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ORIGINAL ARTICLE

Added assessment of middle cerebral artery and atrial fibrillation to FLAIR vascular hyperintensity-DWI mismatch would improve the outcome prediction of acute infarction in patients with acute internal carotid artery occlusion

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Abstract

Background and aims Whether fluid-attenuated inversion recovery (FLAIR) vascular hyperintensities (FVH)-DWI mismatch could predict the outcome or not remains in debate. The aim of this study was to identify if FVH combined with the other markers improved favorable outcome prediction of acute infarctions in patients with unilateral acute internal carotid artery (ICA) occlusion.

Methods Consecutive 68 adult acute middle cerebral artery (MCA) territory infarction patients caused by acute ICA occlusion, including favorable ($n = 38$, mRS ≤ 2) and unfavorable ($n = 30$, mRS > 2) groups, were enrolled in this retrospective analysis. The diagnostic efficiency of favorable clinical outcome of FVH-DWI mismatch was compared with those of DWI lesions volumetry and the combined marker of FVH-DWI mismatch and other factors.

Results There were more prominent FVH-DWI mismatch (≥ 3 sections) (84%), less atrial fibrillation (AFib) (13%), and more tandem MCA normal or mild stenosis (63%) in favorable outcome group than those (30%, 40%, and 27%, respectively) in unfavorable group. Univariate and multivariate analyses showed that the prominent FVH-DWI mismatch was the positive predictive factor for favorable outcome (OR = 2.643 and 3.200). Prominent FVH-DWI mismatch, in combination with tandem MCA normal or mild stenosis, and absence of Afib, had better performance (AUC = 0.875) than that of initial DWI lesion volumetry (AUC = 0.854) and any other single factor (AUC = 0.634~0.820) in predicting favorable outcome.

Conclusions Prominent FVH-DWI mismatch was associated with favorable outcome in acute infarctions in unilateral ICA occlusion patients. Its predictive performance would be improved when combined with the assessment of tandem lesions of MCA and AFib.

Keywords Stroke · Internal carotid artery · Magnetic resonance imaging · Fluid-attenuated inversion recovery · Outcome

Introduction

The occlusion or severe stenosis of internal carotid artery (ICA) will lead to abnormal hemodynamics in ipsilateral cerebral hemisphere and massive cerebral infarction [1, 2]. Favorable collateral circulation for infarct patients would be in favor of recanalization, reducing hemorrhagic transformation, and extending the time window for thrombolytic treatment and improving the clinical outcome [3–7]. Thus, appropriate evaluation of the collateral circulation after ICA occlusion plays an important role in ischemic stroke management [4, 6]. Recently, non-invasive and non-contrast imaging techniques, such as fluid-attenuated inversion recovery (FLAIR), susceptibility-weighted imaging (SWI), and arterial spin labeling (ASL) perfusion-weighted imaging, have been used to provide information of collaterals for those patients

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who are inadequacy for conventional angiography and contrast injection [4].

In previous studies, several authors investigated the role of FLAIR on the evaluation of the collateral circulation after ICA occlusion [8–10]. Mismatch of FLAIR vascular hyperintensities (FVH) and diffusion-weighted imaging (DWI), namely FVH beyond the DWI lesion boundaries [8], was taken as the image maker for evaluating the collaterals and predicting the clinical outcome. To our knowledge, the role of FVH in the evaluation of the outcome of AIS was in debate [8–13], not only because of the heterogeneous population and different therapies, the diversity of methodologies for prognostic evaluation criteria, but also other factors, such as the patency of ipsilateral middle cerebral artery (MCA) was not included in the evaluation [5, 13–18].

Our priori hypothesis is that prominent FVH-DWI mismatch, which means this kind of mismatch was detected in more sections, indicates more abundant collateral circulation for infarctions in ICA occlusion. We furthermore deduce that less MCA tandem stenosis is also in favor of better collaterals and therefore more favorable outcome to these patients. Therefore, the purpose of this retrospective study was to explore the role of prominent FVH-DWI mismatch and in combination with other factors, in predicting the favorable outcome of cerebral infarction caused by unilateral acute ICA occlusion.

Subjects and methods

Patients

We retrospectively collected data from consecutive MCA territory infarction patients with acute ICA occlusion who were admitted between July 2014 and July 2016. The inclusion criteria were as follows: (1) patients with acute cerebral infarction in MCA territories and the acute obliterated ipsilateral ICA were detected meanwhile; (2) MR imaging was made within 72 h after ictus; (3) 3-month clinical follow-up, including modified Rankin Scale score (mRS) [15]; (4) if there was a history of previously ischemic attacks, no sequelae left over, or mRS < 3 and the fluctuation of mRS ≤ 1 [16]; (5) no contraindication for MR examination. The exclusion criteria were as follows: (1) patients who failed to complete MR examination; (2) patients with bilateral acute infarction foci; (3) patients with the infarction in posterior cerebral circulation territories meanwhile; (4) patients with a history of chronic ICA occlusion, or with contralateral ICA stenosis or occlusion; (5) patients without sufficient MRI and clinical data.

