JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2024;20(2):175-185 / https://doi.org/10.3988/jcn.2023.0181

Brain Frailty and Outcomes of Acute Minor Ischemic Stroke With Large-Vessel Occlusion

Je-Woo Park[a], Joon-Tae Kim[a], Ji Sung Lee[b], Beom Joon Kim[c], Joonsang Yoo[d], Jung Hoon Han[e], Bum Joon Kim[f], Chi Kyung Kim[e], Jae Guk Kim[g], Sung Hyun Baik[h], Jong-Moo Park[i], Kyusik Kang[j], Soo Joo Lee[g], Hyungjong Park[k], Jae-Kwan Cha[l], Tai Hwan Park[m], Kyungbok Lee[n], Jun Lee[o], Keun-Sik Hong[p], Byung-Chul Lee[q], Dong-Eog Kim[r], Jay Chol Choi[s], Jee-Hyun Kwon[t], Dong-Ick Shin[u], Sung Il Sohn[k], Sang-Hwa Lee[v], Wi-Sun Ryu[w], Juneyoung Lee[x], Hee-Joon Bae[c]

[a]Department of Neurology, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea
[b]Clinical Research Center, Asan Institute for Life Sciences, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[c]Department of Neurology, Cerebrovascular Center, Seoul National University Bundang Hospital, Seongnam, Korea
[d]Department of Neurology, Yongin Severance Hospital, Yongin, Korea
[e]Department of Neurology, Korea University Guro Hospital, Seoul, Korea
[f]Department of Neurology, Asan Medical Center, Seoul, Korea
[g]Department of Neurology, Daejeon Eulji Medical Center, Eulji University School of Medicine, Daejeon, Korea
[h]Department of Radiology, Seoul National University Bundang Hospital, Seongnam, Korea
[i]Department of Neurology, Uijeongbu Eulji Medical Center, Eulji University School of Medicine, Uijeongbu, Korea
[j]Department of Neurology, Nowon Eulji Medical Center, Eulji University School of Medicine, Seoul, Korea
[k]Department of Neurology, Keimyung University Dongsan Medical Center, Keimyung University School of Medicine, Daegu, Korea
[l]Department of Neurology, Dong-A University Hospital, Busan, Korea
[m]Department of Neurology, Seoul Medical Center, Seoul, Korea
[n]Department of Neurology, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Korea
[o]Department of Neurology, Yeungnam University Medical Center, Daegu, Korea
[p]Department of Neurology, Inje University Ilsan Paik Hospital, Goyang, Korea
[q]Department of Neurology, Hallym University Sacred Heart Hospital, Anyang, Korea
[r]Department of Neurology, Dongguk University Ilsan Hospital, Goyang, Korea
[s]Department of Neurology, Jeju National University Hospital, Jeju National University School of Medicine, Jeju, Korea
[t]Department of Neurology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea
[u]Department of Neurology, Chungbuk National University Hospital, Cheongju, Korea
[v]Department of Neurology, Hallym University Chuncheon Sacred Heart Hospital, Chuncheon, Korea
[w]Artificial Intelligence Research Center, JLK Inc., Seoul, Korea
[x]Department of Biostatistics, Korea University, Seoul, Korea

Received May 19, 2023
Revised June 30, 2023
Accepted July 4, 2023

Correspondence
Joon-Tae Kim, MD, PhD
Department of Neurology,
Chonnam National University Hospital,
Chonnam National University
Medical School,
42 Jebong-ro, Dong-gu,
Gwangju 61469, Korea
Tel +82-62-220-6180
Fax +82-62-228-3461
E-mail alldelight2@jnu.ac.kr

Beom Joon Kim, MD, PhD
Department of Neurology,
Cerebrovascular Center,
Seoul National University
Bundang Hospital,
82 Gumi-ro 173beon-gil, Bundang-gu,
Seongnam 13620, Korea
Tel +82-31-787-7467
Fax +82-31-787-4059
E-mail kim.bj.stroke@gmail.com

Background and Purpose The influence of imaging features of brain frailty on outcomes were investigated in acute ischemic stroke patients with minor symptoms and large-vessel occlusion (LVO).

Methods This was a retrospective analysis of a prospective, multicenter, nationwide registry of consecutive patients with acute (within 24 h) minor (National Institutes of Health Stroke Scale score=0−5) ischemic stroke with anterior circulation LVO (acute minor LVO). Brain frailty was stratified according to the presence of an advanced white-matter hyperintensity (WMH) (Fazekas grade 2 or 3), silent/old brain infarct, or cerebral microbleeds. The primary outcome was a composite of stroke, myocardial infarction, and all-cause mortality within 1 year.

Results In total, 1,067 patients (age=67.2±13.1 years [mean±SD], 61.3% males) were analyzed. The proportions of patients according to the numbers of brain frailty burdens were as follows: no burden in 49.2%, one burden in 30.0%, two burdens in 17.3%, and three burdens in 3.5%. In the Cox proportional-hazards analysis, the presence of more brain frailty burdens was associated with a higher risk of 1-year primary outcomes, but after adjusting for clinically relevant variables there were no significant associations between burdens of brain frailty and 1-year vascular outcomes. For individual components of brain frailty, an advanced WMH was independently associated with an increased risk of 1-year primary outcomes (adjusted hazard ratio [aHR]=1.33, 95% confidence interval [CI]=1.03−1.71) and stroke (aHR=1.32, 95% CI=1.00−1.75).

Conclusions The baseline imaging markers of brain frailty were common in acute minor ischemic stroke patients with LVO. An advanced WMH was the only frailty marker associated with an increased risk of vascular events. Further research is needed into the association between brain frailty and prognosis in patients with acute minor LVO.

Key Words brain frailty; white-matter hyperintensity; acute ischemic stroke; large-vessel occlusion; acute minor stroke.

INTRODUCTION

A substantial proportion of patients with acute minor ischemic stroke and large-vessel occlusion (acute minor LVO) neurologically deteriorate during the acute periods and experience unfavorable outcomes.[1] Further research is therefore warranted into the factors related to worse outcomes in patients with acute minor LVO.

