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Hyperintense Vessel Sign in Large-Vessel Occlusion Stroke of Mild-to-Moderate Severity Ineligible for Recanalization

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Background and Purpose The impact of fluid-attenuated inversion recovery hyperintense vessels (FHVs) on outcomes in patients ineligible for recanalization therapy with large-vessel occlusion (LVO) is unclear. We investigated the impact of FHVs determined using the FHV–Alberta Stroke Program Early CT Score (ASPECTS) on clinical outcomes in patients with LVO stroke of mild-to-moderate severity ineligible for recanalization therapy.

Methods Sixty-eight consecutive patients with M1-middle cerebral artery occlusion who underwent magnetic resonance imaging within 24 hours of symptom onset and were ineligible for recanalization were included. Patients were dichotomized into a severe-FHV group (FHV-ASPECTS ≤4; *n*=33) and a mild-FHV group (FHV-ASPECTS >4; *n*=35), and multiple logistic regression analysis was used to examine the relationships of FHV scores with early neurological deterioration (END) and an unfavorable 3-month outcome (modified Rankin Scale score ≥3).

Results Mean age was 66.2±13.5 years (mean±SD), and 30 (44%) were female. The severe-FHV group had a larger infarct volume (median, 5.5 mL vs. 3 mL) and more frequently exhibited the susceptibility vessel sign (30% vs. 3%) than the mild-FHV group. Ipsilateral old nonlacunar infarct was more frequent in the mild-FHV group than in the severe-FHV group (37% vs. 15%). The severe-FHV group had a fivefold higher risk of END (odds ratio [OR] 5.02, 95% confidence interval [CI] 1.36−18.45) and unfavorable outcome (OR 5.97, 95% CI 1.18−33.31, *p*=0.03) compared with the mild-FHV group.

Conclusions Greater FHV extent was associated with higher risk of END and unfavorable outcome in patients with LVO stroke of mild-to-moderate severity.

Keywords cerebral infarction; magnetic resonance imaging; hyperintense vessel sign.

INTRODUCTION

Despite initially mild symptoms, patients with stroke of mild-to-moderate severity (National Institutes of Health Stroke Scale [NIHSS] score of <10) and intracranial large-vessel occlusion (LVO) often experience early neurological deterioration (END),[1] and a substantial proportion of these patients are unlikely to gain functional independence.[1-3] A recent report on acute minor ischemic stroke (NIHSS score of ≤5) with LVO confirmed by computed tomography (CT) indicated that about 20% of patients had END.[4] Hence, imaging markers that can discern patients with LVO of mild-to-moderate severity who are at a high risk of END might be helpful for identifying those who are currently ineligible for endovascular treatment but possibly benefit from this treatment.

Fluid-attenuated inversion recovery (FLAIR) hyperintense vessels (FHVs) are a common brain magnetic resonance imaging (MRI) sign in stroke patients with LVO,[5] and may be ascribed to slow blood flow via collateral flow. Studies on the clinical implications of FHVs

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have produced inconsistent results,[6] with some finding FHVs to be related to neurological improvement and favorable functional outcomes,[7,8] and others finding FHVs to be related to neurological deterioration and unfavorable outcomes.[9,10] Potential reasons for this discrepancy include differences in the study designs, techniques used to assess FHVs, and study populations. For example, in severe or rapidly progressive strokes, FHVs may represent ample collateral flow, and thus be related to favorable outcomes.[8,11] In contrast, in mild or slowly progressive strokes, the absence of FHVs might indicate chronic stabilized perfusion and so also be related to favorable outcomes.

The present study investigated the impact of FHVs (assessed using the validated FHV–Alberta Stroke Program Early CT Score [ASPECTS][8]) on outcomes with respect to END and 3-month functional outcomes in patients with LVO of mild-to-moderate severity who were ineligible for recanalization therapy. In addition, we also hypothesized that imaging markers indicating acute or chronic arterial occlusion, such as the susceptibility vessel sign and old nonlacunar infarct, respectively, are associated with the severity of FHVs.

