Neurological Sciences (2019) 40:1675–1682
https://doi.org/10.1007/s10072-019-03909-0

ORIGINAL ARTICLE

Fluid-attenuated inversion recovery vascular hyperintensities in anterior circulation acute ischemic stroke: associations with cortical brain infarct volume and 90-day prognosis

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Received: 30 October 2018 / Accepted: 19 April 2019 / Published online: 29 April 2019

Abstract

Background and purpose Fluid-attenuated inversion recovery vascular hyperintensity (FVH) is often observed in conjunction with acute ischemic stroke (AIS) of the carotid system. However, the significance of FVH in patients with AIS has not been fully elucidated. The purpose of this study is to investigate the effects of FVH on the final infarct volume (including cortical and deep brain infarct volume) and on 90-day prognosis in AIS patients.

Material and methods We analyzed data of 160 patients who had AIS of anterior circulation. FVH was identified and the cortical brain infarct volume (CBIV) and deep brain infarct volume (DBIV) were calculated. We assessed 90-day clinical outcome using the modified Rankin Scale (mRS).

Results FVH was identified in 83 of the 160 patients (51.88%). Patients with FVH showed larger CBIV (13.94 ± 25.55 vs. 6.56 ± 13.49 ml; $p = 0.025$), more frequent intracranial-large artery disease (74.70 vs. 27.27%; $p < 0.001$), and more severe clinical impairment on admission (NIHSS 7.22 ± 4.01 vs. 5.42 ± 4.52; $p = 0.009$). Considering the factors influencing prognosis, FVH positivity (OR = 2.12, 95% CI 1.13–3.99; $p = 0.02$) and NIHSS (at discharge) (OR = 2.14, 95% CI 1.64–2.78; $p < 0.001$) were independently associated with 90-day clinical outcome of AIS patients.

Conclusion FVH is a more common finding associated with larger CBIV, intracranial-large artery disease, and more severe strokes on admission. In the presence of good collateral circulation, FVH may be a predictor of better outcome in anterior circulation AIS patients at 90 days.

Keywords Acute ischemic stroke magnetic resonance imaging · Fluid-attenuated inversion recovery vascular hyperintensity · Collateral circulation · Brain infarction volume · Prognosis

Introduction

Acute ischemic stroke (AIS) in the anterior circulation accounts for approximately three quarters of all AIS and can cause varying degrees of disability [1]. A large number of studies have explained some of the diversity of outcomes in AIS patients, including the effects of collateral circulation [2]. Collaterals are defined as a network of vascular connections that provide alternative routes for blood flow when the main supplying artery is blocked [3]. Although these collaterals are dynamic, good collateral circulation is believed to be one of the major influence factors on better outcome in AIS patients [2, 4].

Fluid-attenuated inversion recovery vascular hyperintensities (FVHs) refer to focal hyperintensities that can be frequently observed near the cerebral surface along the cortical sulcus in AIS patients [5]. FVHs are usually identified as tubular or serpentine hyperintensities in the subarachnoid space, especially in the Sylvian fissure, but could also extend to the anterior and posterior territories [6]. It has been also confirmed as a higher grade of leptomeningeal collateral circulation in patients with chronic intracranial atherosclerotic disease [7]. However, the incidence rate and effects of FVH on the prognosis of patients with AIS are still controversial. The incidence of FVH can range from < 10% to > 90% in different studies and different screening time points [8, 9]. In determining the prognostic value of FVH, some studies

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concluded that the presence of FVH was correlated with worse clinical outcome, if FVH persisted for more than 2 h [10], while Lee et al. observed that the presence of FVH distal to arterial occlusion was associated with better prognosis and smaller infarct size [11]. Since FVH is often seen near the cerebral surface along the cortical sulcus, and the collateral flow to the anterior circulation largely supplies the cortical areas, the deep brain tissue (basal ganglia and corona radiata) has little or no collateral supply [12]. Whether there is different impact of FVH on CBIV and DBIV has not been reported yet.

The purpose of this study was to investigate the effect of FVH on the infarct volume in anterior circulation AIS patients. We sought to differentiate between the effects of FVH on CBIV and DBIV, and to determine the relation between FVH and clinical outcome of anterior circulation AIS patients at 90 days.