The following data were recorded: age, gender, the side of occluded ICA, treatment, vascular risk factors (smoke, hypertension, diabetes mellitus, hyperlipemia, atrial fibrillation) [17], previous ischemic attacks, National Institute of Health stroke scale (NIHSS) scores at admission and discharge, and 3-month mRS after ictus. Scores of NIHSS and mRS were evaluated by 14- and 21-year-experienced neurologists. Favorable clinical outcome was defined as a mRS score ≤ 2 at 3 months after ictus [15]. The included patients were divided into two groups, i.e., favorable and unfavorable outcome groups.

As the time span from the stroke attack to medical consultation beyond the time window of intravascular treatment, all the enrolled patients had neither mechanical thrombectomy (MT), nor intravenous thrombolysis (IVT). The treatment included oral statins, antithrombotic therapy, anticoagulant, and antiplatelet for the two groups.

MRI examination

All MR images were acquired using a 3.0-Tesla MR scanner (3.0T Philips MR Systems Achieva, Netherlands), with a standard quadrature transmit/receive radio frequency head coil. The MR protocol included transverse T_1-weighted imaging (T_1WI), transverse and sagittal T_2-weighted imaging (T_2WI), transverse T_2 fluid-attenuated inversion recovery (FLAIR), transverse diffusion-weighted imaging (DWI), and time-of-flight MR angiography (TOF MRA). Specific parameters of the above sequences were as follows: (1) for transverse T_2 FLAIR, TR, 9000 msec; TE, 140 msec; time of inversion, 2600 msecl; flip angle, 120°; matrix, 232 × 181; FOV, 230 mm × 220 mm; section thickness, 6.5 mm; NEX, 1; (2) for transverse DWI, TR, 2208 msec; TE, 96 msec; flip angle, 90°; matrix, 168 × 105; FOV, 220 mm × 204 mm; section thickness, 6.5 mm; NEX, 1.

Image analysis

All MR image data were analyzed on a workstation, Philips Extended MR WorkSpace 2.6.3.4. FVH-DWI mismatch, normal, or mild MCA stenosis was independently reviewed by two neuroradiologists (with 11 years and 24 years of experience in neuroradiology, respectively), blinded to the prognosis information. The definition of FVH was as follows [9]: focal, tubular serpentine hyperintensity in the subarachnoid space relative to cerebrospinal fluid on FLAIR images. FVH-DWI mismatch was considered present when FVH extended beyond the boundaries of the cortical DWI lesion [18–20]. The number of FVH-DWI mismatch sections (≥ 1) was counted. The M1 segment of MCA stenosis was measured on conventional angiography images. When multiple stenoses, we measured the most severe stenosis. The degree of tandem stenosis of MCA was calculated on conventional angiography as follows: (1 − luminal area of stenosed segment / luminal area of the proximal segment) × 100%. (1) Normal: no noticeable stenosis; (2) mild stenosis: the degree of stenosis was ≤ 49%; (3) moderate stenosis: the degree of stenosis was ≥ 50% and ≤ 69%; (4) severe stenosis: the degree of stenosis was 70~99%; (4) occlusion: the vascular lumen could not be displayed [3, 10].

Statistical analysis

Gaussian distribution data were expressed as mean ± deviation (SD). The non-normal distribution data were presented as a percentage or median and interquartile range (sexuality, number of sections of FVH-DWI mismatch, admission and discharge NIHSS scores, mRS at the third month, the time point of initial and follow-up MR examination). Based on the clinical outcome, namely mRs at the third month, the cut-off point of the number of FVH-DWI mismatch sections was obtained through the receiver operating characteristic (ROC) curve. Logistical regression was employed to analyze whether age, risk factors (smoke, hypertension, diabetes mellitus, hyperlipemia, atrial fibrillation) [17], previous ischemic attack, NIHSS scores at admission and discharge, would influence the clinical outcome. Chi-square test was used to evaluate the difference of MCA stenosis between two groups. Univariate and multivariate regression analyses were performed to calculate the odds ratio (OR). Then ROC curve analysis was performed to analyze the difference of various clinical and MR markers between the two groups. Intraclass correlation coefficient (ICC) was used to evaluate the inter-readers agreement for evaluation of admission and discharge NIHSS scoring, 3-month mRS scoring, and the number of FVH-DWI mismatch sections.