METHODS

Study population

Patients admitted to Dongguk University Ilsan Hospital between May 2011 and August 2018 were screened, and those conforming with the following criteria were initially included: 1) underwent brain MRI within 24 hours of ictus, 2) pre-stroke modified Rankin Scale (mRS) score of 0 or 1, 3) M1-middle cerebral artery (MCA) occlusion as assessed using MR or CT angiography, 4) NIHSS score of <10 at admission, 5) ineligible for intravenous thrombolysis based on current guidelines, and 6) ineligible for thrombectomy according to the DAWN criteria (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo).[12] We excluded patients 1) with MRI findings inadequate for determining the FHV-ASPECTS, 2) lost to follow-up, or 3) with uncommon causes of stroke, such as dissection and moyamoya disease. The Institutional Review Board of Dongguk University Ilsan Hospital approved the study protocol (approval number 2011-98). All patients or their legal proxies provided written consent.

Clinical data collection

Admission NIHSS and 3-month mRS scores after stroke were collected prospectively. A standardized protocol[13-16] was used to collect demographic data, prior medication history, laboratory data, and the presence of risk factors. Stroke subtypes were determined by consensus between experienced neurologists using a validated MRI-based algorithm.[17] Blood pressure data were collected during the first 24 hours of admission from electronic medical records. END was defined as any new neurological symptom or sign or neurological worsening within 3 days of stroke onset, using the following criteria: 1) an increase in the total NIHSS score of ≥2, 2) an increase in the NIHSS consciousness score (1a–1c) of ≥1, 3) an increase in the NIHSS motor score (5a–6b) of ≥1, or 4) any new neurological deficit not assessed by the NIHSS.[13,14]

Image analysis

FHVs were defined as circular or serpentine hyperintensities present on at least two consecutive slices representing seven vascular territories of the MCA: segments M1−M3, the insular ribbon next to basal ganglia, and segments M4−M6 superior to basal ganglia and next to lateral ventricles (Fig. 1).[8] We quantified FHVs on axial FLAIR images using the FHV-ASPECTS system as described previously.[18] Briefly, the detection of FHVs in each MCA territory was scored as 1, and the summed score for the seven territories was subtracted from 7. Thus, FHV-ASPECTSs ranged from 0 (FHVs visible in all territories) to 7 (no FHVs visible). Two raters independently performed FHV-ASPECTS ratings while blinded to clinical information; when their scores differed, a consensus decision was made.

We defined an old nonlacunar infarct on the ipsilateral side of index stroke as 3- to 15-mm lesions in the cortex or subcortical area, or lesions larger than 15 mm in any area for right-to-left or anterior-to-posterior measurements (Fig. 1).[19] Susceptibility vessel signs on gradient-echo MRI were assessed as described by Rovira et al. (Fig. 1).[20]

MIPAV statistical software (Medical Image Processing, Analysis, and Visualization, National Institutes of Health, Bethesda, MD, USA) was used to measure infarct volumes in diffusion-weighted imaging (DWI). Infarct volumes on DWI were calculated using b1000 images and apparent diffusion coefficient maps with an apparent diffusion coefficient threshold of <600. One of the authors (H.S. Yoon) reviewed the angiographic images and determined the presence and location (proximal or distal) of M1-MCA occlusions.

Statistical analysis

Patients were dichotomized using a median FHV-ASPECTS of 4 into a severe-FHV group (score ≤4) and a mild-FHV group (score >4). To compare characteristics between two groups, we used the rank-sum test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables, as appropriate. Bivariate and multivariable logistic regression analyses were used to investigate associations of dichotomized FHV-ASPECTSs and other variables with END and func-

