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Incremental value of plaque enhancement in predicting stroke recurrence in symptomatic intracranial atherosclerosis

Xiaowei Song[1] · Xihai Zhao[2,3] · David S. Liebeskind[4] · Lixue Wang[2] · Wendeng Xu[1] · Yilan Xu[2] · Duoduo Hou[1] · Zhuozhao Zheng[2] · Jian Wu[1,5]

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Abstract

Purpose To investigate the association between plaque enhancement and stroke recurrence in subjects with intracranial atherosclerosis.

Methods Ischemic stroke patients with symptomatic intracranial atherosclerosis were prospectively included and followed in a comprehensive stroke center. Pre- and post-contrast vessel wall images were used to evaluate plaque enhancement. Other established suggestive imaging markers were also acquired simultaneously. Univariate- and multivariate-adjusted Cox proportional hazard regression models were used to determine the association between plaque enhancement and stroke recurrence. Finally, receiver operating characteristic (ROC) curves were used to demonstrate the predictive value of different imaging markers.

Results Of the 60 subjects included, 12 (20.0%) patients presented with ipsilateral stroke recurrence during the median 12-month follow-up. Cox proportional hazard regression models indicated that plaque enhancement was an independent risk factor associated with stroke recurrence after adjusted covariates, with a hazard ratio (HR) of 14.24 and 95% confidence interval (95% CI) (1.21, 168.11), $p = 0.04$. In addition, border zone infarction was also statistically significant in predicting stroke recurrence in multi-variable regression (HR = 3.80; 95% CI = 1.04, 13.80; $p = 0.04$). Collateral status was in marginal significance (HR = 0.25; 95% CI = 0.06, 1.08; $p = 0.06$). ROC analysis indicated that the area under the curve and 95% CI to identify stroke recurrence are 0.67 (0.51, 0.82) for plaque enhancement and 0.71 (0.54, 0.88) for infarction pattern and collateral status and may increase to 0.82 (0.70, 0.93) by combining the three markers above.

Conclusion Plaque enhancement is independently associated with stroke recurrence in subjects with intracranial atherosclerosis and has added value to hemodynamic indicators in predicting stroke recurrence.

Keywords Atherosclerosis · Vessel wall imaging · Stroke recurrence · Imaging markers

✉ Jian Wu
wujianxuanwu@126.com

[1] Department of Neurology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, No.168 of Litang Road, Changping District, Beijing 102218, China

[2] Department of Radiology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing 102218, China

[3] Center for Biomedical Imaging Research, Department of Biomedical Engineering, Tsinghua University School of Medicine, Beijing 100084, China

[4] Neurovascular Imaging Research Core and Stroke Center, Department of Neurology, University of California at Los Angeles, Los Angeles, CA 90024, USA

[5] Tsinghua University Hospital, Beijing 100084, China

Introduction

Intracranial atherosclerosis is one of the leading causes of ischemic stroke worldwide [1, 2], and the presence of intracranial atherosclerosis could significantly increase stroke recurrence risk [3]. Despite aggressive medication, patients with intracranial atherosclerosis have an annual recurrence risk of 14.9% [4]. To identify the specific markers associated with stroke recurrence will be useful for risk stratification.

Of the multiple factors associated with stroke recurrence in intracranial atherosclerosis, intracranial atherosclerosis burden, infarct pattern, and collateral status have already been widely established. There were studies indicating that the burden of intracranial atherosclerosis is associated with stroke recurrence independently where a greater degree of stenosis

equates with higher recurrence risk [3, 5]. Further analysis of stroke mechanism in patients with intracranial atherosclerosis also noted that the infarct pattern and collateral status are critical factors affecting stroke recurrence [6]. Stroke patients with border zone infarction and poor collaterals are more likely to suffer from a recurrent stroke. However, in addition to these hemodynamic factors, studies about intracranial artery stenosis mechanism also indicate that the high-risk plaque on vessel wall imaging may also contribute to recurrent events.

Several studies regarding vessel wall imaging and stroke events were conducted during the last few years, with the results indicating that intraplaque hemorrhage (IPH) and enhancement are correlated with recent ischemic stroke [7, 8]. Association between plaque enhancement and recent ischemic events has been reviewed in a meta-analysis [8], but prospective data about its association with stroke recurrence is limited. Most importantly, none of the previous studies investigate the combined role of hemodynamic factors and vessel wall plaque characteristics in predicting stroke recurrence within the same population.