Materials and methods

Patients

Between April 2017 and May 2018, consecutive patients who were diagnosed with anterior circulation AIS at the Department of Neurology in Shengjing Hospital of China Medical University were enrolled in our study ($n = 241$). All patients underwent MRI within 48 h of symptom onset, MRI data included FLAIR sequences, diffusion-weighted imaging (DWI), and magnetic resonance angiography (MRA), followed by intracranial and extracranial vascular imaging. Each diagnosis of AIS was made jointly by at least two neurologists according to the diagnostic criteria [13]. We collected baseline data on demographic and clinical parameters and cerebral vascular risk factors, including sex, age, diabetes mellitus, hypertension, coronary heart disease, atrial fibrillation, current smoking, and alcohol drinking. Laboratory data regarding lipid profile and levels of uric acid and homocysteine were also assessed. We screened all AIS patients who had an admission National Institute of Health Stroke Scale (NIHSS) ≥ 5 [14]; in addition, we used the NIHSS score (at discharge) and modified Rankin Scale (mRS) at 90 days to assess clinical outcome. Patients treated with thrombolysis or endovascular therapy were not included in this study. In our study, the treatment of patients with AIS included statin and anti-platelet drugs (aspirin 200 mg or clopidogrel 75 mg) at the discretion of American Heart Association (AHA) guidelines [15].

Radiological assessment

Magnetic resonance scans were performed on an Achieva 3.0 Tesla scanner (Philips Healthcare, Amsterdam, the Netherlands), with an eight-channel phased array coil for brain imaging. A standardized protocol was used in all patients including T1-weighted images; T2-weighted images; DWI; FLAIR image (RT, 8000 ms; ET, 160 ms; inversion time, 1200 ms; matrix, 182 × 256; field of view, 23 cm; flip angle, 150° (180°); section thickness, 5 mm (4 mm); and intersection gap, 1 mm (2 mm)). Time-of-flight MRA (RT, 17 ms; ET, 6.23 ms; flip angle, 25° (20°); field of view, 260 mm; matrix, 256 × 256; and slice thickness, 0.9 mm). A 22-color ultrasonography unit (Philips Healthcare) was used to detect degrees of stenosis in the main, internal, and external branches of the carotid artery.

Image analysis

FVHs were defined as hyperintensities in FLAIR corresponding to the typical course of a blood vessel that was considered the proximal, occluded main artery ipsilateral to the diffusion restriction (Fig. 1). By MRA, focal loss of signal with distal arterial signal resumption was interpreted as severe stenosis, whereas complete absence of signal intensity, including distal branches, was considered occlusion [16]. Ultrasonographic assessment of stenosis of the internal carotid artery (ICA) complies with North American criteria for symptomatic carotid endarterectomy. Stenosis more than 50% is considered to be a serious luminal compromise. [17]. According to the ORG 10172 trial in the TOAST classification system, LAD was defined as severe stenosis or intracranial or extracranial vascular occlusion [18]. Presence of FVH was rated by two observers and consensus reached in cases of disagreement. Both observers were independent from each other and blinded to clinical information and blinded to results from MRA.

Infarct volume was measured on a follow-up scan 48–72 h after admission; the observers mapped both cortical and deep brain infarcts separately, using the natural separating line of the corona radiata. The area of DWI abnormality was outlined manually on the MR series. To calculate the total DWI lesion volume for each patient, the areas of DWI abnormality were summed and multiplied by section thickness (mm) and intersection gap (mm). The average of the volume measurements was used as the volume of the ischemic lesion (Fig. 2). Both observers were blinded to the clinical parameter of the patients.

Follow-up monitoring

In the present study, clinical outcome was stratified by mRS at 90 days and evaluated by a neurologist who was certified in mRS adjudication. mRS of 0 to 2 identified better outcome for functional independence, and 3 to 6 identified poor outcomes. Finally, 160 patients completed a 90-day reassessment by a neurologist at the outpatient stroke clinic. If the patient was unable to go to the clinic for follow-up, telephone interviews or instant messaging via Wechat would be used as follow-up.