Baseline imaging features of small-vessel disease (SVD) and brain frailty are commonly associated with worse outcomes after acute stroke, particularly in the small-vessel stroke subtype.[2] Imaging markers of brain frailty including white-matter hyperintensities (WMHs), cerebral atrophy, and silent brain infarct (SBI) are shared with markers of SVD, including WMHs, microbleeds (MBs), prominent perivascular spaces, cerebral atrophy, and lacunes, all of which are linked to poor outcomes.[3,4] Although individual imaging features of SVD or brain frailty (except WMH) might not be directly related to the overall prognosis, combined features representing global brain health, such as the SVD score or brain frailty score, have been linked to outcomes,[5,6] mainly in the small-vessel stroke subtype.[2,7] Impairment of functional connectivity might partly account for poor outcomes, especially in the small-vessel stroke subtype.

However, there have been conflicting findings for whether imaging features of SVD (including WMH) are associated with an increased risk of poor outcomes in LVO strokes treated with or without endovascular thrombectomy.[8,9] LVO stroke differs from small-vessel stroke in its clinical presentation, risk factors, and outcomes.[10] Nonetheless, the total burden of SVD has predictive value for stroke recurrence in stroke patients with the large-artery atherosclerosis subtype.[11] Determining how the imaging features of brain frailty or SVD influence outcomes may help to identify useful therapeutic strategies for the specific stroke populations of acute minor LVO.

This study therefore investigated whether the 1-year vascular outcomes of patients with acute minor LVO were associated with individual and combined imaging markers of brain frailty or SVD, including WMH, SBI, and MB.

METHODS

Subjects

This study performed a post-hoc analysis of an imaging registry for acute minor LVO that was derived from the Clinical Research Center for Stroke–Korea (CRCS-K) registry. The CRCS-K registry is a prospective, multicenter, nationwide registry of consecutive patients with acute stroke or transient ischemic attack (TIA) admitted to 17 academic hospitals in South Korea. Detailed methodology information about the CRCS-K registry and the acute minor LVO registry has been reported previously.[12-14] We identified patients with acute ischemic stroke admitted between January 2015 and March 2019. We included patients who 1) presented within 24 h after the last known time when they were well (n=24,596), 2) had a baseline National Institutes of Health Stroke Scale (NIHSS) score of 0 to 5 points (n=15,436), 3) had anterior circulation LVO (ICA, or M1 or proximal M2 segment of the MCA) confirmed by neuroimaging (n=1,083), and 4) underwent imaging analysis of brain frailty (n=1,067). A detailed patient selection flowchart is shown in Supplementary Fig. 1 (in the online-only Data Supplement).

Ethics statement

Clinical information was collected from the CRCS-K registry and the acute minor LVO registry with approval from the local institutional review boards of all participating centers. A waiver of the need to obtain informed consents was provided because the study subjects were anonymous and there was minimal risk to the participants. The secondary use of the registry data and additional reviews of the medical records and imaging data by this study were approved by the Institutional Review Boards (IRB No. CNUH-2023-243). The data used in this study are available upon reasonable request following the submission of a legitimate academic research proposal, which would be assessed by the CRCS-K steering committee.

Data collection

Demographic, clinical, and laboratory data were collected prospectively, as detailed in the Supplementary Methods (in

the online-only Data Supplement). The ischemic stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, which were refined to incorporate additional information from more-recent imaging studies.[15]

All neuroimaging data were collected retrospectively and independently evaluated by a central imaging laboratory. The details of the imaging analysis method are available elsewhere[14] and in the Supplemental Methods. In briefly, the images were assessed for the Alberta Stroke Program Emergent CT Score (ASPECTS), location of cerebral artery occlusion, tandem occlusion, WMH (Fazekas grade), SBI, and MB. An advanced WMH was defined as Fazekas grade 2 or 3. Brain frailty was stratified according to the presence of an advanced WMH (grade 2 or 3), SBI, or cerebral MB.[2] These three findings were summed to generate a score for the burden of brain frailty or SVD (we described this as the brain frailty burden for this study), which ranged from 0 to 3.

The central imaging laboratory consisted of vascular neurologists (J.H.H., B.J.K., B.J.K., C.K.K., and J.T.K.), interventional neurologists (J.G.K., H.P., and J.S.Y.), and an interventional radiologist (S.H.B.). All images were independently evaluated by at least two raters. Any discrepancy in the readings between the raters was adjudicated by a panel (B.J.K., J.S.Y., and S.H.B.) to reach the final assessment. Details on the collection, anonymization, storage, and backing-up of images as well as on the image reading process are available elsewhere.[14]

Outcomes

To explore several hypotheses from previous studies, the outcomes of interest were in two domains: 1) 1-year vascular events and 2) early functional outcomes at 3 months. The primary outcome for vascular events was a composite of stroke (either ischemic or hemorrhagic), myocardial infarction (MI), and all-cause mortality within 1 year. Stroke events included neurological progression associated with enlarged or discrete new lesions during the acute period. The secondary outcomes were individual outcomes except for MI due to a low event rate: 1) stroke and 2) all-cause mortality. Detailed definitions of the vascular outcome events and the methods used for outcome capture in the current study are available elsewhere.[12]

The main functional outcome was no or minimal disability at 3 months, defined as a modified Rankin Scale (mRS) score of 0 or 1. The secondary outcomes were functional independence at 3 months (mRS score=0−2), hemorrhagic transformation (HT), and parenchymal hematoma (PH).

Statistical analysis

The baseline characteristics and outcomes were compared according to the brain frailty burdens using the chi-square test, ANOVA, or Kruskal−Wallis test as appropriate. The event probabilities of 1-year vascular outcomes according to the total number of brain frailty burdens and each brain frailty were calculated using the Kaplan−Meier method, and the log-rank test was performed to analyze the differences among the groups. Hazard ratios (HRs) and 95% confidence intervals (CIs) of 1-year vascular outcomes were analyzed using the Cox proportional-hazards model. We tested the proportional-hazards assumption using the numerical method proposed by Lin et al.[16] derived from cumulative sums of Martingale residuals. Adjustments were made for the following predetermined variables with clinically relevant associations with the outcome variables: age, sex, initial NIHSS score, arrival delay, TOAST stroke subtype, history of stroke, history of coronary artery disease, hypertension (HTN), diabetes mellitus (DM), atrial fibrillation, dyslipidemia, artery occlusion, glucose, and systolic blood pressure. Interactions among WMH, SBI, and MB were evaluated using the Wald test in a Cox model.

A logistic regression model was used to explore the relationships of each brain frailty and the total number of brain frailty burdens with the functional outcomes at 3 months (mRS score=0 or 1, mRS score=0−2, HT, and PH). Estimates of the effect size are provided as adjusted odds ratio (aOR) and 95% CI values.

