequently had hypertension ($p = 0.011$) and less frequently were current smokers ($p=0.001$) (Table 1).

Table 1. Baseline characteristics of patients according to presence of severe white matter hyperintensity

	Total	Severe	Mild	No	*p*-value
	556	286 (51.44)	266 (47.8)	4 (0.7)	
Age, yrs					
mean ± SD	65.65 ± 10.3	68.70 ± 8.60	62.70 ± 10.61	43.25 ± 17.46	
median	66.50 [59.0-73.0]	69.0 [63.0-75.0]	63.0 [55.0-71.0]	42.5 [29.5-57.0]	<0.001
	258 (46.4)	37 (12.9)	104 (39.1)	3 (75.0)	
	287 (51.6)	223 (78.0)	149 (56.0)	1 (25.0)	
	11 (2.0)	26 (9.1)	13 (4.9)	0	
Sex, men	372 (66.9)	184 (64.3)	187 (70.3)	1 (25.0)	0.058
Hypertension	429 (77.2)	234 (81.8)	193 (72.6)	2 (50.0)	0.011
Diabetes	226 (40.6)	116 (40.5)	109 (41.0)	1 (25.0)	0.905
Hyperlipidemia	70 (12.6)	32 (11.2)	37 (13.9)	1 (25.0)	0.297
Smoking	275 (49.5)	123 (43.0)	151 (56.8)	1 (25.0)	0.002
Initial NIHSS scores	4 [2–9]	4[1.0-9.0]	4 [2.0-8.0]	9 [7.5-11.0]	0.094
≤ 2	200 (36.0)	114 (39.9)	86 (32.3)	0	
3-5	134 (24.1)	63 (22.0)	71 (26.7)	0	
≥6	222 (39.9)	109 (38.1)	109 (41.0)	4 (100)	

Data are expressed as mean ± SD, median [interquartile range] or a number (%).

NIHSS: National Institute of Health Stroke Scale.

Table 2. Distribution of patients according to deep and periventricular white matter hyperintensity ratings

	DWMH			
PVWMH	0	1	2,3	Total
0	4	2	0	6 (1.1)
1	4	260	16	280 (50.4)
2,3	0	112	158	270 (48.6)
Total	8 (1.4)	374 (67.3)	174 (31.3)	556 (100)

For categorical variables, results are indicated as number (%).

DWMH : deep white matter hyperintensity, PVWMH : periventricular white matter hyperintensity.

2. Functional outcome at 3 months

Univariable analyses showed that patients with old age, hypertension, or higher initial NIHSS score more likely had poor functional outcomes at 3 months. In multivariable analysis, age ≥80 and initial stroke severity were independent predictors of poor outcome at 3 months. However, there was no difference in functional outcome at 3 months according to the presence of severe WMH (OR 1.06, 95% CI 0.67-1.68, p = 0.808) (Table 3).

Table 3. Univariable and multivariable analyses for poor outcome at 3 months (mRS 3-6).

	mRS 3-6	Univariable		Multivariable*	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (years)		1.03 (1.01-1.05)	0.003		
<60	30 (18.2)	1		1	
60-79	115 (69.7)	1.69 (1.07-2.68)	0.024	1.70 (0.98-2.96)	0.059
≥80	20 (12.1)	4.00 (1.90-8.43)	<0.001	6.35 (2.40-16.79)	<0.001
Sex (men)	108 (65.5)	0.91 (0.62-1.34)	0.637	0.89 (0.56-1.42)	0.892
Hypertension	137 (83.0)	1.66 (1.04-2.64)	0.033	1.68 (0.97-2.92)	0.065
Diabetes	71 (43.0)	1.15 (0.80-1.66)	0.458		
Smoking	81 (49.1)	0.98 (0.68-1.41)	0.91		
Hyperlipidemia	22 (13.3)	1.10 (0.64-1.89)	0.731		
Initial NIHSS score					
0-2	9 (5.5)	1		1	
3-5	30 (18.2)	6.12 (2.80-13.39)	<0.001	6.47 (2.91-14.40)	<0.001
≥6	126 (76.4)	27.85 (13.57-57.19)	<0.001	31.32(14.87-65.97)	<0.001
Severe WMH	88 (53.3)	1.11 (0.77-1.60)	0.562	1.06 (0.67-1.68)	0.808

Data are expressed as number (%) or hazard ratio (95% CI).