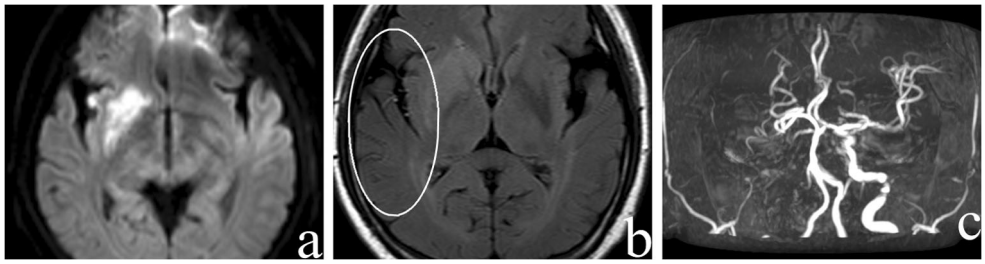

Fig. 1 A patient with persistent left hemiparesis and dysarthria. DWI showing regional hyperintensity in right basal ganglion (**a**). FLAIR imaging showing FVH in the region of the right MCA (**b**) and MRA showing occlusion of the right intracranial internal carotid (**c**), performed 24 h after the appearance of the initial symptom

Statistical analyses

Statistical analysis was performed using SPSS 17.0 software (SPSS Inc. [IBM], Chicago, IL, USA), with statistical significance at $p < 0.05$. Continuous variables were expressed as mean ± SD. The *t* test was used to compare continuous variables and the chi-squared test to compare categorical variables, between groups (absent or present FVH sign). In binary logistic regression analysis, a backward stepwise variable selection method was used to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for factors influencing FVH and evaluating the independent predictive factors associated with clinical outcome in anterior circulation AIS patients.

Result

Baseline characteristics

A total of 241 patients with anterior circulation AIS were included, of whom 160 (males, 97; mean age, 64.01 ± 11.81 years) completed the follow-up between April 2017 and May 2018 and enrolled in our study finally. The mean time interval from symptom onset and MRI was 24.72 ± 16.24 h, and the presence of FVH was observed in 83 patients (51.88%). The demographics, vascular risk factors, and characteristics of AIS are shown in Table 1.

Comparison of demographic, clinical, and laboratory data in FVH-positive and FVH-negative patients

In comparing AIS patients, those who were FVH-positive had higher incidence of hypertension (61.45 vs. 42.86%; $p = 0.019$), more frequent intracranial-LAD (74.70 vs. 27.27%; $p < 0.001$), larger CBIV (13.94 ± 25.55 vs. 6.56 ± 13.49 ml; $p = 0.025$), more severe impairment (NIHSS score on admission 7.22 ± 4.01 vs. 5.42 ± 4.52; $p = 0.009$), and more common anticoagulant use (13.25 vs. 3.90%; $p = 0.014$), compared to patients who were FVH-negative (Table 1; Fig. 3). There were no differences in DBIV and other parameters. In the binary logistic regression model, only intracranial-LAD was significantly associated with presence of FVH (odds ratio 6.18; 95% CI 2.92–13.06; $p < 0.001$), whereas NIHSS score, CBIV, and hypertension were not (Table 2).

Comparison of demographic, clinical, and laboratory data of AIS patients, stratified by modified Rankin Scale

At 90 days, 72 patients (45.0%) had worse clinical outcome, patients with better clinical outcome had younger age (62.30 ± 10.72 vs. 66.10 ± 12.78; $p = 0.042$), more frequent presence of FVH (60.23 vs. 41.67%; $p = 0.019$), higher level of uric acid (329.95 ± 123.43 vs. 286.86 ± 124.03 μmol/L; $p = 0.03$), minor impairment NIHSS score on admission (5.11 ± 3.68 vs. 7.68 ± 4.68; $p < 0.001$), minor impairment NIHSS score at discharge (3.70 ± 2.74 vs. 8.31 ± 3.55; $p < 0.001$),