Statistical analyses were performed with R software using the "rms" package (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria) and SAS software (version 9.4, SAS Institute, Cary, NC, USA).

RESULTS

General characteristics

Among the 24,596 patients with stroke or TIA registered in the CRCS-K database during the study period, 1,067 patients (age=67.2±13.1 years [mean±SD], 61.3% males) were finally included. The median baseline NIHSS score was 2 (interquartile range [IQR]=1−4). The proportion of patients with different numbers of brain frailty burdens were as follows: no burden in 49.2%, one burden in 30.0%, two burdens in 17.3%, and three burdens in 3.5%. Patients with more brain frailty burdens were more likely to have HTN, DM, and a history of stroke, while patients without a brain frailty burden were younger (Table 1). The imaging findings of the subjects and the characteristics of the individual and combined features of brain frailty are presented in Supplementary Tables 1 and 2 (in the online-only Data Supplement). An ad-

Table 1. General characteristics of the subjects according to the number of brain frailty burdens

	No burden	1 burden	2 burdens	3 burdens	*p**
Number of subjects	525	320	185	37	1,067
Age, years	62.9±13.3	69.6±11.8	74.0±10.7	72.5±11.3	<0.001
Sex, male	336 (64.0)	191 (59.7)	106 (57.3)	21 (56.8)	0.316
Arrival delay					0.010
≤6 h	135 (25.7)	112 (35.0)	62 (33.5)	15 (40.5)	
>6 h	390 (74.3)	208 (65.0)	123 (66.5)	22 (59.5)	
Weight, kg	66.0±12.5	63.6±11.3	61.5±12.1	62.2±12.2	<0.001
Height, cm	164.9±8.2	163.1±8.4	161.4±8.7	161.3±9.6	<0.001
BMI, kg/m^2	24.1±3.7	23.7±3.5	23.3±4.1	23.7±2.8	0.069
NIHSS score	2 [1–4]	2 [1–4]	3 [1–4]	3 [1–4]	0.177
Prestroke mRS 0–1	503 (95.8)	292 (91.3)	158 (85.4)	32 (86.5)	<0.001
TOAST stroke subtype					0.153
LAA	165 (31.4)	111 (34.7)	80 (43.2)	14 (37.8)	
CE	170 (32.4)	91 (28.4)	49 (26.5)	11 (29.7)	
UD/OE	190 (36.2)	118 (36.9)	56 (30.3)	12 (32.4)	
Medical history					
History of stroke	48 (9.1)	75 (23.4)	71 (38.4)	18 (48.6)	<0.001
History of TIA	22 (4.2)	11 (3.4)	8 (4.3)	1 (2.7)	0.914
History of CAD	34 (6.5)	35 (10.9)	22 (11.9)	4 (10.8)	0.054
History of PAD	3 (0.6)	5 (1.6)	3 (1.6)	0 (0.0)	0.340
Hypertension	276 (52.6)	214 (66.9)	136 (73.5)	29 (78.4)	<0.001
Diabetes mellitus	122 (23.2)	108 (33.8)	63 (34.1)	17 (45.9)	<0.001
Dyslipidemia	120 (22.9)	96 (30.0)	49 (26.5)	10 (27.0)	0.145
Atrial fibrillation	150 (28.6)	86 (26.9)	51 (27.6)	11 (29.7)	0.949
Smoking, current	154 (29.3)	67 (20.9)	26 (14.1)	8 (21.6)	<0.001
Medication history					
Antihypertensive	200 (38.1)	176 (55.0)	116 (62.7)	23 (62.2)	<0.001
Antidiabetic	83 (15.8)	90 (28.1)	45 (24.3)	12 (32.4)	<0.001
Statin	80 (15.2)	76 (23.8)	43 (23.2)	13 (35.1)	<0.001
Antiplatelet	115 (21.9)	108 (33.8)	67 (36.2)	15 (40.5)	<0.001
Laboratory findings					
WBC count, ×10^3/μL	8.2±2.9	8.1±3.1	8.1±2.7	8.1±2.5	0.940
Creatinine, mg/dL	0.95±1.10	0.96±0.41	1.00±0.49	1.01±0.51	0.918
Hemoglobin, g/dL	14.1±1.8	13.5±2.0	13.4±2.0	13.5±2.0	<0.001
LDL, mg/dL	105.0±32.1	101.8±36.4	97.0±36.0	103.5±36.7	0.049
Glucose, mg/dL	136.7±56.6	146.3±74.3	149.1±70.9	138.8±52.4	0.065
PT, INR	1.03±0.16	1.07±0.36	1.09±0.45	1.05±0.13	0.088
SBP, mm Hg	144.7±26.2	144.6±25.2	144.2±27.6	160.1±31.1	0.006
Reperfusion therapy					0.145
No	376 (71.6)	246 (76.9)	146 (78.9)	32 (86.5)	
IVT	62 (11.8)	31 (9.7)	14 (7.6)	3 (8.1)	
IAT	54 (10.3)	33 (10.3)	20 (10.8)	1 (2.7)	
IVT+IAT	33 (6.3)	10 (3.1)	5 (2.7)	1 (2.7)	
In-hospital treatment					
Antihypertensive	165 (31.4)	137 (42.8)	91 (49.2)	27 (73.0)	<0.001
Antidiabetic	468 (89.1)	283 (88.4)	160 (86.5)	34 (91.9)	0.712
Statin	91 (17.3)	76 (23.8)	51 (27.6)	13 (35.1)	0.002

Table 1. General characteristics of the subjects according to the number of brain frailty burdens (continued)

	No burden	1 burden	2 burdens	3 burdens	*p**
Antithrombotic treatment					0.450
No antiplatelet	154 (29.3)	107 (33.4)	60 (32.4)	12 (32.4)	
Monotherapy	264 (50.3)	140 (43.8)	78 (42.2)	17 (45.9)	
Dual therapy	107 (20.4)	73 (22.8)	47 (25.4)	8 (21.6)	
Oral anticoagulation	156 (29.7)	94 (29.4)	42 (22.7)	10 (27.0)	0.310

Data are mean±SD, *n* (%), or median [interquartile range] values.
**p* value in the chi-square test, Fisher's exact test, ANOVA, or Kruskal–Wallis test.
BMI, body mass index; CAD, coronary artery disease; CE, cardio-embolism; IAT, intra-arterial therapy; INR, international normalized ratio; IVT, intravenous thrombolysis; LAA, large-artery atherosclerosis; LDL, low-density lipoprotein; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PAD, peripheral artery disease; PT, prothrombin time; SBP, systolic blood pressure; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment; UD/OE, undetermined/other determined etiology; WBC, white blood cell.

vanced WMH (grade 2 or 3), MB, and SBI were observed in 28.6%, 11.1%, and 35.4% of the patients, respectively.