* Variables (age, hypertension and initial NIHSS scores), which showed p <0.1 in the univariable analyses, sex and severe WMH were included in the multivariable analysis.

NIHSS: National Institute of Health Stroke Scale, WMH : white matter hyperintensity.

3. Cumulative death rates

During the follow-up period, 208 patients (37.4%) died. The Kaplan-Meier survival analysis showed that more patients with severe WMH died during long-term follow-up compared without severe WMH ($p<0.001$ by Log-rank test, Figure 1).

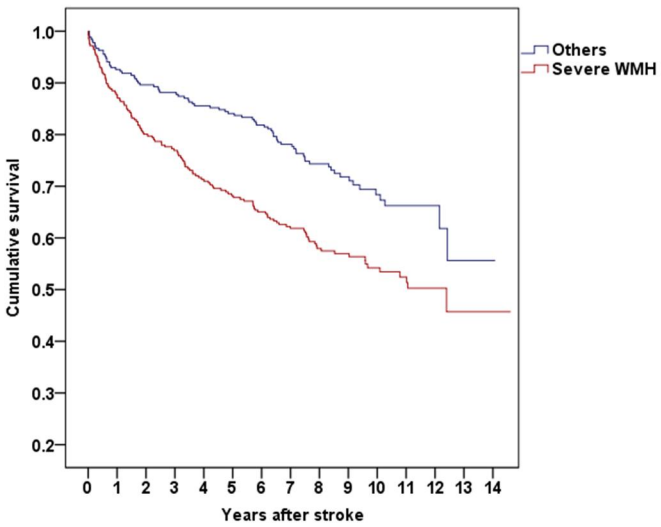

Figure 1. Kaplan-Meier survival curve according to the presence of severe white matter hyperintensity. Univariable Kaplan-Meier survival analysis revealed that LAA patients with severe WMH showed higher mortality during follow-up than those with mild or no WMH ($p<0.001$).

LAA : large artery atherosclerosis, WMH : white matter hyperintensity.

4. Univariable and multivariable analyses of long-term mortality

Univariable Cox regression analyses revealed that older age, a history of diabetes, initial stroke severity, or the presence of severe WMH was associated with long-term mortality (Table 4). Multivariable Cox regression analysis revealed that older age, a history of diabetes, initial stroke severity, and the presence of severe WMH were independent predictors of long-term mortality (Table 4). The patients with severe WMH showed higher death rate compared with mild or no WMH after adjustment (HR 1.57, 95% CI 1.17-2.11, p=0.003, Table 4).

Table 4. Cox regression analyses of long-term mortality

	Death	Univariable		Multivariable*	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (years)					
<60	28 (19.4)	1		1	
60-79	149 (39.9)	2.38 (1.59-3.57)	<0.001	2.13 (1.40-3.25)	<0.001
≥80	31 (79.5)	7.66 (4.58-12.82)	<0.001	7.40 (4.32-12.67)	<0.001
Sex (men)	148 (39.8)	1.23 (0.91-1.65)	0.184	1.29 (0.96-1.75)	0.096
Hypertension	157 (36.6)	0.94 (0.69 (1.29)	0.709		
Diabetes	96 (42.5)	1.32 (1.00-1.73)	0.047	1.35 (1.02-1.77)	0.034
Smoking	104 (37.8)	1.00 (0.76-1.31)	0.995		
Hyperlipidemia	22 (31.4)	0.793 (0.51-1.23)	0.304		
Initial NIHSS score					
0-2	47 (23.5)	1		1	
3-5	52 (38.8)	1.85 (1.24-2.74)	0.002	1.94 (1.30-2.90)	0.001
≥6	109 (49.1)	2.73 (1.94-3.85)	<0.001	3.14 (2.22-4.44)	<0.001
Severe WMH	127 (44.7)	1.71 (1.29-2.26)	<0.001	1.57 (1.17-2.11)	0.003

Data are expressed as number (%) or hazard ratio (95% CI).

* Variables (age, diabetes, initial NIHSS score, presence of severe WMH), which showed p <0.1 in the univariable analyses and sex were included in the multivariable analysis. Abbreviations are the same as in Table 3.