The purpose of this study was to prospectively investigate the association between plaque enhancement and stroke recurrence in subjects with symptomatic atherosclerotic and to discern the combined impact of various imaging markers in predicting stroke recurrence.

Methods

Subjects

Ischemic stroke with symptomatic atherosclerotic middle cerebral artery (MCA) stenosis was prospectively and consecutively screened during a 1.5-year period in a comprehensive stroke center. Patients were included if they (1) presented with more than one atherosclerotic risk factor, including hypertension (systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or self-reported use of any anti-hypertensive drugs during the past 2 weeks), diabetes (fasting glucose ≥7 mmol/L or non-fasting glucose ≥11.1 mmol/L or on anti-diabetic medication), or hyperlipidemia (total cholesterol (TC) ≥240 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥160 mg/dL, or high-density lipoprotein cholesterol (HDL-C) <40 mg/dL or lipid-lowering medication use); (2) are > 18 years old; (3) have been diagnosed with ischemic stroke attributed to symptomatic MCA stenosis when in discharge and within 4 weeks from symptom onset; (4) have no contraindications to MRI. Patients were excluded if (1) carotid artery vessel examination indicated significant extracranial artery stenosis (>50%); (2) ischemic stroke was caused by cardio embolism; (3) vessel wall imaging evaluation suggested non-atherosclerosis causes, including moyamoya disease, dissection, or vasculitis; and (4) they received bypass or stent therapy during follow-up.

Written informed consent was obtained from individuals before participation in the study, and the protocol was approved by the local ethics committee.

MRI protocol

All brain and vessel imaging were performed on a 3.0 Tesla MRI with an eight-channel head coil (GE Discovery 750). The MRI protocol included a routine brain MRI followed by a contrast enhancement high-resolution MRA. 3D time-of-flight (TOF) MRA and pre- and post-contrast Cube-T1W were used for visualizing stenosis and plaque characteristics. The vessel wall imaging parameters for this study were as follows: 3D TOF-MRA obtained in axial plane, repetition time (TR)/echo time (TE) 22/2.5 ms, flip angle 20°, field of view (FOV) 22×18 cm^2, and spatial resolution $0.6 \times 1.0 \times 1.2$ mm^3; 3D Cube-T1W was scanned in coronal plane: TR/TE 800/16 ms, flip angle 90°, FOV 23×18.4 cm^2, and spatial resolution $0.7 \times 0.6 \times 0.6$ mm^3. For all patients, repeated Cube-T1W was performed within 10 min after intravenous administration of gadodiamide injection (GE Healthcare, Ireland; 0.1 mmol per kilogram of body weight and a maximum of 10 mmol for every patient).

Imaging analysis

Vessel wall images were interpreted by two neuroradiologists independently after post-processing using the GE-Extend Workstation. Two stroke neurologists blind to clinical information evaluated the infarct pattern and collateral scores from the corresponding sequences. Subjects with inadequate image quality were excluded from this analysis (image quality score [9] <2; 1 = poor, 2 = adequate, 3 = good, 4 = excellent). In this study, ten cases were randomly selected to test inter-rater consistency in identifying plaque enhancement, IPH, and maximum wall thickness (max WT) measurement.

Infarction distribution

The infarct pattern was divided into border zone infarction and non-border zone infarction in this study. The former category included internal border zone region (corona radiata or centrum semiovale) and the cortical border zone (between the anterior cerebral artery and MCA or MCA and posterior cerebral artery) [10, 11] (Fig. 1).

Pial collateral evaluation

Pial collaterals (PCs) of the affected hemisphere were measured on the axial TOF-MRA source images at the level of the lateral ventricle body, referring to previous MCA pial