P values < 0.05 was considered statistically significant. All statistical analyses were carried out using SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 159 consecutive patients were diagnosed as acute cerebral infarction caused by acute occlusion of unilateral ICA and had MR examination within 72 h after ictus. Ninety-one patients were excluded due to stent implantation in carotid artery ($n = 12$), absence of FVH-DWI mismatch ($n = 62$), without sufficient MRI data ($n = 11$), and loss to follow-up ($n = 6$). As a result, a total of 68 patients were enrolled in this study. Of these patients, 38 (56%) had a favorable outcome with mRS score of 0–2, and 30 (44%) had an unfavorable outcome with mRS score of 3–5. The average or median input NIHSS and mRS score were 5 and 2 respectively for favorable outcome group, 8 and 3 for unfavorable outcome group respectively (Table 1). There was no significant difference for other factors, i.e., age, gender, initial MRI from ictus, previous ischemic attack, diabetes mellitus, smoke, and hyperlipemia, between the two groups.

Based on the ROC curve analysis, the optimal cut-off of FVH-DWI mismatch sections for discriminating the favorable and unfavorable clinical outcome was 3 (AUC, 0.903; 95%CI, 0.824, 0.981). There was a significant difference of mRS scores between the patients with prominent (≥ 3 sections) and less (< 3 sections) FVH-DWI mismatch (Fig. 1).

Both in univariate and multivariate analyses, the prominent FVH-DWI mismatch (OR 2.643, $P = 0.024$; OR 3.200, $P < 0.001$) was an independent predictor of favorable outcome (Table 2). Although the obvious difference of atrial fibrillation (AFib) ($P = 0.011$) and normal or mild tandem stenosis of MCA ($P = 0.003$) was found between the two groups, these two factors were not independent predictors of favorable outcome neither in univariate analysis nor in the multivariate analysis.

There were obvious differences in the three factors, i.e., the prominent FVH-DWI mismatch, normal or mild tandem stenosis of MCA, and AFib, between two groups. We used ROC

Table 1 Population characteristics of 68 patients with acute infarction in unilateral ICA occlusion

Characters	Favorable ($n = 38$)	Unfavorable ($n = 30$)	*P*
Age (years old)	61 (57.5, 70.25)	60 (50.25, 64.25)	0.511
Male	25 (0.658)	24 (0.80)	0.195
Input NIHSS	5 (3, 9)	8 (7, 12)	0.166
mRS	2 (1.0, 2.25)	3 (2.75, 4.0)	< 0.001*
Initial MRI from ictus (h)	66 (45.0, 68.0)	53.75 (36.75, 69.50)	0.096
Previous ischemic attack	14 (0.37)	7 (0.23)	0.231
Hypertension	20 (0.53)	21 (0.70)	0.146
Diabetes mellitus	9 (0.24)	3 (0.10)	0.142
Smoke	14 (0.37)	15 (0.50)	0.276
Atrial fibrillation	5 (0.13)	12 (0.40)	0.011*
Hyperlipemia	3 (0.08)	1 (0.03)	0.427
Initial DWI volume (mL)	33.03 (7.82, 213.22)	96 (16.05, 396.12)	0.012*
Prominent FVH-DWI mismatch	32 (0.84)	9 (0.30)	< 0.001*
MCA normal and mild stenosis	24 (0.63)	8 (0.27)	0.003*

DWI, diffusion-weighted imaging; *FVH*, fluid-attenuated inversion recovery (FLAIR) vascular hyperintensity; *ICA*, internal carotid artery; *mRS*, modified Rankin Scale scoring; *NIHSS*, National Institute of Health stroke scale; *with significant difference

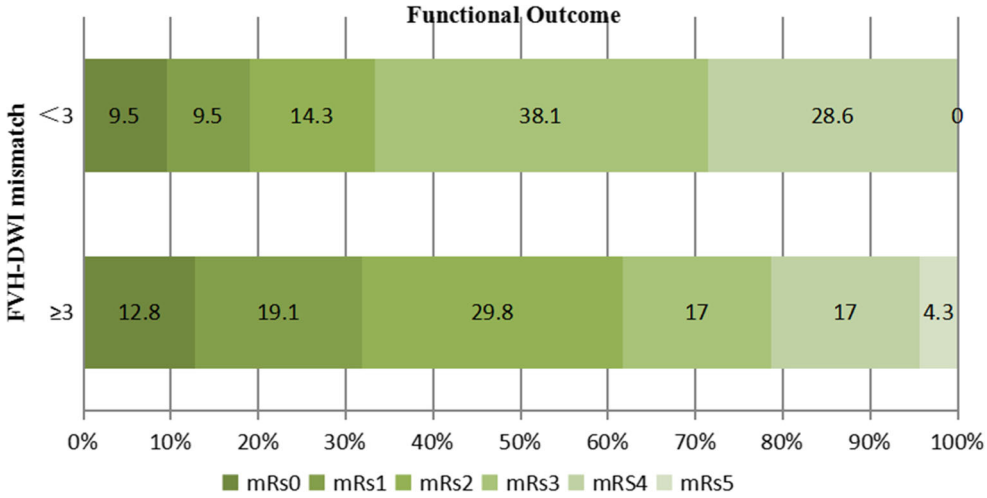

Fig. 1 Functional outcomes (percentages) at 90 days, according to the modified Rankin Scale (mRS) scores by FVH-DWI mismatch grouping