5. Subgroup analysis of cumulative death rate according to age

We additionally dichotomized into 2 subgroups according to age (Age <65 years vs. Age ≥65 years) according to median of age (65 years). The median ages of the subgroup were 58 years (IQR, 52-62) and 72 years (IQR, 68-77) respectively. The patients of Age ≥65 years were less frequently men (p = 0.038), current smoker (p =0.001). Older age group was more likely to have severe WMH compared to younger group (62% vs. 37%, p<0.001) (Table 5).

Table 5. Subgroup analysis according to median age

	Age <65 243	Age ≥65 313	*p*-value
Age, years			
mean ± SD	56.3 ± 6.99	72.90 ± 5.48	
median	58 [52-62]	72 [68-77]	<0.001
Sex, men	174 (71.6)	198 (63.3)	0.038
Hypertension	182 (74.9)	247 (78.9)	0.263
Diabetes	106 (43.6)	120 (38.3)	0.208
Hyperlipidemia	33 (13.6)	37 (11.8)	0.535
Smoking	140 (57.6)	135 (43.1)	0.001
Initial NIHSS scores	4 [2-8]	4 [2-9]	0.801
≤ 2	86 (35.4)	114 (36.4)	
3-5	60 (24.7)	74 (23.6)	
≥6	97 (39.9)	125 (39.9)	
Severe WMH	90 (37.0)	194 (62.0)	<0.001
Death	52 (21.4)	156 (49.8)	<0.001

Data are expressed as mean ± SD, median [interquartile range], or a number (%). Abbreviations are the same as in Table 3.

The Kaplan-Meier survival analysis showed that more patients with severe WMH died during long-term follow-up compared those with mild or no WMH among the older patient group (p=0.032 by log rank test, Figure 2A). In contrast, there was no statistical difference in long-term mortality among younger patients (HR 1.07, 95% CI 0.61-1.88, p = 0.804, Figure 2B).

Multivariable Cox regression analyses revealed that older age, initial stroke severity, and the presence of severe WMH were independent predictors of long-term mortality in the subgroup of age ≥ 65 years (Table 6). These patients with severe WMHs showed higher death rate compared with those with mild or no WHM after adjustments (HR 1.69, 95% CI 1.11-2.57, p = 0.014, Table 6).

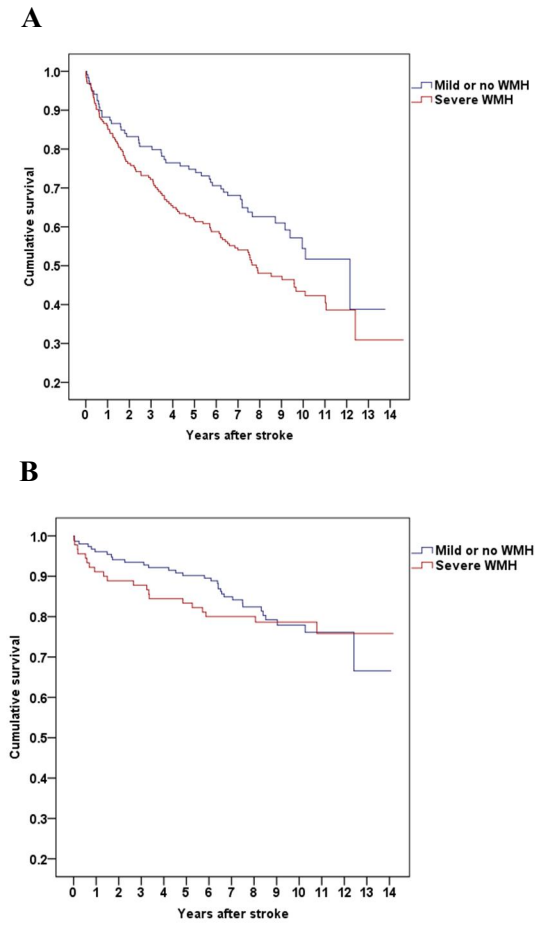

Figure 2. Kaplan-Meier survival curve according to the presence of severe white matter hyperintensity in the subgroup of (A) older (age ≥65) and (B) younger (age <65) patient. Older patients with severe WMH showed higher mortality during follow-up than those with mild or no WMH (p=0.032), however younger patients group showed no difference of long-term mortality according to the severity of WMH (p=0.804).