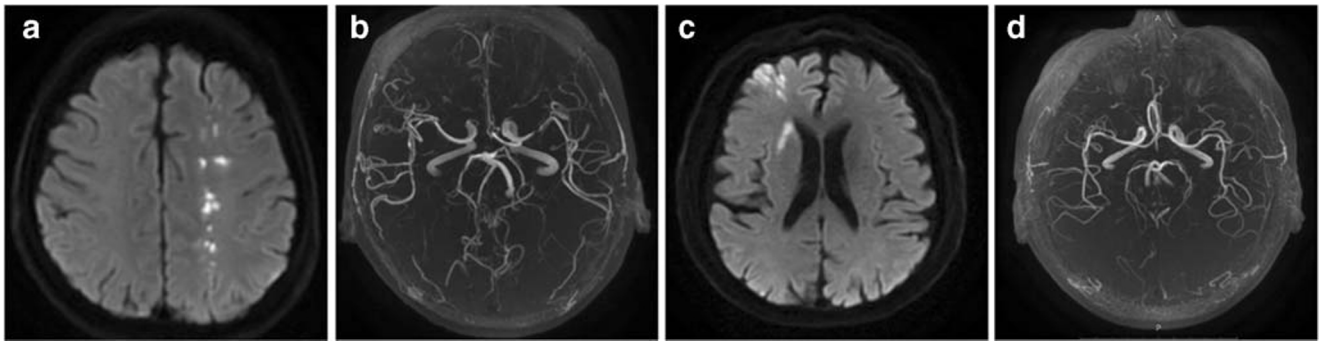

Fig. 1 Infarct pattern. Internal border zone infarction (**a**, DWI) in a patient with left MCA stenosis (**b**, TOF-MRA). Cortical border zone infarction (**c**, DWI) and right MCA stenosis (**d**, TOF-MRA)

collateral evaluation criteria [12, 13]. Collaterals were graded as grade 0, almost no vascular signals in the lesion MCA territory; grade 1, decreased collaterals with vascular signal intensity in the lesion MCA territory <50% than the contralateral side; grade 2, decreased collateral but vascular signal intensity ≥50% of the reference side; and grade 3, the vascular signal intensity is equal to or more than the reference side (Fig. 2). We defined grade 0–1 as poor PCs and grade 2–3 as good PCs in this analysis.

Vessel wall imaging assessment and definition of plaque enhancement

The degree of stenosis, max WT, the presence of IPH, and plaque enhancement were evaluated individually for every patient, and only plaques in the culprit vessel were included in this study. First, luminal stenosis was measured from the TOF-MRA using the WASID criteria [14] and divided into four grades in this study (0 for <30%, 1 for 30–49%, 2 for 50–69%, and 3 for ≥70%). The vessel wall images were reconstructed perpendicular to the centerline of the blood vessel. Atherosclerosis plaque was considered in those eccentric wall thicknesses with or without significant luminal stenosis. Max WT was measured on the most severe segment shown in the TOF-MRA. IPH was defined as T1 hyperintensity plaque with the signal intensity 1.5 times higher than the adjacent brain tissue or muscle [15]. Plaque enhancement was graded by using a previously published grading scale: grade 0, enhancement was similar to or less than that of intracranial arterial walls without plaque in the same individual; grade 1, enhancement was greater than that of grade 0 but less than that of the pituitary infundibulum; grade 2, enhancement was similar to or greater than that of the infundibulum; this method has been established as having good consistency and repeatability [16, 17] (Fig. 3). We combined grade 1 and grade 2 together as the plaque enhancement group during this analysis due to the limited number of cases.

Follow-up and outcome assessment

All subjects were followed up for stroke recurrence and medication review at the 3rd month, 6th month, and 12th month after discharge by vascular neurologists in the outpatient clinic. In cases of stroke recurrence, repeated imaging including diffusion weighted imaging (DWI) was performed to confirm the diagnosis, the medical records were also reviewed, and the exact date of the event was recorded. Whether the recurrent stroke that occurred is relevant to the lesion vessel was also evaluated.