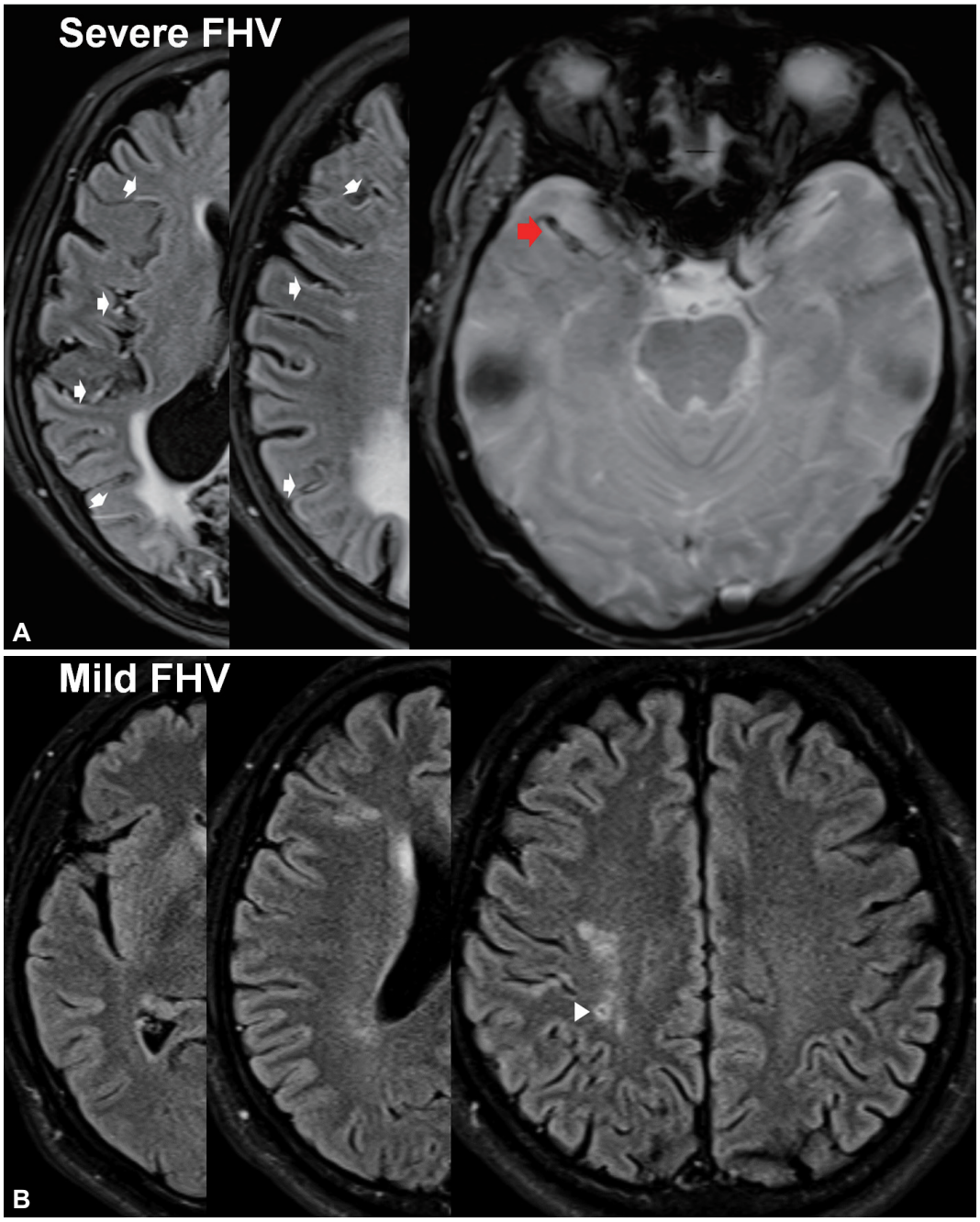

Fig. 1. Representative images for severe vs. mild FHVs. A: A patient showing prominent FHVs in seven vascular territories of the middle cerebral artery (FHV-ASPECTS=0, white arrow) and susceptibility vessel sign on gradient-echo MRI (red arrow). B: A patient with no visible FHVs (FHV-ASPECTS=7) and an old cortical infarct (white arrowhead). ASPECTS, Alberta Stroke Program Early CT Score; FHV, fluid-attenuated inversion recovery hyperintense vessel.