WMH : white matter hyperintensity

Table 6. Cox regression analysis of long-term mortality in subgroup of older patients (age ≥65)

	Death	Univariable		Multivariable*	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (years)					
65-74	78 (39.4)	1		1	
≥75	78 (67.8)	2.42 (1.76-3.32)	<0.001	2.41 (1.75-3.34)	<0.001
Sex (men)	108 (54.5)	1.32 (0.94-1.86)	0.106	1.26 (0.89-1.77)	0.189
Hypertension	119 (48.2)	0.90 (0.62-1.30)	0.562		
Diabetes	66 (55.0)	1.25 (0.91-1.72)	0.167		
Smoking	73 (54.1)	1.20 (0.88-1.65)	0.252		
Hyperlipidemia	14 (37.8)	0.68 (0.39-1.18)	0.174		
Initial NIHSS Score					
0-2	34 (29.8)	1		1	
3-5	41 (55.4)	2.34 (1.49-3.70)	<0.001	2.55(1.60-4.05)	<0.001
≥6	81 (64.8)	3.58 (2.39-5.37)	<0.001	3.89 (2.58-5.86)	<0.001
Severe WMH	107 (55.2)	1.44 (1.03-2.03)	0.033	1.61 (1.14-2.27)	0.007

* Variables (age, initial NIHSS scores, presence of severe WMH), which showed p <0.1 in the univariable analyses and sex were included in the multivariable analysis. Abbreviations are the same as in Table 3.

Data are expressed as number (%) or hazard ratio (95% CI).

6. Subgroup analysis of cumulative death rate according to sex

We additionally analyzed Kaplan-Meier survival analyses in each sex subgroup. Women with severe WMH showed higher death rate than those with mild or no WMH (HR 1.49, 95% CI 0.88-2.52, p = 0.138, Figure 3A). Men with severe WMH showed higher death rate than those with mild or no WMH (HR 1.86, 95% CI 1.33-2.58, p <0.001, Figure 3B).

There was no statistically significant difference in the women subgroup. We additionally analyzed 5 year and 10 year mortality because most women patients with severe WMH were censored after 9 years. In that analysis the women with severe WMH showed trends of higher death rate than those with mild or no WHM (10-year mortality, HR 1.57, 95% CI 0.92-2.67, p=0.099, Figure 4A; 5-year mortality, HR 1.90, 95% CI 0.99-3.66, p=0.054, Figure 4B).

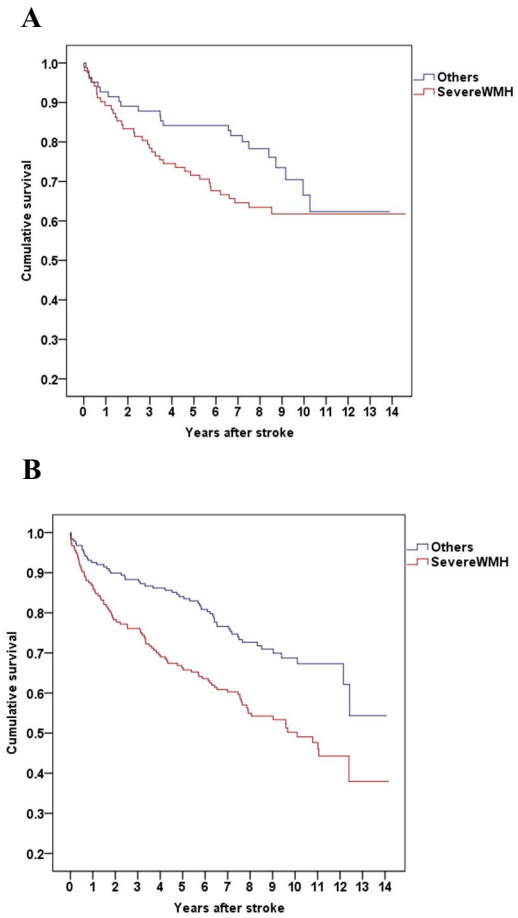

Figure 3. Kaplan-Meier survival curve according to the presence of severe white matter hyperintensity (A) in women and (B) men. Among men, univariable Kaplan-Meier survival analysis revealed that LAA patients with severe WMH showed higher mortality during follow-up than those with mild or no WMH ($p<0.001$). However, there was no significant difference in women ($p = 0.138$).