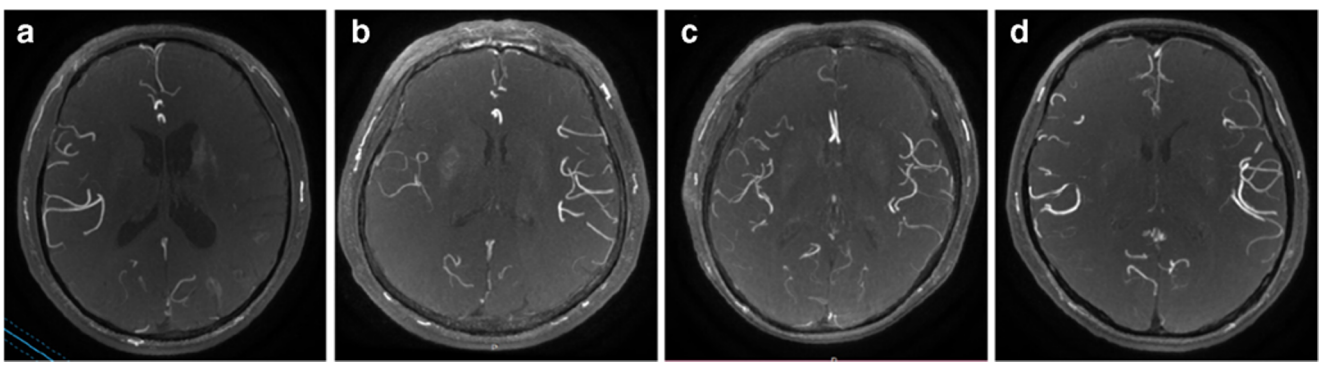

Fig. 2 Pial collateral grades from MRA source images. **a** Left MCA stenosis, grade = 0. **b** Right MCA stenosis, grade = 1. **c** Right MCA stenosis, grade = 2. **d** Left MCA stenosis, grade = 3

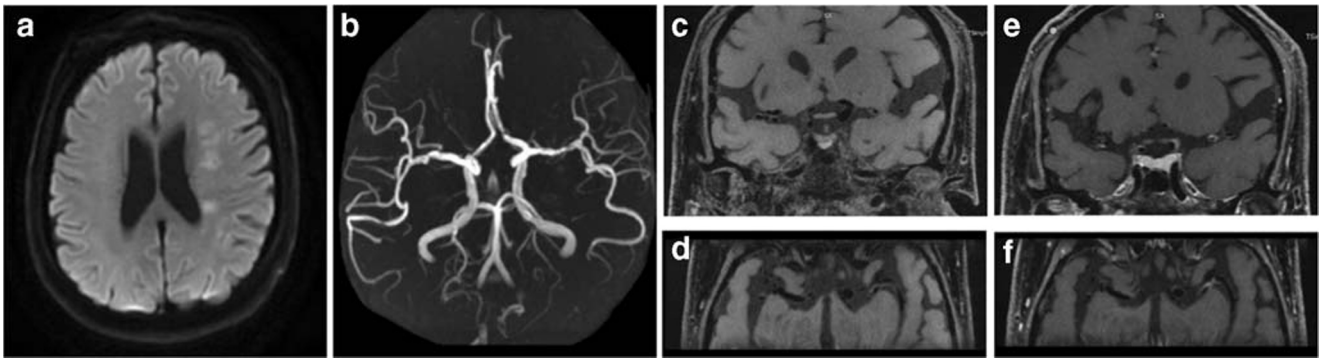

Fig. 3 A 62-year-old male presented with L-MCA area infarction (**a**, DWI); TOF-MRA (**b**) shows L-MCA1 distal stenosis; pre- (**c** coronal, **d** axial planes) and post-contrast (**e** coronal, **f** axial planes) Cube-T1W show vessel wall plaque enhancement

Statistical analysis

Category variables were described as a percentage, and continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on variable characteristics and distribution. χ^2 test, *t*-test, and Mann-Whitney *U* test were used for the statistical comparison between groups. Cohen's kappa test and intraclass correlation coefficient (ICC) were accessed to compare inter-rater reliability (IRR) in identifying plaque enhancement, IPH, and max WT measurement. Kaplan-Meier survival analysis was used to present the cumulative stroke-free rates between plaque enhancement and non-enhancement groups. Univariate and multivariate Cox proportional hazards regression models were used to calculate the hazard ratio (HR) and corresponding 95% confidence interval (95% CI). Lastly, receiver-operator characteristic (ROC) curve analyses were performed to compare the predictive value of different imaging markers in identifying stroke recurrence. All statistical analyses were performed by IBM SPSS 22.0.

Results

A total of 60 patients (mean age 58 years old; 43 men) were included in this study. Of all subjects included, 17 (28.3%) patients presented with border zone infarction, 34 (56.7%) patients had good collaterals (pial collateral score 2–3), 14 (23.3%) presented with IPH, and 39 (65%) subjects had plaque enhancement. The two readers demonstrated substantial consistency in vessel wall evaluation, with $\kappa = 1.0$ for identifying IPH and plaque enhancement, ICC = 0.94, 95% CI (0.85, 0.97) for max WT measurement.

Characteristics of subjects between plaque enhancement and non-enhancement groups

The median time from symptom onset to vessel wall imaging was 12 and 10 days for the plaque enhancement and non-enhancement group ($p = 0.76$, Table 1). The characteristics between subjects with and without plaque enhancement were balanced except for patient sex and hypertension history. The plaque enhancement group had a higher proportion of women and hypertension, correspondingly with a higher percentage of anti-hypertensive medication use, yet none of the baseline blood pressure indices differed between groups.