tional outcomes at 3 months after stroke. An unfavorable outcome was defined as a 3-month mRS score of ≥3. We additionally examined the association of uncategorized FHV-ASPECTS (0–7) with END and 3-month outcomes. Variables with $p<0.1$ in bivariate analyses were entered into a multivariable model. The statistical analyses were conducted using Stata (version 16; StataCorp, College of Station, TX, USA).

RESULTS

The study inclusion criteria were initially met by 75 of the 2,768 screened patients. Two patients without adequate FLAIR images, 2 lost to follow-up, and 3 with an uncommon cause of stroke (2 with moyamoya disease and 1 with dissection) were excluded, and hence the remaining 68 patients were

analyzed. Mean age was 66.2 (SD 13.5) years, 30 (44%) were female, and their median NIHSS score was 4 (interquartile range 1–6). Twenty (29%) of these 68 patients arrived within 4.5 hours of onset and had nondisabling symptoms with an NIHSS score of ≤2. In addition, 6 (9%) and 42 (62%) patients arrived at 4.5–6 and 6–24 hours, respectively, and they did not meet the threshold NIHSS scores based on American Stroke Association guidelines (6 and 10 points, respectively).

The severe-FHV group had a higher median NIHSS score at admission (5 vs. 3), a higher hypertension rate (85% vs. 66%), a larger infarct volume on DWI (median, 5.5 mL vs. 3 mL), and more frequently displayed the susceptibility vessel sign (30% vs. 3%) than the mild-FHV group (Table 1). Atrial fibrillation and prestroke statin use tended to be more prevalent in the severe-FHV group. However, ipsilateral old nonlacunar infarct was less frequent in the severe-FHV group (15% vs. 37%). Stroke subtypes did not differ between the two groups, but undetermined stroke was more frequent in the severe-FHV group. The 24-hour mean blood pressures were similar in the two groups. Cronbach's α for interobserver reliability of the FHV-ASPECTS was 0.81.

The severe-FHV group had a higher END rate (55% vs. 20%) than the mild-FHV group. The distribution of FHV-ASPECTSs according to END also demonstrated a relationship between these scores and END (p=0.01) (Supplementary Fig. 1A in the online-only Data Supplement). Twenty-five (37%) of the study subjects experienced END, and its most common cause was stroke progression (n=23, 92%). Bivariate analysis showed that the median FHV-ASPECTS was lower in patients with END than in those without END (4 vs. 6, p=0.02 by the rank-sum test) (Table 2). Patients in the severe-FHV group had a nearly fivefold higher risk of END than those in the mild-FHV group (95% confidence interval [CI] 1.64–14.06, p=0.004). After adjusting for covariates, the asso-

Table 1. Patient characteristics categorized by severe vs. mild FHV-ASPECTS dichotomized at the median value

Variable	Severe FHV (FHV-ASPECTS ≤4) (n=33)	Mild FHV (FHV-ASPECTS >4) (n=35)	p
Age (yr)	70 [60–77]	58 [53–79]	0.12*
Sex, male	17 (45)	21 (55)	0.48†
Onset to imaging (hr)	9.5 [6.2–18.7]	7.9 [2.5–18.9]	0.29*
NIHSS score at admission	5 [3–8]	3 [1–4]	0.006*
Right hemispheric infarction	20 (61)	14 (41)	0.13†
Previous history of stroke	7 (21)	6 (17)	0.67†
Hypertension	28 (85)	23 (66)	0.069†
Diabetes	16 (48)	12 (34)	0.23†
Hyperlipidemia	21 (64)	22 (63)	0.95†
Smoking, stopped within past 5 years or current smoker	17 (52)	21 (60)	0.48†
Atrial fibrillation	9 (27)	4 (11)	0.13†
Subtype			
Large-artery atherosclerosis	23 (72)	29 (83)	0.46
Cardioembolism	3 (9)	3 (9)	
Undetermined	6 (19)	3 (9)	
Prestroke antiplatelet use	9 (27)	7 (20)	0.48†
Prestroke statin use	9 (27)	3 (9)	0.059‡
Infarct volume (mL)	5.5 [3–8]	3 [1.5–7]	0.03*
Occlusion site (M1)			0.15†
Proximal	16 (48)	23 (66)	
Distal	17 (51)	12 (34)	
Susceptibility vessel sign	10 (30)	1 (3)	0.003‡
Ipsilateral old nonlacunar infarct	5 (15)	13 (37)	0.04†
SBP/DBP over 24 hours (mm Hg)	141±21/82±11	138±21/82±13	0.57/0.72*
END	18 (55)	7 (20)	0.003†
Unfavorable outcome§	22 (71)	10 (29)	0.001†