WMH : white matter hyperintensity

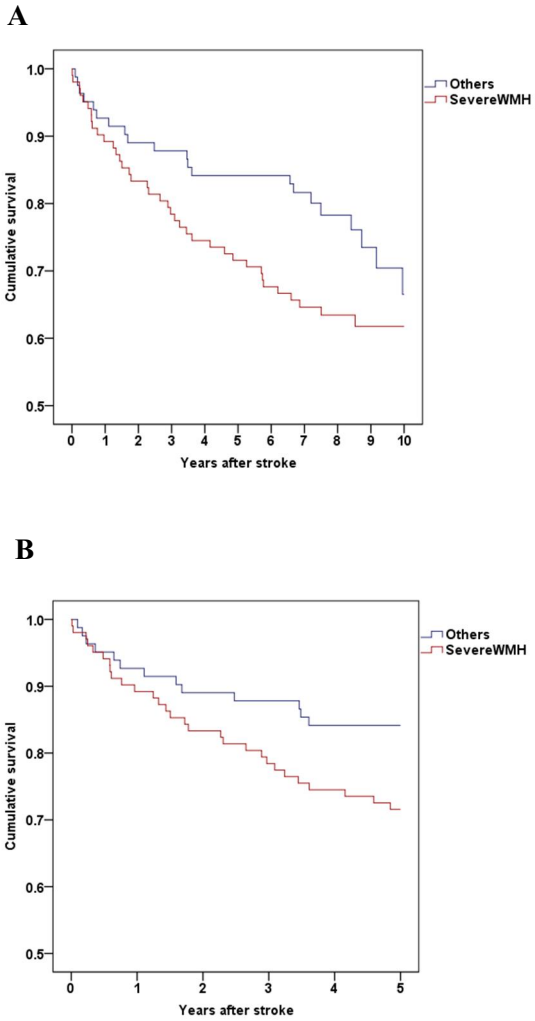

Figure 4. Analyses of (A) 5 year and (B) 10 year mortality according to the presence of severe white matter hyperintensity in women subgroup. Univariable Kaplan-Meier survival analyses revealed that LAA women patients with severe WMH showed trends of higher mortality during follow-up than those with mild or no WMH (10 years mortality p = 0.099 and 5 years mortality p = 0.054).

WMH : white matter hyperintensity

7. Subgroup analysis of cumulative death rate according to hypertension

We analyzed Kaplan-Meier survival analyses in each subgroup according to the presence of hypertension. Patients with both hypertension and severe WMH showed higher death rate than those with mild or no WMH (HR 1.78, 95% CI 1.28-2.47, p = 0.001, Figure 5A). In the patients without hypertension, there was no statistical difference in death rate between patients with severe WMH and with mild or no WMH (HR 1.64, 95% CI 0.94-2.83, p=0.08, Figure 5B).