curve to evaluate the diagnostic performance of these markers for a favorable outcome. The AUC of FVH-DWI mismatch (0.820) was larger than those of the other two factors (0.682 for normal or mild tandem stenosis of MCA, and 0.634 for without AFib). But the diagnostic performance of FVH-DWI mismatch was improved when FVH-DWI mismatch combined with the other two markers. The combined model, including prominent FVH-DWI mismatch, normal or mild MCA tandem stenosis, and absence of AFib (AUC = 0.875) had better diagnostic performance in predicting favorable outcome than any other single marker or other markers combination did (Fig. 2) (Table 3).

The initial DWI lesion volume in favorable outcome patients [33.03 mL (7.82, 213.22)] was smaller than that of unfavorable outcome patients [96 mL (16.05, 396.12)] ($P = 0.012$). The AUC of initial DWI lesions volume for diagnosing favorable outcome (0.854) was higher than that of FVH-DWI mismatch (0.820) but comparable with that of a combination of FVH-DWI mismatch and MCA normal and mild stenosis (0.857), and lower than that of combination model of three markers (0.875).

The classic example cases are shown in Fig. 3 (unfavorable outcome with FVH-DWI mismatch sections of 2) and Fig. 4 (favorable outcome with FVH-DWI mismatch sections of 4).

The results of consistent test about admission and discharge NIHSS scoring, mRS scoring, and sections of FVH-DWI mismatch are following: The coincidence was excellent between two neurologists for NIHSS scoring and 3-month mRs scoring ($P < 0.001$) and between two radiologists for evaluation of FVH-DWI mismatch ($P < 0.001$).

Discussion

Our preliminarily study demonstrated the following in patients with infarction in unilateral ICA occlusion: (1) Prominent FVH-DWI mismatch was a useful MR marker of favorable clinical outcome; (2) Prominent FVH-DWI mismatch, in combination with less MCA tandem stenosis, and absence of AFib, would improve diagnostic performance in predicting a favorable outcome compared with initial DWI lesion volumetry.

In this study, we assessed the prognostic value of the prominent FVH-DWI mismatch. Discrimination of prominent and less FVH-DWI mismatch offers several advantages. First, this method is time saved. The counting of mismatch sections only takes several minutes. Thus, it is suitable for treatment decision in acute stroke. Second, this method is relatively simple, avoiding more complicated scoring and additional train. It can even be made at the bedside. Third, counting the number of mismatch sections only focuses on those sections which FVH beyond the boundaries of DWI lesions. Therefore, it is reproducible [8]. The

Table 2 Predictors of favorable outcome of acute infarction in 68 patients with unilateral ICA occlusion

Characteristics	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Atrial fibrillation	0.75 (0.154, 3.653)	0.722		
MCA normal and mild stenosis	1.292 (0.298, 5.609)	0.732		
Prominent FVH-DWI mismatch	2.643 (1.134, 6.161)	0.024*	3.200 (1.941, 4.208)	< 0.001*

ICA, internal carotid artery; *MCA*, middle cerebral artery; *OR*, odds ratio; "MCA normal and mild stenosis" referred the tandem disease of the acute unilateral ICA occlusion

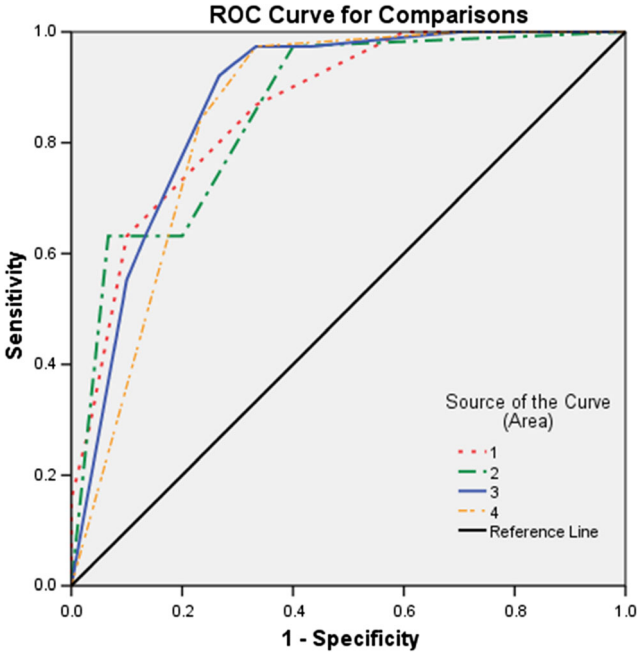

Fig. 2 ROC curve analysis of various factors and combined factors in diagnosis of favorable outcome. (1) Prominent FVH-DWI mismatch. (2) FVH-DWI mismatch combined with normal or mild MAC stenosis. (3) FVH-DWI mismatch combined with normal or mild MAC stenosis and without AFib. (4) Prominent FVH-DWI mismatch + without AFib. Afib, atrial fibrillation