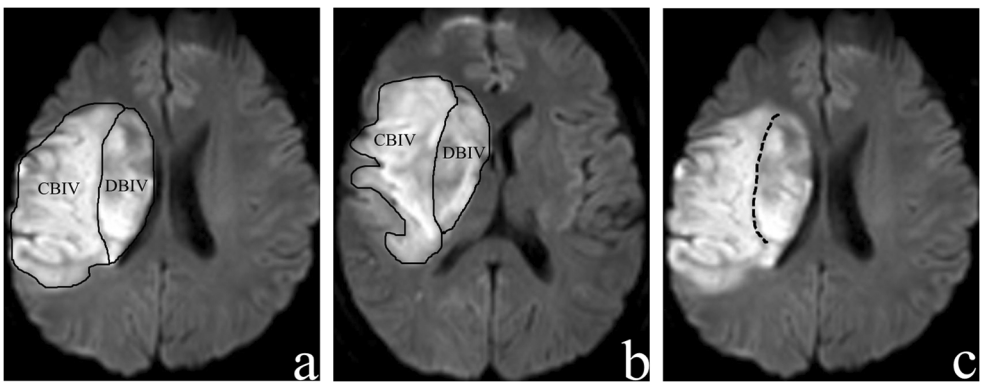

Fig. 2 Representative DWI images of the segmentation between the cortical and deep infarct areas. **a**, **b** demonstration of CBIV and DBIV. **c** Demonstration of the natural separating line of the corona radiata. CBIV, cortical brain infarct volume in ml; DBIV deep brain infarct volume in ml

Table 1 Demographic, clinical, and laboratory data in FVH-positive and FVH-negative patients

	All ($n = 160$)	FVH-positive ($n = 83$)	FVH-negative ($n = 77$)	p Value
Man	97 (60.63)	49 (59.04)	48 (62.34)	0.669
Age, year (mean ± SD)	64.01 ± 11.81	63.30 ± 11.42	64.77 ± 11.23	0.435
Risk factors				
Diabetes mellitus	50 (31.25)	24 (28.92)	26 (33.77)	0.508
Hypertension	84 (52.50)	51 (61.45)	33 (42.86)	0.019
CHD	22 (13.75)	15 (18.07)	7 (9.09)	0.099
Atrial fibrillation	10 (6.25)	5 (6.02)	5 (6.49)	0.902
Smoking	69 (43.13)	32 (38.55)	37 (48.05)	0.225
Alcohol drinking	22 (13.75)	9 (10.84)	13 (16.88)	0.268
Extracranial-LAD	41 (25.63)	21 (25.30)	20 (25.97)	0.922
Intracranial-LAD	83 (51.88)	62 (74.70)	21 (27.27)	<0.001
CBIV	10.38 ± 20.91	13.94 ± 25.55	6.56 ± 13.49	0.025
DBIV	1.01 ± 2.66	1.24 ± 3.13	0.76 ± 2.03	0.254
Triglyceride	1.46 ± 0.78	1.49 ± 0.74	1.44 ± 0.82	0.664
Total cholesterol	4.64 ± 1.16	4.63 ± 1.13	4.65 ± 1.20	0.950
LDL	3.06 ± 1.04	3.03 ± 1.00	3.09 ± 1.09	0.696
Uric acid	310.56 ± 125.17	315.18 ± 137.68	305.57 ± 110.81	0.629
Homocysteine	17.18 ± 7.94	16.94 ± 7.56	17.43 ± 8.37	0.696
NIHSS (on admission)	6.35 ± 4.37	7.22 ± 4.01	5.42 ± 4.52	0.009
NIHSS (at discharge)	5.78 ± 3.87	6.23 ± 3.85	5.29 ± 3.87	0.124
Treatment				
Anti-platelet treatment	93 (58.13)	52 (32.50)	41 (53.25)	0.228
Stain treatment	47 (29.38)	25 (30.12)	22 (28.57)	0.949
Anticoagulant	13 (8.13)	11 (13.25)	3 (3.90)	0.014

Figures in parentheses are percentages, unless indicated otherwise

CHD coronary heart disease, *CBIV* cortical brain infarction volume, *FVH* fluid-attenuated inversion recovery vascular hyperintensity, *DBIV* deep brain infarction volume, *LAD* large artery disease, *LDL* Low density lipoprotein, *NIHSS* National institute of Health Stroke Scale

and anti-platelet treatment (67.05 vs. 47.22%; $p = 0.011$) (Table 3). Logistic regression analysis showed that presence of FVH (odds ratio 2.12; 95% CI 1.13–3.99; $p = 0.02$) and NIHSS score at discharge (odds ratio 2.14; 95% CI 1.64–2.78; $p < 0.001$) were significantly associated with better clinical outcome in anterior circulation AIS patients, whereas age, uric acid level, and anti-platelet treatment were not (Table 4).