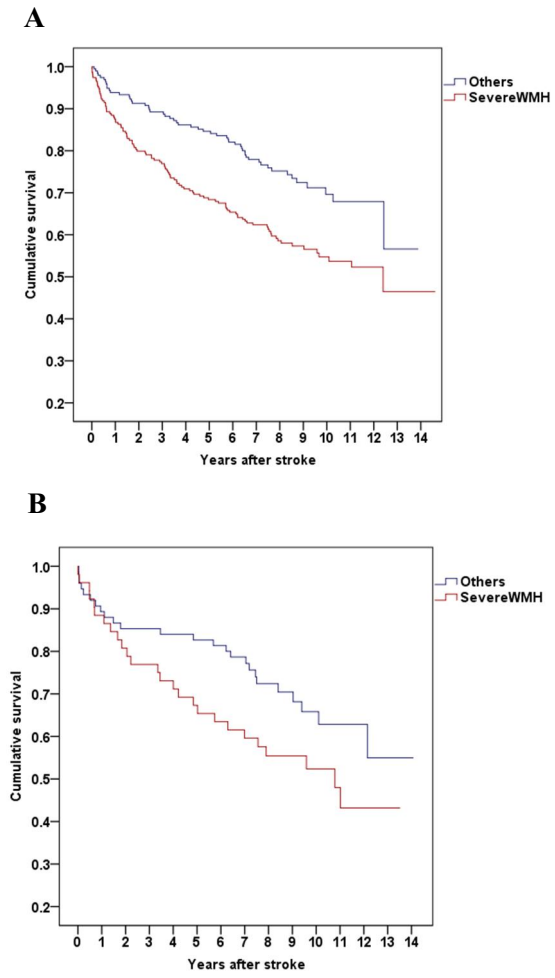

Figure 5. Kaplan-Meier survival curve according to the presence of severe white matter hyperintensity (A) with hypertension and (B) without hypertension. Univariable Kaplan-Meier survival analysis revealed that LAA patients with severe WMH and hypertension showed higher mortality during follow-up than those with mild or no WMH ($p = 0.001$). However, there was no statistically significant difference in patients without hypertension group ($p = 0.08$).

WMH : white matter hyperintensity,

Because cumulative death rates were similar between the subgroups of hypertension during early period and the aim of study was to investigate long-term mortality, we further analyzed 5 year and 10 year mortality in the subgroup of patients without hypertension who lived more than one month after symptom onset.. Among patients died in 1 month, there was no statistical difference in demographic characteristics according to the presence of severe WMH (Table 7). Among patients without hypertension, those with severe WMH showed higher death rate than those with mild or no WMH (10-year mortality, HR 1.74, 95% CI 0.95-3.19, p=0.073, Figure 6A; 5-year mortality, HR 2.29, 95% CI 1.03-5.10, p=0.042, Figure 6B).

Table 7. Baseline characteristics of patients who died whithin 1 month according to presence of severe white matter hyperintensity in the subgroup of patients without hypertension.

	Total N = 11	Severe N = 8	Mild or no N = 3	*p*-value
Age, years				
mean ± SD	66.55 ± 11.16	69.00 ± 7.52	60.00 ± 18.33	
median	70 [58.5-72.5]	71 [65.5-72.5]	56 [50.0-68.0]	0.538
<60	3 (27.3)	1 (12.5)	2 (66.7)	
60-79	7 (63.6)	7 (87.5)	0 (0.0)	
≥80	1 (9.1)	0 (0.0)	1 (33.3)	
Sex, men	9 (81.8)	6 (75.0)	3 (100.0)	1.000
Hypertension	6 (54.5)	6 (75.0)	0 (0.0)	0.061
Diabetes	3 (27.3)	3 (37.5)	0 (0.0)	0.491
Hyperlipidemia	1 (9.1)	1 (12.5)	0(0.0)	> 0.999
Smoking	5 (45.5)	3 (37.5)	2 (66.7)	0.545
Initial NIHSS scores	13 [11.5-15.5]	13 [11.5-16.5]	12 [9.0-13.5]	0.356
≤ 2	0 (0.0)	0 (0.0)	0 (0.0)	
3-5	0 (0.0)	0 (0.0)	0 (0.0)	
≥6	11 (100.0)	8 (100.0)	3(100.0)	

Data are expressed as mean ± SD, median [interquartile range], or a number (%).

NIHSS: National Institute of Health Stroke Scale.