One-year vascular outcomes

The median follow-up duration was 365 days (IQR=355–374 days, 342±93 days), with 91% of the patients completing the 1-year follow-up. The primary composite outcome of stroke, MI, and all-cause mortality occurred in 315 patients, and the 1-year cumulative event rate was 30.2%. For individual components of the composite outcome, the 1-year event rates were 26.2% for stroke, 0.7% for MI, and 6.9% for all-cause mortality. Early progressive/recurrent stroke during hospitalization occurred in 226 patients (21.2%).

In the crude analysis, the primary outcome events at 1 year occurred in 49.5%, 35.8%, 31.9%, and 25.8% of the patients with three, two, one, and no burden, respectively (*p* value in log-rank test=0.006). The rate of all-cause mortality was lowest in the no-burden group (4.4%) and highest in the three-burdens group (11.4%) (*p* value in log-rank test=0.014). Table 2 lists the 1-year event rates according to the individual components and burdens of brain frailty. The 1-year rates of primary outcomes, stroke, and all-cause mortality differed significantly according to the presence of an advanced WMH and the WMH severity.

In the Cox proportional-hazards analysis, a larger number of brain frailty burdens (compared with no burden) was associated with 1-year primary outcomes, all-cause mortality, and stroke. However, there was no longer a significant association between brain frailty burdens and 1-year vascular outcomes after adjusting for clinically relevant variables (Table 3). Regarding the individual components of brain frailty, an advanced WMH (grade 2 or 3) was independently associated with an increased risk of 1-year primary outcomes (adjusted HR [aHR]=1.33, 95% CI=1.03–1.71) and stroke (aHR=1.32, 95% CI=1.00–1.75). Compared with no WMH, more-severe WMH was associated with higher risks of 1-year primary outcomes (mild WMH: aHR=1.43, 95% CI=0.97–2.10; moderate WMH: aHR=1.68, 95% CI=1.07–2.62; and severe WMH: aHR=2.32, 95% CI=1.38–3.90) and stroke (mild WMH: aHR=1.53, 95% CI=1.02–2.30; moderate WMH: aHR=1.79, 95% CI=1.11–2.88; and severe WMH: aHR=2.42, 95% CI=1.38–4.25).

The associations of the different components of brain frailty with 1-year vascular outcomes are presented in Table 3. Kaplan–Meier curves of event-free survival for 1-year primary outcomes according to brain frailty burdens and the presence of individual brain frailty components in brain MRI are shown in Figs. 1 and 2. Additionally, Kaplan–Meier curves of event-free survival for individual vascular outcomes within 1 year are shown in Supplementary Fig. 2 (for brain frailty burden), Supplementary Table 3, Supplementary Fig. 3 (for all-cause mortality), and Supplementary Table 4, Supplementary Fig. 4 (for stroke) in the online-only Data Supplement.

Three-month functional outcomes

Three months of mRS scores were available for 1,056 patients, among whom 569 (53.9%) had excellent outcomes (no or minimal disability; mRS score=0 or 1) at 3 months. Excellent outcomes at 3 months were significantly more common in the patients with fewer brain frailty burdens (no burden, 62.8%; one burden, 50.2%; two burdens, 6.6%; and three burdens, 44.4%, $p<0.001$). The frequency of a good outcome at 3 months (functional independence; mRS score=0–2) also differed significantly according to brain frailty burdens (Supplementary Table 5 in the online-only Data Supplement). However, the prevalence rates of HT and PH did not differ significantly with the number of brain frailty burdens. The 3-month functional outcomes according to the imaging markers of brain frailty are presented in Supplementary Table 6 (in the online-only Data Supplement).

The associations of the 3-month functional outcomes with brain frailty burdens are presented in Supplementary Tables 7 and 8 (in the online-only Data Supplement). In the crude analysis, the brain frailty burdens and the presence of indi-

Table 2. One-year event rates according to brain frailty

	Composite of all-stroke, MI, and all-cause mortality		p^*	All-cause mortality		p^*	All-stroke mortality		p^*
	No. of events/ no. of patients	1-year event rate		No. of events/ no. of patients	1-year event rate		No. of events/ no. of patients	1-year event rate	
SBI			0.052			0.121			0.246
Absent	189/689	28.0 (24.6–31.4)		37/689	6.0 (4.1–7.9)		169/689	24.8 (21.5–28.0)	
Present	126/378	34.2 (29.4–39.1)		29/378	8.6 (5.6–11.7)		105/378	28.8 (24.1–33.5)	
WMH severity			<0.001			<0.001			0.002
None	36/185	19.8 (14.0–25.6)		5/185	2.9 (0.4–5.5)		32/185	17.6 (12.1–23.1)	
Mild	163/577	28.8 (25.0–32.5)		31/577	6.0 (3.9–8.2)		146/577	25.6 (22.0–29.2)	
Moderate	79/227	35.9 (29.5–42.2)		18/227	8.9 (5.0–12.9)		66/227	29.8 (23.8–35.9)	
Severe	37/78	48.4 (37.1–59.6)		12/78	17.1 (8.3–25.9)		30/78	40.9 (29.3–52.5)	
Advanced WMH			<0.001			0.002			0.006
Grade 0 or 1	199/762	26.6 (23.4–29.8)		36/762	5.3 (3.6–7.0)		178/762	23.7 (20.6–26.7)	
Grade 2 or 3	116/305	39.1 (33.5–44.7)		30/305	11.0 (7.3–14.7)		96/305	32.6 (27.2–38.0)	
MB			0.243			0.147			0.634
Absent	274/949	29.5 (26.5–32.5)		55/949	6.6 (4.9–8.3)		241/949	25.7 (22.9–28.6)	
Present	41/118	35.6 (26.8–44.3)		11/118	9.7 (4.2–15.1)		33/118	29.6 (21.0–38.1)	
Brain frailty			0.005			0.001			0.100
No burden	133/525	25.8 (22.0–29.6)		20/525	4.4 (2.4–6.3)		123/525	23.6 (19.9–27.2)	
One or more burdens	182/542	34.5 (30.4–38.6)		46/542	9.5 (6.8–12.1)		151/542	28.8 (24.9–32.8)	
Brain frailty burdens			0.006			0.014			0.124
None	133/525	25.8 (22.0–29.6)		20/525	4.4 (2.4–6.3)		123/525	23.6 (19.9–27.2)	
One	99/320	31.9 (26.7–37.1)		26/320	9.1 (5.7–12.5)		83/320	26.7 (21.8–31.7)	
Two	65/185	35.8 (28.8–42.8)		16/185	9.6 (5.1–14.1)		53/185	29.1 (22.5–35.7)	
Three	18/37	49.5 (33.1–65.8)		4/37	11.4 (0.8–22.0)		15/37	43.1 (26.4–59.8)	
Types of burdens			0.022			0.013			0.219
WMH (–)/SBI (–)/MB (–)	133/525	25.8 (22.0–29.6)		20/525	4.4 (2.4–6.3)		123/525	23.6 (19.9–27.2)	
WMH (–)/SBI (–)/MB (+)	10/39	25.8 (12.0–39.6)		2/39	5.1 (0.0–12.1)		9/39	23.5 (10.0–37.0)	
WMH (–)/SBI (+)/MB (–)	51/177	29.7 (22.8–36.6)		11/177	7.0 (2.9–11.1)		43/177	25.2 (18.6–31.8)	
WMH (–)/SBI (+)/MB (+)	5/21	24.4 (5.7–43.2)		3/21	15.6 (0.0–31.9)		3/21	14.3 (0.0–29.3)	
WMH (+)/SBI (–)/MB (–)	38/104	38.2 (28.5–47.9)		13/104	14.4 (7.1–21.8)		31/104	30.4 (21.4–39.4)	
WMH (+)/SBI (–)/MB (+)	8/21	38.9 (17.7–60.1)		2/21	9.5 (0.0–22.1)		6/21	30.2 (9.6–50.7)	
WMH (+)/SBI (+)/MB (–)	52/143	37.0 (29.0–45.0)		11/143	8.8 (3.8–13.8)		44/143	31.1 (23.4–38.7)	
WMH (+)/SBI (+)/MB (+)	18/37	49.5 (33.1–65.8)		4/37	11.4 (0.8–22.0)		15/37	43.1 (26.4–59.8)	