Data are median [IQR] or mean±SD values for continuous data, and frequency (percentage) values for categorical data.
*Rank-sum test; †χ^2 test; ‡Fisher's exact test; §3-month modified Rankin Scale score ≥3.
ASPECTS, Alberta Stroke Program Early CT Score; DBP, diastolic blood pressure; END, early neurological deterioration; FHV, fluid-attenuated inversion recovery hyperintense vessel; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure.

Table 2. Bivariate associations of patient characteristics with early neurological deterioration

Variable	No END (*n*=43)	END (*n*=25)	Odds ratio (95% confidence interval)	*p*
Age (yr)	58 [53–77]	70 [63–79]	1.04 (1.00–1.08)	0.066
Sex, male	30 (70)	8 (32)	0.20 (0.07–0.59)	0.003
Onset to imaging (hr)	7.7 [2.6–19.4]	9.8 [7.9–16.6]	1.01 (0.94–1.07)	0.85
NIHSS score at admission, per 1 score	3 [1–5]	5 [3–8]	1.28 (1.07–1.53)	0.008
Right hemispheric infarction	20 (47)	14 (56)	1.46 (0.54–3.94)	0.45
Previous history of stroke	8 (19)	5 (20)	1.09 (0.31–3.80)	0.89
Hypertension	30 (70)	21 (84)	2.28 (0.65–7.95)	0.20
Diabetes	17 (40)	11 (44)	1.20 (0.44–3.26)	0.72
Hyperlipidemia	28 (65)	15 (60)	0.80 (0.29–2.22)	0.67
Smoking, stopped within past 5 years or current smoker	26 (60)	12 (48)	0.60 (0.22–1.63)	0.32
Atrial fibrillation	7 (16)	6 (24)	1.62 (0.48–5.52)	0.44
Prestroke antiplatelet use	12 (28)	4 (16)	0.49 (0.14–1.73)	0.27
Prestroke statin use	7 (16)	5 (20)	1.29 (0.36–4.58)	0.70
Infarct volume (mL)	4 [1.5–7]	4 [1–9]	1.02 (0.98–1.08)	0.25
Occlusion site (M1)				
Proximal	26 (60)	13 (52)	Reference	
Distal	17 (40)	12 (48)	1.41 (0.52–3.82)	0.50
Susceptibility vessel sign	6 (14)	5 (20)	1.54 (0.42–5.69)	0.52
Ipsilateral old nonlacunar infarct	13 (30)	5 (20)	0.58 (0.18–1.87)	0.36
SBP/DBP over 24 hours (mm Hg)	136±20/81±12	145±22/84±12	1.03 (0.99–1.05)/1.02 (0.98–1.06)	0.08/0.36
FHV-ASPECTS	6 [4–7]	4 [3–5]		
FHV-ASPECTS ≤4	15 (35)	18 (72)	4.80 (1.64–14.06)	0.004

Data are median [IQR] or mean±SD values for continuous data, and frequency (percentage) values for categorical data (except where indicated otherwise).
ASPECTS, Alberta Stroke Program Early CT Score; DBP, diastolic blood pressure; END, early neurological deterioration; FHV, fluid-attenuated inversion recovery hyperintense vessel; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure.

ciation between FHV and END remained significant (odds ratio [OR] 5.02, 95% CI 1.36–18.45, p=0.015). When uncategorized FHV-ASPECTSs were used, scores of 3 and 4 were associated with an increased risk of END compared with a score of 7 (no visible FHVs) (Supplementary Table 1 in the online-only Data Supplement).