Discussion

FVH is often observed in AIS patients, especially in anterior circulation [19]. However, the mechanisms and clinical implications of FVH have been a matter of debate in past decades [7, 20]. At present, most current studies indicate that FVH does not represent thrombus but rather a sluggish or disordered blood flow through vessels, most often leptomeningeal collaterals [21]. Its presence usually indicates abnormal blood flow in acute stroke and potentially remedial areas of brain tissue. In determining the prognostic value provided by FVH, the data are seemingly split. The influence of FVH on the volume of AIS and prognosis of AIS is mostly controversial. In our study, we aimed to elucidate the clinical and imaging findings of FVH and clarify the prognostic value of FVH in a typical anterior circulation AIS population.

FVH is best characterized in the setting of AIS. Kamran et al. showed that the incidence of FVH was > 90% in middle cerebral artery (MCA) occlusion in the first 24 h in AIS patients [22]. FVH can also be seen in the setting of chronic intracerebral arterial steno-occlusive disease and Moyamoya disease [23, 24]. In the present study, 160 patients with moderate to severe anterior circulation AIS were included. By MRI analysis within 48 h of symptom onset, more than half of the patients (51.88%) were FVH positive. As a main finding, FVH was associated with hypertension, intracranial-LAD, larger CBIV, and more severely impaired neurological function (NIHSS score on admission). Multivariable logistic regression analysis further confirmed that intracranial-LAD was independently associated with FVH in our cohort. FVH has shown a strong association with intracranial-LAD in some studies, reflecting sluggish flow or retrograde leptomeningeal collateralization [25, 26]. Johnston et al. also concluded in their study that