Datas are % (95% confidence interval) values for the Kaplan–Meier estimates.
*p value in the log-rank test.
MB, microbleed; MI, myocardial infarction; SBI, silent brain infarct; WMH, white-matter hyperintensity.

Table 3. Associations of brain frailty with 1-year primary outcomes

	Crude HR (95% CI)	*p*	*p**	Adjusted HR (95% CI)	*p*	*p**
SBI						
Absent	1 (ref)			1 (ref)		
Present	1.24 (0.99–1.55)	0.064	0.068	1.09 (0.85–1.39)	0.509	0.496
WMH severity						
None	1 (ref)			1 (ref)		
Mild	1.50 (1.04–2.15)	0.028	0.922	1.43 (0.97–2.10)	0.071	0.532
Moderate	1.88 (1.27–2.79)	0.002	0.155	1.68 (1.07–2.62)	0.023	0.749
Severe	2.64 (1.67–4.18)	<0.001	0.028	2.32 (1.38–3.90)	0.002	0.327
Advanced WMH						
Grade 0 or 1	1 (ref)			1 (ref)		
Grade 2 or 3	1.51 (1.20–1.90)	<0.001	0.003	1.33 (1.03–1.71)	0.029	0.066
Cerebral MB						
Absent	1 (ref)			1 (ref)		
Present	1.20 (0.87–1.67)	0.266	0.088	1.07 (0.77–1.50)	0.677	0.272
Brain frailty						
No burden	1 (ref)			1 (ref)		
One or more burdens	1.36 (1.09–1.70)	0.007		1.18 (0.92–1.51)	0.196	
Brain frailty burdens						
None	1 (ref)			1 (ref)		
One	1.24 (0.96–1.61)	0.104	0.011	1.12 (0.86–1.48)	0.402	0.077
Two	1.44 (1.07–1.93)	0.017	0.090	1.22 (0.88–1.69)	0.240	0.500
Three	1.98 (1.21–3.24)	0.006	0.002	1.55 (0.92–2.62)	0.102	0.032
Types of burdens						
WMH (–)/SBI (–)/MB (–)	1 (ref)			1 (ref)		
WMH (–)/SBI (–)/MB (+)	1.00 (0.53–1.90)	0.999		0.87 (0.65–1.17)	0.361	
WMH (–)/SBI (+)/MB (–)	1.15 (0.83–1.59)	0.394		1.06 (0.91–1.24)	0.433	
WMH (–)/SBI (+)/MB (+)	0.94 (0.39–2.30)	0.896		0.89 (0.60–1.34)	0.585	
WMH (+)/SBI (–)/MB (–)	1.49 (1.04–2.14)	0.029		1.35 (1.14–1.61)	<0.001	
WMH (+)/SBI (–)/MB (+)	1.56 (0.77–3.19)	0.221		1.43 (1.03–1.99)	0.033	
WMH (+)/SBI (+)/MB (–)	1.49 (1.08–2.06)	0.014		1.25 (1.07–1.47)	0.006	
WMH (+)/SBI (+)/MB (+)	1.98 (1.21–3.24)	0.006		1.55 (1.22–1.96)	<0.001	

Adjusted variables: age, sex, arrival delay, TOAST stroke subtype, history of stroke, history of coronary artery disease, hypertension, diabetes mellitus, atrial fibrillation, dyslipidemia, large-vessel occlusion location, glucose, systolic blood pressure, and initial NIHSS score.
**p* value in proportional-hazards-assumption tests.
CI, confidence interval; HR, hazard ratio; MB, microbleed; NIHSS, National Institutes of Health Stroke Scale; ref, reference; SBI, silent brain infarct; TOAST, Trial of Org 10172 in Acute Stroke Treatment; WMH, white-matter hyperintensity.

vidual brain frailty were significantly associated with a lower probability of excellent and good outcomes at 3 months. After adjusting for clinically relevant variables, the only individual components of brain frailty that were independently associated with functional outcomes at 3 months were the severity of WMH and the presence of advanced WMH (mRS score=0 or 1: aOR=0.70, 95% CI=0.52–0.96; mRS score=0–2: aOR=0.74, 95% CI=0.53–1.02).