At 3 months after stroke onset, 32 (47%) patients had an unfavorable outcome. These patients had a lower median FHV-ASPECTS compared with those with a favorable outcome (6 vs. 4, p=0.03) (Supplementary Table 2 in the online-only Data Supplement). The distribution of FHV-ASPECTSs according to 3-month outcomes also showed that these scores were related to an unfavorable outcome (p=0.013) (Supplementary Fig. 1B in the online-only Data Supplement). Logistic regression analysis showed that patients in the severe-FHV group had a fivefold higher risk of an unfavorable outcome (OR 5.00, 95% CI 1.78–14.01, p=0.002). Multivariable analysis confirmed a significant relationship between severe FHVs and an unfavorable outcome (OR 5.97, 95% CI 1.18–33.31, p=0.03) (Table 3). In addition, FHV-ASPECTSs of 3 and 4 were tended to be associated with an unfavorable outcome compared with an FHV-ASPECTS of 7 (Supplementary Table 1 in the online-only Data Supplement).

DISCUSSION

We found that in patients with stroke of mild-to-moderate severity and MCA occlusion within 24 hours of stroke onset, a greater extent of FHVs was associated with more-severe stroke and a higher risk of END. Furthermore, prominent FHVs were independently associated with an unfavorable outcome at 3 months after stroke. Notably, 55% of patients in the severe-FHV group experienced END, and 71% of these patients had an unfavorable outcome. To the best of our knowledge, this is the first study to describe the associations of FHVs with END and 3-month functional outcomes in patients with MCA occlusion who were ineligible for recanalization therapy based on current guidelines.

Studies related to the association of FHVs with END and functional outcomes have produced conflicting results.[6-11] In general, FHVs tend to be associated with favorable functional outcomes and early neurological improvements in patients who receive recanalization therapy.[7,8] Conversely, in patients who receive conservative treatment, the presence of FHVs is associated with END and an unfavorable functional outcome.[9,10] In LVO strokes that are rapidly progressing, severe, and require urgent recanalization, the greater FHV extent

Table 3. Multivariable logistic regression analysis of early neurological deterioration and unfavorable 3-month outcome

	Early neurological deterioration		Unfavorable outcome	
	Adjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Age	0.98 (0.92–1.06)	0.65	1.12 (1.01–1.25)	0.035
Sex, male	0.15 (0.03–0.68)	0.014	0.25 (0.04–1.74)	0.16
NIHSS score at admission, per 1 score	1.17 (0.94–1.47)	0.16	1.17 (0.90–1.52)	0.25
Hypertension	0.61 (0.09–4.25)	0.62	0.37 (0.04–3.77)	0.40
Diabetes	-		1.82 (0.39–8.44)	0.45
Smoking	-		3.96 (0.52–30.26)	0.19
Atrial fibrillation	-		1.09 (0.15–7.88)	0.93
Prestroke antiplatelet use	-		3.81 (0.42–34.88)	0.24
Prestroke statin use	-		1.36 (0.14–13.24)	0.79
Infarct volume	-		1.02 (0.95–1.09)	0.65
Occlusion site (M1)				
Proximal	Reference		-	
Distal	0.60 (0.16–2.22)	0.44	-	
Mean SBP	1.03 (0.99–1.06)	0.11	1.02 (0.98–1.06)	0.30
FHV-ASPECTS ≤4	5.02 (1.36–18.45)	0.015	5.97 (1.18–33.31)	0.03

ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; FHV, fluid-attenuated inversion recovery hyperintense vessel; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; SBP, systolic blood pressure.

may be associated with better collateral flow,[21] and so FHVs are related to a better response to recanalization therapy in these patients. In contrast, in patients presenting with slowly progressive LVO and mild-to-moderate severity, the absence of FHVs may be associated with chronic, stabilized occlusion, and thus be related to a lower risk of END and hence also to a favorable outcome.