present results strengthen the notion that FVH-DWI mismatch can be used as an MR marker for predicting the outcome of cerebral infarction [18–24]. We further put forward that the optimal cutoff of FVH-DWI mismatch for discriminating favorable and unfavorable outcome. Prominent FVH-DWI mismatch may hint relative better perfusion by pial collateral blood flow and more sections overlying penumbra as well as less severely hypoperfused brain tissue [6, 8].

In patients with ICA occlusion, the MCA tandem disease, rather than ipsilateral tandem ACA diseases, would be the culprit lesions for the infarctions in MCA territories. After the occlusion of ICA, the redistributed blood would come from contralateral ICA via anterior or posterior communicating arteries (AComA and PComA), as well as the secondary collateral flow from ophthalmic and leptomeningeal arteries. Then the retrograde blood flow from collateral vessels may lead to show the ipsilateral MCA on MRA images. Thus, the tandem diseases, i.e., stenosis and occlusion, of ipsilateral MCA itself would hinder this kind of collateral circulation. Therefore, we enrolled the patients with tandem disease of MCA and excluded those patients with the diseases in contralateral MCA.

To the best of our knowledge, this is the first study to investigate whether the tandem disease of MCA would enhance the role of prominent FVH-DWI mismatch in the outcome forecasting. The collateral circulation in unilateral ICA occlusion is different from that in unilateral MCA occlusion: both primary (through Willis' circle) and secondary collateral circulation (through leptomeningeal ophthalmic artery, etc.) may be built up when unilateral ICA occlusion occurs. Whereas, only secondary collateral circulation coming from leptomeningeal arteries may set up after occlusion of unilateral MCA. Therefore, the patency of ipsilateral MCA is another important factor in the evolution of infraction in ICA occlusion.

As FVH may represent the secondary collateral circulation after feeding cerebral arteries occlusion, some authors speculated that FVH sign may play a role in guiding the reperfusion treatment after acute cerebral infarction [10, 17, 25]. However, this point is beyond the scope of the present study. All the included patients in this study had not been undergone thrombolytic therapy. Thus, the value of FVH-DWI mismatch on spontaneous recanalization or intravascular thrombolytic treatment should be investigated in the future.

We also found that the patients without AFib inclined to the favorable outcome of cerebral infarctions, although AFib was not a significant independent predictor of a favorable outcome. Several previous studies [26, 27] had shown a similar negative effect of AFib on the outcome of cerebral infarction. The

Table 3 ROC curve analysis of the FVH-DWI mismatch, MCA normal and mild stenosis, and Atrial fibrillation for favorable outcome (mRs ≤ 2)

Characteristics	AUC	95%CI	Sensitivity	Specificity	PPV	NPV	Youden index	*P* value
Initial DWI volume	0.854	(0.749, 0.960)	0.933	0.789	–	–	0.722	< 0.001*
Prominent FVH-DWI mismatch	0.820	(0.709, 0.931)	0.974	0.667	0.667	0.974	0.641	< 0.001*
Normal or mild MCA stenosis	0.682	(0.554, 0.811)	0.632	0.733	0.733	0.632	0.365	0.010*
Without AFib	0.634	(0.498, 0.770)	0.868	0.400	0.300	0.868	0.268	0.059
Prominent FVH-DWI mismatch + normal or mild MCA stenosis	0.858	(0.768, 0.948)	0.974	0.600	0.600	0.974	0.574	< 0.001*
Prominent FVH-DWI mismatch + without AFib	0.851	(0.749, 0.953)	0.974	0.667	0.300	1.00	0.641	< 0.001*
Prominent FVH-DWI mismatch + normal or mild MCA stenosis + without AFib	0.875	(0.784, 0.965)	0.974	0.667	0.567	0.974	0.641	< 0.001*

AFib, atrial fibrillation; *AUC*, area under curve; *CI*, credible interval; *DWI*, diffusion-weighted imaging; *FVH*, fluid-attenuated inversion recovery (FLAIR) vascular hyperintensity; *PPV*, positive predictive value; *NPV*, negative predictive value