DISCUSSION

The present analysis of 1,067 patients with acute minor ischemic stroke with LVO revealed that baseline imaging markers of brain frailty were common but not significantly associated with increased risks of 1-year vascular outcomes and worse functional outcomes at 3 months. However, an advanced WMH (one of the imaging features of brain frailty) was significantly associated with higher risks of 1-year primary vascular outcomes and 3-month worse functional outcomes.

We observed imaging features of brain frailty in approximately half of the patients with acute minor ischemic stroke with LVO. Multiple imaging features of brain frailty were observed in one of every five patients with acute minor LVO.

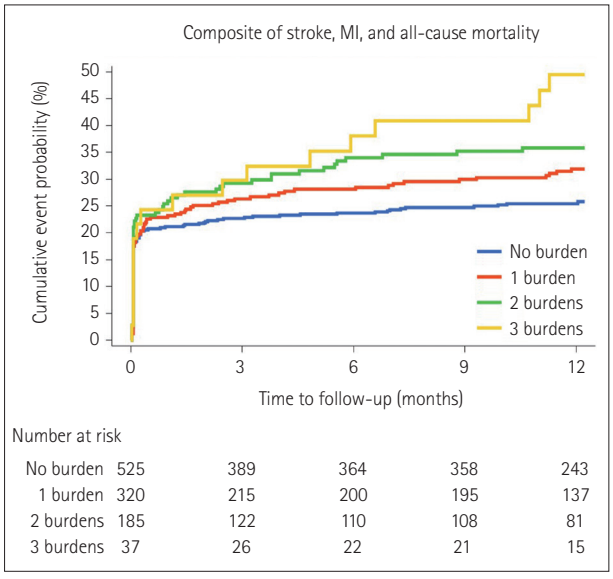

Fig. 1. Kaplan–Meier curves of event-free survival for 1-year primary outcomes according to the number of brain frailty burdens. MI, myocardial infarction.

Although this study did not analyze all imaging markers for SVD and brain frailty, the MRI markers of MB, WMH, and SBI that were used in our study are clinically practical because they can be objectively assessed visually.

The present results are consistent with previous reports that SVD burdens can co-occur with LVO stroke[17] and that there is a potential link between LVO stroke and SVD burdens in terms of risk factors and pathogenesis.[18] While MRI markers such as WMH, SBI, and MB are often associated with small vascular events in the brain, it must be remembered that they can also have other causes.[19,20] Additionally, SVD is commonly attributed to factors such as longstanding HTN, DM, and aging. Hence, brain frailty may arise as a consequence of these underlying conditions rather than being a predictive factor for stroke prognosis. Further research is necessary to characterize this relationship in more detail.

We also found that the number of brain frailty burdens was consistently correlated with the risk of recurrent vascular events for up to 1 year, increasing from 25.8% with no burden to 49.5% with three burdens. Although being statistically not significant, the unadjusted event rates of vascular outcomes numerically increased with the number of brain frailty burdens in our study. A WMH was the imaging frailty marker that contributed the most to the differences in vascular outcomes. It is well known that WMHs are very common in elderly individuals, implying higher morbidity and severity of the related diseases.[21,22] A WMH might be an imaging marker of disruption to the white-matter fiber tracts and/or network architecture of the brain, and widespread changes in white-matter tissue microstructure may result in unfavorable outcomes partially due to impaired brain plasticity.[23,24] Moreover, a WMH may represent advanced impairment of the microvasculature of the brain and increase the risk of ischemic stroke recurrence.

Additionally, patients with more brain frailty burdens seemed to be less likely to have good outcomes at 3 months. More brain frailty burdens, and especially advanced WMHs, represent worse global brain health rather than merely a collection of individual brain lesions, and these patients could be vulnerable to ischemic insult due to impaired autoregulation and compensatory collateral flows.[25,26] Our results are consistent with previous findings of increased brain frailty features or SVD burdens being related to increased risks of recurrent stroke and worse functional outcomes at 3 months.[2,27]

Most ischemic stroke patients present with minor symptoms and are generally considered to have a favorable long-term outcome.[28] In the CRCS-K registry, outcomes after 3 months were good (mRS score=0–2) in 74.4% of an overall stroke population[13] and in 71.5% of those with acute minor LVO.[14] However, a substantial number of patients with acute minor LVO showed neurologically deterioration during the early periods after stroke and had unfavorable outcomes.[1] We found that among patients with acute minor LVO, those with more brain frailty burdens (especially an advanced WMH) are at a higher risk and potentially frail, which could lead to more subsequent vascular events and unfavorable functional outcomes. Further studies are warranted to determine whether the additional factors affecting the risk of worse outcomes are useful in decision-making for such patients.

This study had several limitations. First, certain imaging markers of brain frailty and SVD were not comprehensively assessed, such as prominent perivascular spaces, cerebral atrophy, and lacunes. Although it would be ideal to analyze all markers of brain frailty, this study considered only three imaging markers because they could be visually assessed in actual clinical settings, which is practically useful for determining their clinical significance. This study did not consider the burden and location of cerebral MB, and did not incorporate the recently published Boston criteria for cerebral amyloid angiopathy,[29] since the focus was specifically on patients with acute minor ischemic stroke with LVO. Therefore, the findings might not reflect the impact of these criteria. The study also did not consider the location of SBI and WMHs (deep or periventricular). The lack of a significant association between brain frailty burdens and outcomes may have been due to our sample being statistically underpowered. Further studies with larger samples are therefore warranted. Second, restricting the study population to those with acute minor LVO may have introduced a particular type of selection bias known as collider stratification bias. This can distort the re-