According to our data, patients in the severe-FHV group were more likely to have atrial fibrillation (27% vs. 11%) and display the susceptibility vessel sign (30% vs. 3%) than patients in the mild-FHV group, which suggests that cardioembolism is a more common cause of stroke in the severe-FHV group. Furthermore, an ipsilateral old nonlacunar infarct suggesting chronic occlusion was more prevalent in the mild-FHV group. These observations suggest that the presence and extent of FHV is associated with the nature of the thrombus, the etiology of stroke (large-artery atherosclerosis vs. cardioembolism), and the pace of arterial occlusion in LVO stroke of mild-to-moderate severity.

Previous studies have shown that FHVs measured outside of the DWI infarct lesion are associated with a favorable response to recanalization therapy and thus might be representative of a diffusion–perfusion mismatch.[22,23] Almost all of the present patients (*n*=65, 96%) had FHVs exclusively outside of the DWI lesions, which was due to the inclusion of patients with a small infarct volume. These data indicated that patients with LVO stroke of mild-to-moderate severity with a greater extent of FHVs may have a larger diffusion–perfusion mismatch and so benefit from recanalization therapy.

The current American Stroke Association guidelines[24] do not recommend recanalization therapy for patients with mild nondisabling stroke (NIHSS score of 0–5). However, the most recent clinical trials performed using an extended time window have mostly included patients with severe stroke (median NIHSS score of 16 or 17),[12,25] and so there are few data available on the benefits of recanalization therapy in patients with LVO stroke of mild-to-moderate severity. In the present study, more than half (55%) of the patients in the severe-FHV group who presented with stroke of mild-to-moderate severity experienced END, and 71% of these patients became dependent at 3 months after stroke. One study on LVO stroke with mild symptoms (NIHSS score ≤5) found that the presence of FHVs was associated with an unfavorable 3-month outcome, which concurs with our findings.[10] In another study, the presence of FHVs was associated with poor outcomes in patients with a borderzone infarct.[26] These findings imply that the impact of FHVs depends on the stroke etiology. Hence, the presence and extent of FHVs might be a useful imaging biomarker for selecting patients with LVO stroke of mild-to-moderate severity who are candidates for revascularization therapy.

Our study had several limitations. First, the study was limited by its retrospective design, small sample, and involvement of a single institution, which predispose the findings to selection bias and restrict their generalizability. Second, we did not acquire perfusion images or examine the association between FHVs and perfusion defects. However, we did investigate the impact of FHVs on clinical outcomes, which are more important than imaging findings. Third, data from follow-up brain imaging were unavailable, and thus we did not

evaluate the association between FHVs and infarct growth. However, given that infarct growth is the most common cause of END,[27] our results regarding the impact of FHVs on END might be extrapolated to the association between FHVs and infarct growth. Fourth, we were unable to compare the underlying nature of different types of arterial occlusions such as intracranial atherosclerotic stenosis vs. thromboembolic occlusion, which may be associated with END and clinical outcomes.[28]

Our results demonstrate that among patients with LVO stroke of mild-to-moderate severity, those with lower FHV-ASPECTSs (more-severe FHVs) are more likely to experience END and an unfavorable 3-month functional outcome. The accumulating evidence—including the present findings—suggest that the clinical impact of FHVs is dependent on the etiology of stroke and the pace of arterial occlusion. We suggest larger-scale studies investigate the use of FHVs for selecting candidates for revascularization therapy beyond the current guidelines.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2021.17.4.516.

Availability of Data and Material

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

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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