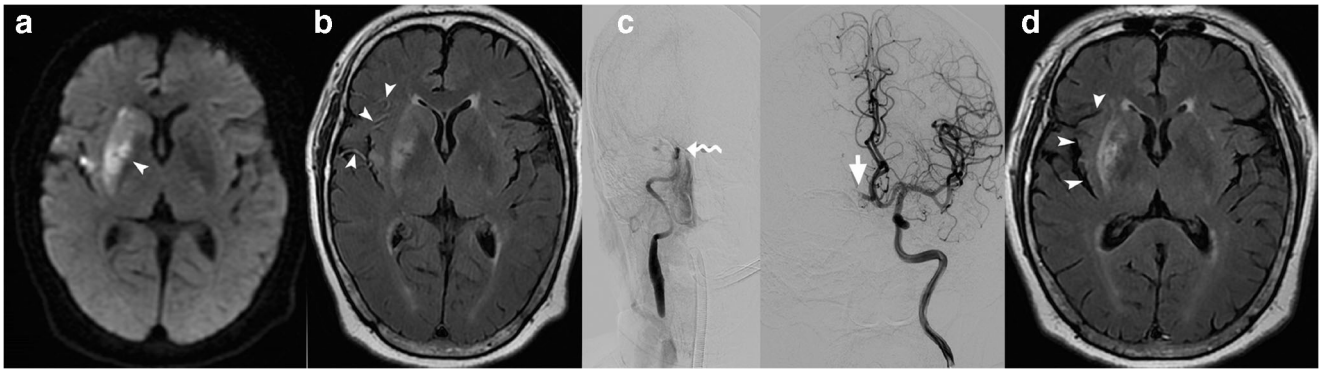

Fig. 3 Female, 78 years old. Unfavorable outcome group. **a** Axial DWI image 28 h after ictus showed hyperintensity in right basal ganglia (arrowhead). **b** Axial FLAIR corresponding to (**a**) illustrated scattered FVH (arrowhead) around the infarction. The number of FVH-DWI mismatch sections was 2. **c** Angiography images showed occlusion of right ICA (arrow) as well as ipsilateral ACA (curve arrow). **d** The follow-up FLAIR image on 91 days after ictus illustrated FVH vanished (arrowhead) and infarction focus enlarged. The mRs score at third month was 3

pathophysiological basis of the adverse effect of AFib may be attributed to sudden onset of embolism from the fallen mural thrombus in cerebral arteries, especially in the vessels in a smaller diameter. Thus, in the absence of AFib, less ischemic tissue may deteriorate to infarction because effective collateral circulation would probably set up in time via patent vessels in small diameter.

Some limitations need to be further addressed. Firstly, as a retrospective and single-center study which enrolled a small number of patients, the conclusion may lead to bias. The database with a larger amount of AIS patients would improve the confidence and prediction performance of the outcome study. Secondly, there was no comparison between FVH-DWI mismatch and PWI-DWI mismatch. Legrand et al. found that FVH-DWI mismatch was associated with PWI-DWI mismatch and smaller lesions [8]. Thus we can speculate that FVH may offer certain perfusion information after cerebral arteries occlusion. Although prominent FVH-DWI mismatch will unlikely replace PWI-DWI mismatch as a marker of penumbra, it may take a role in patients with contraindication for gadolinium agents, including renal failure and contrast hypersensitivity. Thirdly, as a pure dichotomizing endpoint outcome analysis, this study probably reduces the study power for discarding some meaningful factors. In the future study, combined with the ordinal shift, the analysis could be employed to improve study power for the advantages of the achievable goal of evaluating every patient, ability of greater number achievable goals, and least assumptions of the patient types [28].

In conclusion, the results of the present study confirmed that prominent FVH-DWI mismatch, which may represent relative adequate collateral circulation, can be used as an imaging marker to predict a favorable clinical outcome of patients with acute infarction in unilateral ICA occlusion. In addition, for the first time, we found that the prominent FVH-DWI mismatch, in combination with other factors, including the absence of tandem MCA disease and Afib, could improve predicting the performance of favorable outcome.