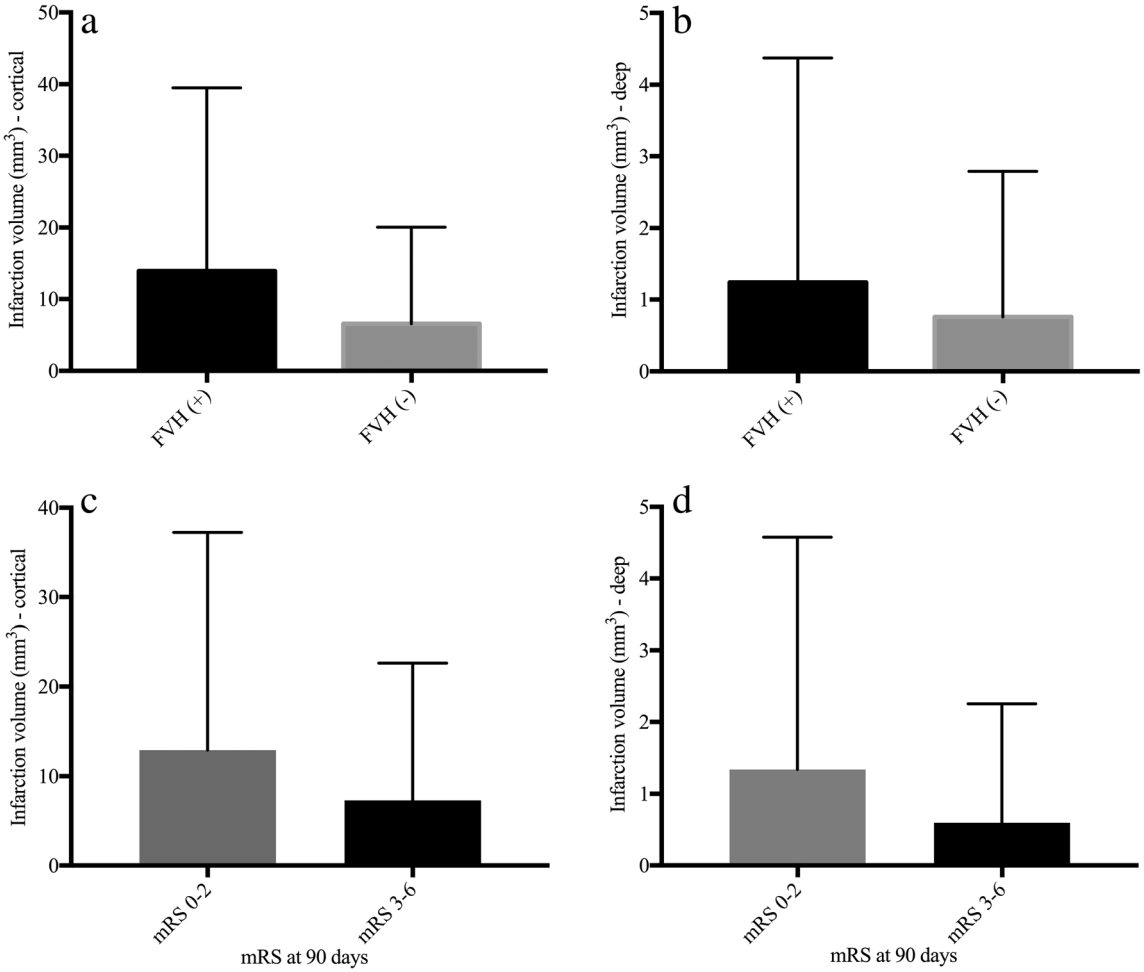

Fig. 3 The relation of infarct volume to FVH (**a**, **b**) and clinical outcome (**c**, **d**). CBIV, cortical infarct volume in ml; DBIV, deep infarct volume in ml. Error bars represent standard error of the mean

FVH represented persistent large-vessel stenosis or occlusion [27]. That is why FVH can be interpreted as a marker of intracranial-LAD, and the presence of FVH could help the clinician identify patients at higher risk for ischemic stroke in the future. Kamran et al. found that the presence of FVH was correlated with larger infarct volume and a higher NIHSS score [8], and we came to a similar conclusion. However, in our study, FVH was only associated with CBIV and NIHSS score on admission, whereas DBIV and NIHSS score at discharge were not. In this part of the study, we determined the relationship between FVH and intracranial-LAD, where FVH predicted vessel occlusion with high diagnostic accuracy. This finding also supported the results from previous studies analyzing the diagnostic value of FVH regarding the detection of proximal large-vessel occlusion [6]. FVH may be related to CBIV and the degree of neurological deficit at admission. However, its role in prognosis at 90 days remains unclear.

Table 2 Logistic regression analysis of parameters associated with FVH positive

	OR	95% CI	*p* Value
CBIV	1.01	0.87–1.18	0.862
Hypertension	1.79	0.85–3.78	0.127
Anticoagulant	4.35	0.74–25.47	0.103
NIHSS (On admission)	1.08	0.99–1.18	0.086
Intracranial-LAD	6.18	2.92–13.06	< 0.001

CBIV cortical brain infarction volume, *FVH* fluid-attenuated inversion recovery vascular hyperintensity, *LAD* large artery disease, *NIHSS* National institute of Health Stroke Scale

To further elucidate the prognostic implications of FVH, we performed an additional univariate and multivariate analysis on the clinical and radiological factors known to influence clinical outcomes. The univariate analysis showed that better outcome was associated with younger age, more frequent presence of FVH, higher uric acid level, minor impairment on admission/at discharge, and anti-platelet treatment (Table 3). We next performed multiple logistic regression analysis and showed that the presence of FVH was independently correlated with better outcome (at 90 days) in anterior circulation AIS patients (Table 4). This seems to be different from the conclusions of previous studies. Lee et al. found

Table 3 Comparison of demographic, clinical, and laboratory of AIS patients, stratified by modified Rankin Scale

	Poor Outcome ($n = 72$)	Better Outcome ($n = 88$)	p Value
Man	43 (59.72)	54 (63.64)	0.833
Age, year (mean ± SD)	66.10 ± 12.78	62.30 ± 10.72	0.042
Risk factors			
Diabetes mellitus	20 (27.78)	30 (34.09)	0.391
Hypertension	34 (47.22)	50 (56.82)	0.227
CHD	10 (13.89)	12 (13.64)	0.963
Atrial fibrillation	7 (9.72)	3 (3.41)	0.101
Smoking	31 (43.06)	38 (43.18)	0.987
Alcohol drinking	13 (18.06)	9 (10.23)	0.153
Extracranial-LAD	22 (30.56)	19 (21.59)	0.196
Intracranial-LAD	41 (56.94)	42 (47.73)	0.246
CBIV	7.32 ± 15.34	12.89 ± 24.35	0.093
DBIV	0.60 ± 1.66	1.34 ± 3.24	0.079
FVH positive	30 (41.67)	53 (60.23)	0.019
Triglyceride	1.39 ± 0.67	1.52 ± 0.85	0.286
Total cholesterol	4.66 ± 1.25	4.62 ± 1.09	0.816
LDL	3.10 ± 1.12	3.02 ± 0.97	0.622
Uric acid	286.86 ± 124.03	329.95 ± 123.43	0.030
Homocysteine	16.73 ± 7.15	17.54 ± 8.55	0.526
NIHSS (on admission)	7.68 ± 4.68	5.11 ± 3.68	<0.001
NIHSS (at discharge)	8.31 ± 3.55	3.70 ± 2.74	<0.001
Treatment			
Anti-platelet	34 (47.22)	59 (67.05)	0.011
Anticoagulant	8 (11.11)	5 (5.68)	0.211