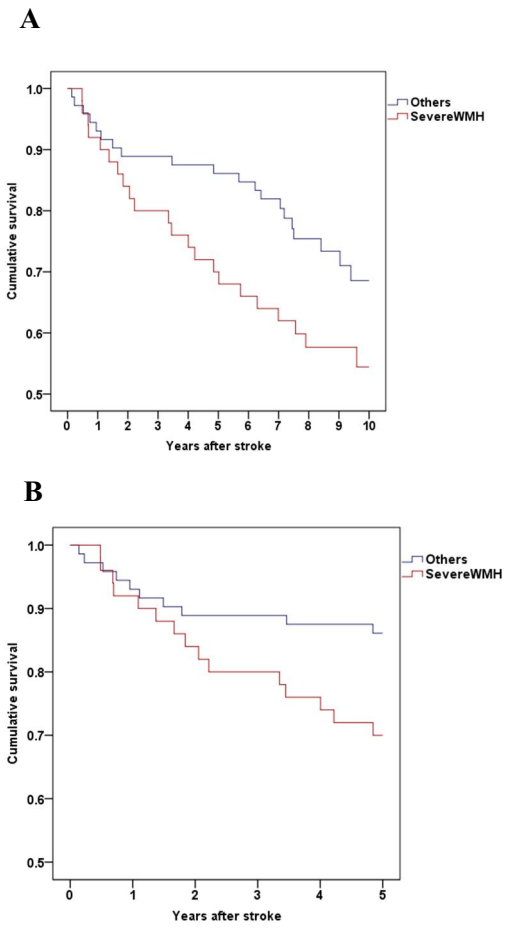

Figure 6. Analyses of (A) 5 year and (B)10 year mortality according to the presence of severe white matter hyperintensity in the subgroup of patients without hypertension who lived more than one month. Univariable Kaplan-Meier survival analysis revealed that patients without hypertension and with severe WMH showed higher mortality during follow-up than those with mild or no WMH (10 years mortality p = 0.073 and 5 years mortality p = 0.042).

WMH : white matter hyperintensity

IV. DISCUSSION

This study demonstrated that WMH was independently associated with long-term outcome after ischemic stroke of LAA subtype, especially in older patients. Relationship between WMH and mortality remained significant after adjustment of well-known predictors including age and initial stroke severity.

Our study showed that WMH was an independent predictor of long-term morality in patients with LAA. The association between WMH and large artery stenosis itself has been controversial in previous studies. WMH was less frequent in patients with territorial infarcts than in those with other stroke subtypes, especially LAC subtype.[28] One study showed that severity of arterial stenosis was not related with the severity of WMH.[39] However, other studies have supported the association between WMH and LAA pathology. In 100 stroke patients of LAC without intracranial artery stenosis, carotid stenosis was an important risk factor for WMH.[40] In a single study of 594 Korean patients with stroke of LAA subtype, the LAA group was more likely to have WMH than did the other groups. In the subgroup analysis of LAA group, WMH had tendency to be more prevalent in the intracranial stenosis group than did the extracranial stenosis group.[41] In another study, 12 patients who underwent a therapeutically occlusion of the internal carotid artery, 4 developed WMH during follow-up.[42]

Although, previous studies have suggested an association between the severity of WMH and long-term mortality in stroke patients, underlying mechanisms have not been clearly elucidated.[17-20,26,43,44] One possible hypothesis was based on the association between SVD and arterial stiffness. The presence of cerebral SVD was correlated with increased augmentation index and pulse wave velocity which represent arterial stiffness.[45] Arterial stiffness increases the pulse pressure

and contributes to systemic hypertensive injury. Because brain vessels have a low vascular resistance, cerebral SVD is vulnerable to theses increased pulse pressure.[46-48] Besides, increased arterial stiffness was strongly associated with atherosclerosis at various large arterial trees.[49,50] Furthermore, increased arterial stiffness was an independent predictor of long-term mortality.[51] Considering WMH usually occurs in the territory of the superficial penetrating branches of large cerebral arteries, not in the territory of deep penetrating arteries.[52] Taken all together, in stroke of LAA subtype, WMH might be one of surrogate marker of accompanying small artery pathology. Further studies are needed to clarify the direct association between the WMH and large artery pathology.

In our study, functional outcomes at 3 months were similar regardless of the presence of severe WMH. In the multivariable analysis, age over 80 years and initial stroke severity were independent predictors of poor outcome at 3 months. In the population-based Greater Cincinnati Stroke Study with 451 ischemic stroke subjects, ischemic stroke patients with severe WMH had a 3 month mRS score that was, on average, 0.47 points higher than patients without WMH.[16] In stroke of LAA subtype, large artery pathology may play a major role in initially severe stroke, which is a strong predictor of 3-month functional outcome and encompass the effect of WMH.[22,53,54] Short-term outcome (mRS at 3 months) was associated with initial stroke severity, not with WMH severity. In stroke of LAA subtype, the major determinant of short-term outcome might be stroke severity and infarction growth that is dependent of burdens of large vessel disease. But in terms of long-term mortality, the influence of both large and small vessel burden might play a synergistic effect on the mortality.

In subgroup analyses of our study, the patents ≥65 years with severe WMH was associated with higher mortality, even after adjustment for strong confounders, age and initial stroke severity.[22-24] In contrast, there was no

association between severe WMH and mortality in the younger patient group (age under 65). A previous study showed moderate to severe WMH was independently associated with all-cause mortality even in young patients (age range, 15-49). This discrepancy of the results of previous study may be due to the difference in the age of study population, which might cause different baseline characteristics, and stroke subtypes.[18] Our findings suggest that the WMH and aging may synergistically increase the risk of death after initial stroke events.