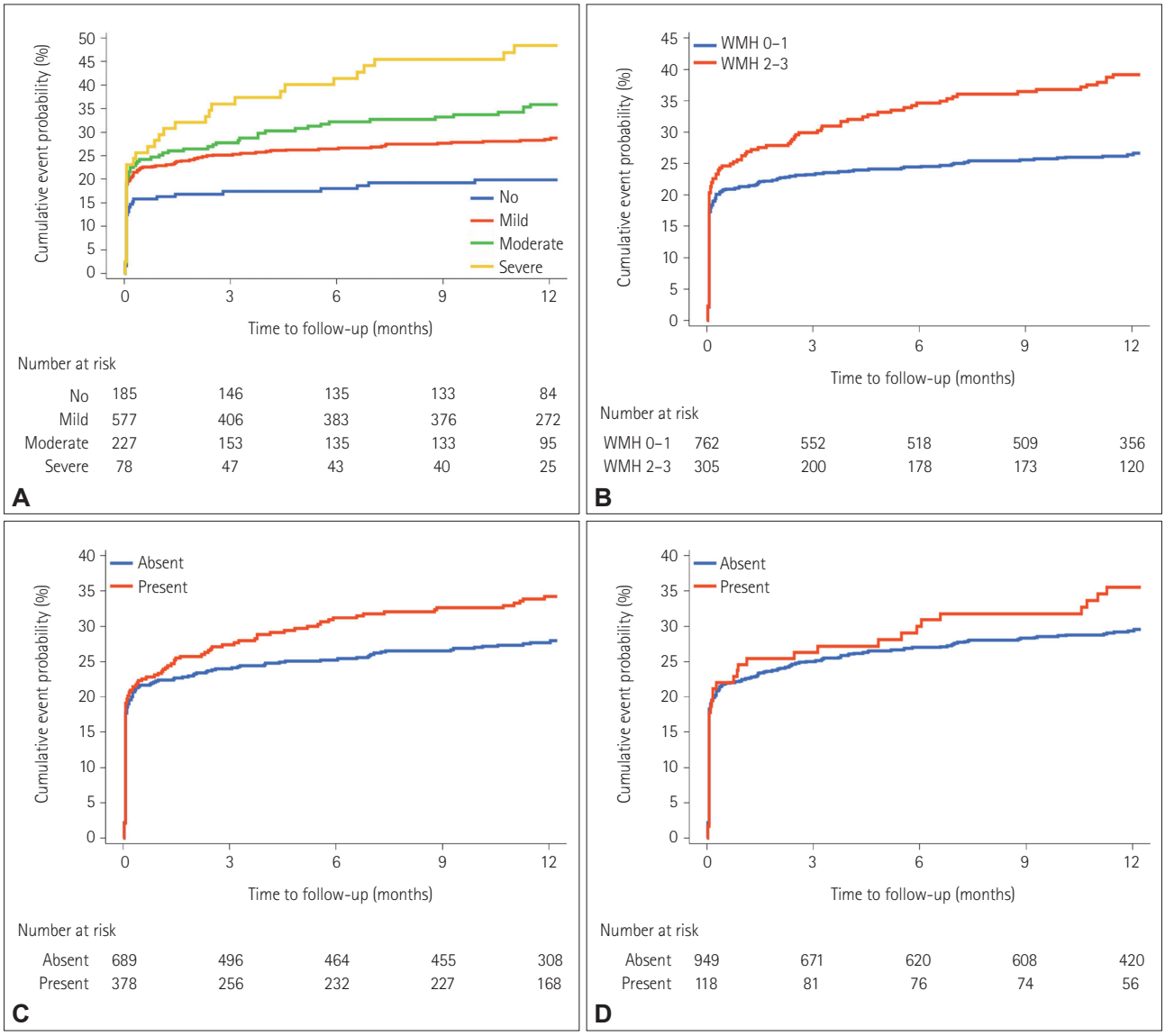

Fig. 2. Kaplan–Meier curves of event-free survival for 1-year primary outcomes according to WMH severity (A) and the presence of advanced WMH (B), silent brain infarct (C) and cerebral microbleed (D) on MRI. WMH, white-matter hyperintensity.

lationship of baseline risk factors with the outcome of interest. Third, the rate of stroke events within 1 year was substantially higher than in previous stroke studies. Because this study included patients with acute minor ischemic stroke with LVO, early progressive or recurrent stroke events were included as stroke events. Additionally, the participating hospitals were tertiary (university) hospitals or regional stroke centers (e.g., comprehensive stroke centers). Fourth, this study had inherent limitations associated with its registry-based retrospective design. Although rigorous adjusting for clinically relevant variables was used to mitigate the baseline differences, the possibility of unmeasured or residual confounding cannot be excluded. Fifth, although this was a large, prospective, nationwide study, the patient cohort was restricted to an Asian population (South Korea), and so studies involving other racial and ethnic groups are needed to confirm the generalizability of the present results.

In conclusion, imaging markers of brain frailty were common among the included acute minor ischemic stroke patients with LVO. In particular, advanced WMHs were significantly associated with higher risks of 1-year vascular outcomes and 3-month worse functional outcomes. These results might necessitate a more-vigilant approach for mild LVO patients with advanced WMHs; this possibly needs to be elucidated in future studies.

Supplementary Materials

The online-only Data Supplement is available with this arti-

cle at https://doi.org/10.3988/jcn.2023.0181.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

ORCID iDs

Joon-Tae Kim	https://orcid.org/0000-0003-4028-8339
Ji Sung Lee	https://orcid.org/0000-0001-8194-3462
Beom Joon Kim	https://orcid.org/0000-0002-2719-3012
Jae Guk Kim	https://orcid.org/0000-0003-1418-0033
Jong-Moo Park	https://orcid.org/0000-0002-4199-3024
Kyusik Kang	https://orcid.org/0000-0002-4021-4439
Soo Joo Lee	https://orcid.org/0000-0001-8622-7000
Hyungjong Park	https://orcid.org/0000-0002-6112-2939
Jae-Kwan Cha	https://orcid.org/0000-0002-1049-5196
Tai Hwan Park	https://orcid.org/0000-0002-5148-1663
Kyungbok Lee	https://orcid.org/0000-0003-2663-7483
Jun Lee	https://orcid.org/0000-0001-8643-0797
Keun-Sik Hong	https://orcid.org/0000-0002-4684-6111
Byung-Chul Lee	https://orcid.org/0000-0002-3885-981X
Dong-Eog Kim	https://orcid.org/0000-0002-9339-6539
Jay Chol Choi	https://orcid.org/0000-0002-3550-2196
Jee-Hyun Kwon	https://orcid.org/0000-0002-5894-3146
Dong-Ick Shin	https://orcid.org/0000-0001-5770-0268
Sung Il Sohn	https://orcid.org/0000-0002-6900-1242
Juneyoung Lee	https://orcid.org/0000-0001-8073-9304
Hee-Joon Bae	https://orcid.org/0000-0003-0051-1997

Author Contributions

Conceptualization: Je-Woo Park, Joon-Tae Kim. Data curation: Joon-Tae Kim, Ji Sung Lee, Beom Joon Kim. Formal analysis: Ji Sung Lee, Joon-Tae Kim. Funding acquisition: Joon-Tae Kim, Hee-Joon Bae. Investigation: all authors. Methodology: Joon-Tae Kim, Ji Sung Lee, Beom Joon Kim, Writing—original draft: Je-Woo Park, Joon-Tae Kim, Writing—review & editing: all authors.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI22C0454). This research was supported by funding (2023-ER1006-00) from Research of Korea Centers for Disease Control and Prevention. This study was supported by a grant (BCRI22032) of Chonnam National University Hospital Biomedical Research Institute.