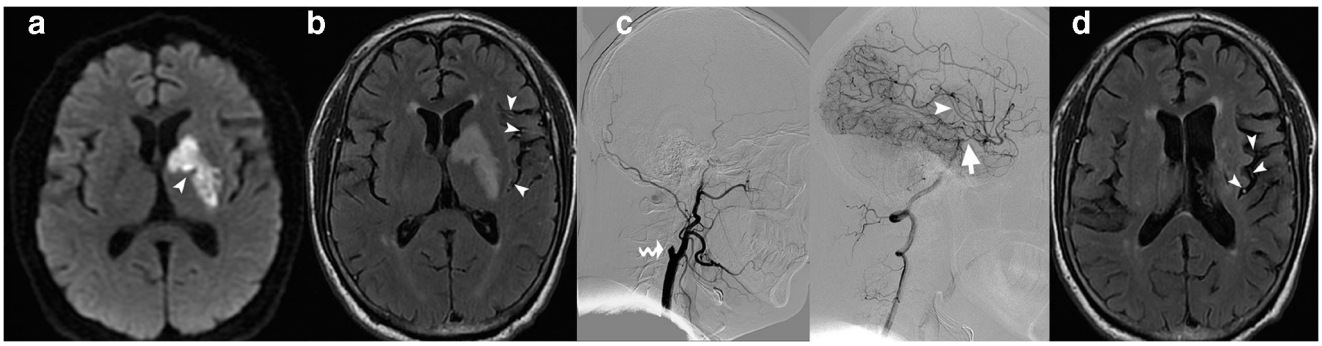

Fig. 4 Male, 56 years old. Favorable group. **a** Axial DWI image 17 h after ictus showed hyperintensity in left basal ganglia (arrowhead). **b** Axial FLAIR corresponding to (**a**) illustrated multiple FVH (arrowhead) around the infarction. The number of FVH-DWI mismatch sections was 4. **c** Angiography images showed occlusion of right ICA (curve arrow), whereas the patency of ipsilateral MCA was detected (arrowhead). Arrow showed left posterior communication artery. **d** The follow-up FLAIR image made at 33 days after ictus illustrated FVH still be visible (arrowhead) and infarction focus shrunk. The mRs score at third month was 1

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The Ethics Committee of The Second Hospital of Hebei Medical University approved this retrospective study. Due to the retrospective nature of this study, the informed written consent was waved.