Figures in parentheses are percentages, unless indicated otherwise

AIS acute ischemic stroke, *CBIV* cortical brain infarction volume, *DBIV* deep brain infarction volume, *FVH* fluid-attenuated inversion recovery vascular hyperintensity, *LAD* large artery disease, *LDL* low density lipoprotein, *NIHSS* National institute of Health Stroke Scale

smaller ischemic lesion volumes and less clinical severity in association with FVH occurring distal to arterial occlusion [11], while Kamran et al. noted that the presence of FVH was correlated with larger infarct volume and a higher NIHSS score [8].

The question is how to explain these contradictions. Lee et al. used angiographic information to categorize FVH into proximal and distal FVH, and they concluded that the presence of distal FVH was associated with better outcome and that proximal FVHs did not offer prognostic information. The presence of distal FVH may represent the existence of collateral circulation, and good collateral flow distal to an occlusion could promote salvageable brain parenchyma recanalization. In the study by Kamran et al., the authors enrolled a small sample of AIS patients with extracranial internal carotid artery and MCA occlusion, and there was no matched control group.

In our study, we found that FVH was related to larger CBIV and more severely impaired neurological function (NIHSS score on admission), but better clinical outcome at 90 days. We speculate that earlier FVH positive (48 h in the present study) can represent the presence of proximal large artery stenosis or occlusive lesions (e.g., MCA M1) in the patients, and that FVH usually occurs in patients with cerebral infarction with relatively large cortical areas. This degree of infarction can be explained by the high NIHSS score in the early stage. However, as time goes on, the collateral circulation represented by FVH plays the role of distal leptomeningeal collateral supply to the proximal stenosis or occlusion. Early

Table 4 Logistic regression analysis of parameters associated with poor outcome in AIS

	OR	95% CI	p Value
Age	1.01	0.97–1.04	0.758
FVH-positive	2.12	1.13–3.99	0.020
Uric acid	0.99	0.99–1.00	0.275
Anti-platelet treatment	0.99	0.39–2.44	0.976
NIHSS (on admission)	0.87	0.73–1.05	0.140
NIHSS (At discharge)	2.14	1.64–2.78	< 0.001

AIS acute ischemic stroke, *FVH* fluid-attenuated inversion recovery vascular hyperintensity, *NIHSS* National institute of Health Stroke Scale

onset and sustained open collateral circulation improve the prognosis of AIS, which is also the conclusion of previous studies. However, lack of dynamic MRI to observe continuous changes in FVH was one of the major limitations of our study.

Other limitations in the present study included the following. Subjects were restricted to anterior circulation AIS, and the single-center construct was a possible source of selection bias and statistical errors. Second, we only assessed the relationship between FVH and AIS patients with conservative therapy; IV-tPA therapy and endovascular therapy were not included, so not all AIS patients could be represented. Finally, our 90-day follow-up period was comparatively short. Future endeavors should address more time points, monitoring patients for a longer period.

Conclusion

Imaging and clinical findings in our patients with anterior circulation AIS are consistent with the previous conclusion that FVH represent arterial collateral flow in patients with proximal intracranial-LAD. Although FVHs are more common in patients with larger CBIV and higher NIHSS score on admission, the early presence of FVH after AIS was found to be associated with a better prognosis at 90-day follow-up. FVH might be used as valuable data for the clinician to evaluate collaterals and to predict the prognosis of AIS.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Ethical standards This study conformed to Ethical Guidelines for Medical and Health Research Involving Human Subjects endorsed by the Chinese government.

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