REFERENCES

1. Kim JT, Park MS, Chang J, Lee JS, Choi KH, Cho KH. Proximal arterial occlusion in acute ischemic stroke with low NIHSS scores should not be considered as mild stroke. *PLoS One* 2013;8:e70996.
2. Appleton JP, Woodhouse LJ, Adami A, Becker JL, Berge E, Cala LA, et al. Imaging markers of small vessel disease and brain frailty, and outcomes in acute stroke. *Neurology* 2020;94:e439-e452.
3. Wardlaw JM, Doubal FN, Valdes-Hernandez M, Wang X, Chappell FM, Shuler K, et al. Blood-brain barrier permeability and long-term clinical and imaging outcomes in cerebral small vessel disease. *Stroke* 2013;44:525-527.
4. IST-3 Collaborative Group. Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third international stroke trial (IST-3): secondary analysis of a randomised controlled trial. *Lancet Neurol* 2015;14:485-496.
5. Ryu WS, Jeong SW, Kim DE. Total small vessel disease burden and functional outcome in patients with ischemic stroke. *PLoS One* 2020;15:e0242319.
6. Song TJ, Kim J, Song D, Yoo J, Lee HS, Kim YJ, et al. Total cerebral small-vessel disease score is associated with mortality during follow-up after acute ischemic stroke. *J Clin Neurol* 2017;13:187-195.
7. Bu N, Khlif MS, Lemmens R, Wouters A, Fiebach JB, Chamorro A, et al. Imaging markers of brain frailty and outcome in patients with acute ischemic stroke. *Stroke* 2021;52:1004-1011.
8. Derraz I, Abdelrady M, Ahmed R, Gaillard N, Morganti R, Cagnazzo F, et al. Impact of white matter hyperintensity burden on outcome in large-vessel occlusion stroke. *Radiology* 2022;304:145-152.
9. Zheng L, Leng X, Nie X, Yan H, Tian X, Pan Y, et al. Small vessel disease burden may not portend unfavorable outcome after thrombectomy for acute large vessel occlusion. *Eur Radiol* 2022;32:7824-7832.
10. Zhu H, Li Z, Lv J, Zhao R. Effects of cerebral small vessel disease on the outcome of patients with ischemic stroke caused by large artery atherosclerosis. *Neurol Res* 2018;40:381-390.
11. Nam KW, Kwon HM, Lim JS, Han MK, Nam H, Lee YS. The presence and severity of cerebral small vessel disease increases the frequency of stroke in a cohort of patients with large artery occlusive disease. *PLoS One* 2017;12:e0184944.
12. Kim BJ, Han MK, Park TH, Park SS, Lee KB, Lee BC, et al. Current status of acute stroke management in Korea: a report on a multicenter, comprehensive acute stroke registry. *Int J Stroke* 2014;9:514-518.
13. Kim BJ, Park JM, Kang K, Lee SJ, Ko Y, Kim JG, et al. Case characteristics, hyperacute treatment, and outcome information from the clinical research center for stroke-fifth division registry in South Korea. *J Stroke* 2015;17:38-53.
14. Kim BJ, Menon BK, Yoo J, Han JH, Kim BJ, Kim CK, et al. Effectiveness and safety of EVT in patients with acute LVO and low NIHSS. *Front Neurol* 2022;13:955725.
15. Ko Y, Lee S, Chung JW, Han MK, Park JM, Kang K, et al. MRI-based algorithm for acute ischemic stroke subtype classification. *J Stroke* 2014;16:161-172.
16. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika* 1993;80:557-572.
17. Lin PC, Chang FC, Huang HC, Tsai JY, Lin YY, Chung CP. Greater periventricular white matter hyperintensity severity in basilar artery branch atheromatous disease. *BMC Neurol* 2017;17:135.
18. Lee SJ, Kim JS, Chung SW, Kim BS, Ahn KJ, Lee KS. White matter hyperintensities (WMH) are associated with intracranial atherosclerosis rather than extracranial atherosclerosis. *Arch Gerontol Geriatr* 2011;53:e129-e132.
19. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol* 2019;18:684-696.
20. Benveniste H, Nedergaard M. Cerebral small vessel disease: a glymphopathy? *Curr Opin Neurobiol* 2022;72:15-21.
21. Prins ND, Scheltens P. White matter hyperintensities, cognitive impairment and dementia: an update. *Nat Rev Neurol* 2015;11:157-165.
22. Ryu WS, Schellingerhout D, Hong KS, Jeong SW, Jang MU, Park MS, et al. White matter hyperintensity load on stroke recurrence and mortality at 1 year after ischemic stroke. *Neurology* 2019;93:e578-e589.
23. de Groot M, Ikram MA, Akoudad S, Krestin GP, Hofman A, van der Lugt A, et al. Tract-specific white matter degeneration in aging: the Rotterdam study. *Alzheimers Dement* 2015;11:321-330.
24. Onteddu SR, Goddeau RP Jr, Minaeian A, Henninger N. Clinical impact of leukoaraiosis burden and chronological age on neurological deficit recovery and 90-day outcome after minor ischemic stroke. *J Neurol Sci* 2015;359:418-423.
25. Schreiber S, Bueche CZ, Garz C, Braun H. Blood brain barrier breakdown as the starting point of cerebral small vessel disease? - New insights from a rat model. *Exp Transl Stroke Med* 2013;5:4.

26. Wu JS, Chen XC, Chen H, Shi YQ. A study on blood-brain barrier ultrastructural changes induced by cerebral hypoperfusion of different stages. *Neurol Res* 2006;28:50-58.
27. Lau KK, Li L, Schulz U, Simoni M, Chan KH, Ho SL, et al. Total small vessel disease score and risk of recurrent stroke: validation in 2 large cohorts. *Neurology* 2017;88:2260-2267.
28. Reeves M, Khoury J, Alwell K, Moomaw C, Flaherty M, Woo D, et al. Distribution of national institutes of health stroke scale in the Cincinnati/Northern Kentucky stroke study. *Stroke* 2013;44:3211-3213.
29. Charidimou A, Boulouis G, Frosch MP, Baron JC, Pasi M, Albucher JF, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurol* 2022;21:714-725.