References

1. de Weerd M, Greving JP, Hedblad B, Lorenz MW, Mathiesen EB, O'Leary DH, Rosvall M, Sitzer M, Buskens E, Bots ML (2010) Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. Stroke 41: 1294–1297
2. Momjian-Mayor I, Baron JC (2005) The pathophysiology of watershed infarction in internal carotid artery disease: review of cerebral perfusion studies. Stroke 36:567–677
3. Yuan T, Ren G, Quan G, Gao D (2018) Fewer peripheral asymmetrical cortical veins is a predictor of favorable outcome in MCA infarctions with SWI-DWI mismatch. J Magn Reson Imaging 48:964–970
4. Bang OY, Goyal M, Liebeskind DS (2015) Collateral circulation in ischemic stroke: assessment tools and therapeutic strategies. Stroke 46:3302–3309
5. Raymond SB, Schaefer PW (2017) Imaging brain collaterals: quantification, scoring, and potential significance. Top Magn Reson Imaging 26:67–75
6. Christoforidis GA, Karakasis C, Mohammad Y, Caragine LP, Yang M, Slivka AP (2009) Predictors of hemorrhage following intra-arterial thrombolysis for acute ischemic stroke: the role of pial collateral formation. AJNR Am J Neuroradiol 30:165–170
7. Olivot JM, Mlynash M, Inoue M, Marks MP, Wheeler HM, Kemp S, Straka M, Zaharchuk G, Bammer R, Lansberg MG, Albers GW, DEFUSE 2 Investigators (2014) DEFUSE 2 investigators: hypoperfusion intensity ratio predicts infarct progression and functional outcome in the DEFUSE 2 cohort. Stroke 45:1018–1023
8. Legrand L, Tisserand M, Turc G, Naggara O, Edjlali M, Mellerio C, Mas JL, Méder JF, Baron JC, Oppenheim C (2015) Do FLAIR vascular hyperintensities beyond the DWI lesion represent the ischemic penumbra? AJNR Am J Neuroradiol 36:269–274
9. Azizyan A, Sanossian N, Mogensen MA, Liebeskind DS (2011) Fluid-attenuated inversion recovery vascular hyperintensities: an important imaging marker for cerebrovascular disease. AJNR Am J Neuroradiol 32:1771–1775
10. Hohenhaus M, Schmidt WU, Brunecker P, Xu C, Hotter B, Rozanski M, Fiebach JB, Jungehülsing GJ (2012) FLAIR vascular hyperintensities in acute ICA and MCA infarction: a marker for mismatch and stroke severity? Cerebrovasc Dis 34:63–69
11. Mahdjoub E, Turc G, Legrand L, Benzakoun J, Edjlali M, Seners P, Charron S, Ben Hassen W, Naggara O, Meder JF, Mas JL, Baron JC, Oppenheim C (2018) Do fluid-attenuated inversion recovery vascular hyperintensities represent good collaterals before reperfusion therapy? AJNR 39:77–83
12. Haussen DC, Koch S, Saraf-Lavi E, Shang T, Dharmadhikari S, Yavagal DR (2013) FLAIR distal hyperintense vessels as a marker of perfusion-diffusion mismatch in acute stroke. J Neuroimaging 23:397–400
13. Legrand L, Tisserand M, Turc G, Edjlali M, Calvet D, Trystram D, Roca P, Naggara O, Mas JL, Méder JF, Baron JC, Oppenheim C (2016) Fluid-attenuated inversion recovery vascular hyperintensities-diffusion-weighted imaging mismatch identifies acute stroke patients most likely to benefit from recanalization. Stroke 47:424–427
14. Lansberg MG, Straka M, Kemp S, Mlynash M, Wechsler LR, Jovin TG, Wilder MJ, Lutsep HL, Czartoski TJ, Bernstein RA, Chang CW, Warach S, Fazekas F, Inoue M, Tipirneni A, Hamilton SA, Zaharchuk G, Marks MP, Bammer R, Albers GW, DEFUSE 2 study investigators (2012) DEFUSE 2 study investigators: MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study. Lancet Neurol 11:860–867
15. Mundiyanapurath S, Ringleb PA, Diatschuk S, Hansen MB, Mouridsen K, Østergaard L, Wick W1, Bendszus M, Radbruch A (2016) Capillary transit time heterogeneity is associated with modified Rankin Scale score at discharge in patients with bilateral high grade internal carotid artery stenosis. PLoS One 23(11):e0158148
16. Mundiyanapurath S, Ringleb PA, Diatschuk S, Burth S, Möhlenbruch M, Floca RO, Wick W, Bendszus M, Radbruch A (2016) Cortical vessel sign on susceptibility weighted imaging reveals clinically relevant hypoperfusion in internal carotid artery stenosis. Eur J Radiol 85:534–539
17. Kufner A, Nolte CH, Ebinger M (2013) Response to letter regarding article, "smoking-thrombolysis paradox: recanalization and reperfusion rates after intravenous tissue plasminogen activator in smokers with ischemic stroke". Stroke 44: e59
18. Kufner A, Galinovic I, Ambrosi V, Nolte CH, Endres M, Fiebach JB, Ebinger M (2015) Hyperintense vessels on fLAIR: hemodynamic correlates and response to thrombolysis. AJNR Am J Neuroradiol 36:1426–1430
19. Huang X, Liu W, Zhu W, Ni G, Sun W, Ma M, Zhou Z, Wang Q, Xu G, Liu X (2012) Distal hyperintense vessels on FLAIR: a prognostic indicator of acute ischemic stroke. Eur Neurol 68:214–220
20. Kawashima M, Noguchi T, Takase Y, Nakahara Y, Matsushima T (2010) Decrease in leptomeningeal ivy sign on fluid-attenuated inversion recovery images after cerebral revascularization in patients with Moyamoya disease. AJNR Am J Neuroradiol 31: 1713–1718
21. Song J, Ma Z, Meng H, Yu J, Li Y, Hong X, Shi H (2016) Distal hyperintense vessels alleviate insula infarction in proximal middle cerebral artery occlusion. Int J Neurosci 126:1030–1035
22. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, Dowlatshahi D, Frei DF, Kamal NR, Montanera WJ, Poppe AY, Ryckborst KJ, Silver FL, Shuaib A, Tampieri D, Williams D, Bang OY, Baxter BW, Burns PA, Choe H, Heo JH, Holmstedt CA, Jankowitz B, Kelly M, Linares G, Mandzia JL, Shankar J, Sohn SI, Swartz RH, Barber PA, Coutts SB, Smith EE, Morrish WF, Weill A, Subramaniam S, Mitha AP, Wong JH, Lowerison MW, Sajobi TT, Hill MD, ESCAPE Trial Investigators (2015) ESCAPE Trial Investigators: Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 372:1019–1030
23. Gawlitza M, Friedrich B, Quäschling U, Schob S, Schaudinn A, Hobohm C, Hoffmann KT, Lobsien D (2015) Distance to thrombus on MR angiography predicts outcome of middle cerebral artery occlusion treated with IV thrombolysis. Neuroradiology 57:991–997
24. Lee KY, Latour LL, Luby M, Hsia AW, Merino JG, Warach S (2009) Distal hyperintense vessels on FLAIR: an MRI marker for collateral circulation in acute stroke? Neurology 72:1134–1139

25. Legge J, Graham A, Male S, Copeland D, Lee R, Goyal N, Zand R (2017) Fluid-attenuated inversion recovery (FLAIR) signal intensity can identify stroke within 6 and 8 hours. J Stroke Cerebrovasc Dis 26:1582–1587
26. Su YC, Lim SN, Yang FY, Lin SK (2017) Evaluation of cerebral blood flow in acute ischemic stroke patients with atrial fibrillation: a sonographic study. J Formos Med Assoc 116:287–294
27. Boriani G, Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Ricci R, Biffi M, De Santo T, Corbucci G, Lip GY, Italian AT-500 Registry Investigators (2011) Italian AT-500 Registry Investigators: improving stroke risk stratification using the CHADS2 and CHA2DS2-VASc risk scores in patients with paroxysmal atrial fibrillation by continuous arrhythmia burden monitoring. Stroke 42: 1768–1770
28. Saver JL (2007) Novel end point analytic techniques and interpreting shifts across the entire range of outcome scales in acute stroke trials. Stroke 38:3055–3062