When comparing with patients with mild or no WMH, those with severe WMH were less likely to be current smokers. Considering univariable logistic regression analysis showed the inverse correlation between aging and smoking (OR 0.97, 95% CI 0.95-0.99, p <0.001), age may be more strongly associated with WMH, this association may influence the low frequency of smokers in patients with severe WMH.[55]

There were some limitations in our study. First, there exists the possibilities of confounding effect because MRI was performed various machines. However, we thought that grossly dichotomizing the degree of WMH [severe vs. mild or no], not quantifying WMH burden with volumetry would not be influenced by MRI protocol. Second, the design of study is based on retrospective analysis of single center registry. Possible selection bias may influence our results. Third, we did not quantify WMH burden with volumetry, which may be more sensitive for detecting subtle intergroup differences and avoid a ceiling-effect in patients with severe WMH. However the Fazekas scale is well established, frequently used in clinical research, has been shown to correlated well with the WMH volume.[56] Our study also showed high inter-rater reliability. Fourth, patients with only LAA subtype were included. To study association between the severe WMH and long-term mortality of other stroke subtypes might be helpful

understanding that of LAA subtype. Further investigation might be needed in near future.

V. CONCLUSION

Severe WMH was independently associated with long-term clinical outcome in patients with LAA subtype, especially in older patients. Atherosclerotic burdens in both small and large artery might impact on long-term prognosis in ischemic stroke patients.

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ABSTRACT(IN KOREAN)

뇌백질 변화가 동맥경화성성 뇌경색 환자의 장기 예후에 미치는 영향

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백 민 렬

목적 : 뇌백질 변화는 뇌경색 환자의 예후에 나쁜 영향을 주는 중요한 요인이다. 특히, 뇌백질 변화와 열공 경색의 관계는 기존에 잘 밝혀져 있고 뇌백질 변화가 동반된 열공 경색 환자가 장기적인 사망률이 높다고 알려져 있다. 하지만, 동맥경화증 뇌경색 환자의 장기 예후에 뇌백질 변화가 미치는 영향에 대해서는 밝혀진 바가 없다. 본 연구에서는 급성 뇌경색환자의 추적 관찰을 통해서 뇌백질 변화가 장기 예후에 어떤 영향을 주는 지 알아보고자 하였다.

방법 : 연구는 1999년 5월부터 2007년 6월까지 뇌경색을 진단 받은 환자를 대상으로 자기공명영상(magnetic resonance imaging, MRI)으로 액체감약반전회복(Fluid attenuated inversion recovery, FLAIR)

검사를 시행한 환자를 대상으로 하였다. 뇌백질 변화의 정도는 Fazekas 척도로 평가하였다. Fazekas 등급 2 이상을 심한 뇌백질변화로 정의하였다. 환자들은 장기간(중위수 7.7년) 동안 추적 관찰하였고, 사망 여부는 통계청 사망 자료와 병록기록, 전화 설문 등을 이용하였다.

결과 : 총 2913명의 뇌경색 환자 중 동맥경화증 뇌경색 환자는 753명(25.8%)이였고, 이 중에서 액체감약반전회복 영상을 시행한 환자 556명이었다. 중증 백질변화는 286명(51.4%)에서 관찰되었다. 추적 기간 동안 208명(37.4%)의 환자가 사망하였다. 고령, 당뇨병, 초기 뇌경색 중증도 및 심한 뇌백질 변화의 여부가 사망률을 높이는 인자였다. 동맥경화성 뇌경색 환자에서 심한 뇌백질 변화를 가지고 있는 경우 사망률을 1.57배 (95% CI, 1.17-2.11) 증가시켰다.

결론 : 본 연구는 뇌백질 변화의 정도가 동맥 경화성 뇌경색 환자의 장기 예후를 예측하는 독립적인 인자임을 확인하였다. 대혈관 및 소혈관 동맥경화가 함께 있는 뇌경색 환자는 높은 사망률을 보이는 것으로 생각된다.

핵심되는 말 : 동맥경화; 뇌백질 변화; 사망률; 뇌경색