Association between plaque enhancement and stroke recurrence by univariate and multivariate Cox regression analysis

During a median of 12 months (ranges 1–18) follow-up, 12 patients presented with stroke recurrence relevant to lesion vessel. Univariate and multivariate Cox regression were used to identify the factors associated with stroke recurrence. Differential variables of $p < 0.2$ in the univariate analysis, as well as demographic and risk factors, were included in the multivariate regression analysis. As a result, the multivariate-adjusted results demonstrated that plaque enhancement and infarction patterns were significantly and independently associated with stroke recurrence, with HR = 14.24, 95% CI (1.21, 168.11) and HR = 3.80, 95% CI (1.04, 13.80), respectively (Table 2). Collateral status was of marginal statistical significance, HR = 0.25, 95% CI (0.06, 1.08). None of the clinical variables showed any association with stroke recurrence. The Kaplan-Meier survival curves also illustrated a significant difference of stroke recurrence related to plaque enhancement. Patients with plaque enhancement had a higher stroke recurrence risk during the following months ($p < 0.05$), and most of the events occurred within the first 6 months after admission (Fig. 4).

Comparison of different imaging markers in predicting stroke recurrence

Based on the results above, we further explored which imaging markers are more informative in predicting stroke

Table 1 Baseline characteristics of subjects with and without plaque enhancement

Variable(M ± SD or *n*, %)	Plaque enhancement (+)(*n* = 39)	Plaque enhancement (−)(*n* = 21)	*p* value
Age (years)	59 ± 12	56 ± 9	0.31
Sex (M)	24 (61.5)	19 (90.5)	0.02
Hypertension	32 (82.1)	9 (42.9)	<0.01
Anti-hypertensive medications	30 (76.9)	8 (38.1)	<0.01
Diabetes	17 (43.6)	5 (23.8)	0.13
Hyperlipidemia	18 (46.2)	8 (38.1)	0.55
Previous statin use	13 (33.3)	5 (23.8)	0.44
Previous antiplatelet use	11 (28.2)	6 (28.6%)	0.98
Blood pressure (mmHg)			
SBP	138 ± 18	137 ± 14	0.77
DBP	78 ± 13	80 ± 10	0.66
Blood test (mmol/L)			
Total cholesterol	4.93 ± 3.10	4.19 ± 1.21	0.30
LDL-C	2.63 ± 1.05	2.56 ± 1.04	0.80
HDL-C	1.15 ± 0.82	0.98 ± 0.34	0.36
Imaging findings			
Time to imaging[a]	12 (10)	10 (16)	0.76
Border zone Infarction	12 (30.8)	5 (23.8)	0.57
Collateral (good)	23 (59.0)	11 (52.4)	0.62
Vessel stenosis (≥50%)	31 (79.5)	32 (66.7)	0.07
Max WT (mm)	2.7 ± 0.7	2.4 ± 0.8	0.11
IPH	12 (30.8)	2 (9.5)	0.13

[a] Time from symptom onset to imaging, median (IQR)

SBP systolic blood pressure, *DBP* diastolic blood pressure, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Max WT* maximum wall thickness, *IPH* intraplaque hemorrhage

recurrence. As Fig. 5 reveals, the individual area under the curve and corresponding 95% CI is 0.67 (0.51, 0.82) for plaque enhancement, 0.71 (0.54, 0.88) for infarction pattern and collateral status, and 0.82 (0.70, 0.93) for the combination of these three markers.

Discussion

Our study thoroughly investigated the association between plaque enhancement and stroke recurrence, as well as explored the interaction of key imaging markers in predicting stroke recurrence. The main findings of this study establish that (1) plaque enhancement is a common phenomenon in stroke patients with intracranial atherosclerosis, (2) baseline plaque enhancement not only correlated with recent ischemic stroke but was also associated with stroke recurrence, (3) a combination of infarction patterns, collateral status, and plaque enhancement may be used to better predict stroke recurrence risk.

Plaque enhancement pathology and cardiovascular events

Plaque enhancement usually has been regarded as an active or unstable feature of atherosclerosis and may be an indicator of plaque progression [18, 19]. The potential pathophysiological mechanisms of plaque enhancement have not been fully elucidated. Evidence from the carotid and coronary arteries suggest that it may be a result of endothelial cell injury, vessel wall inflammation, neovascularization of atherosclerosis plaque, as well as thrombosis secondary to plaque rupture. The higher proportion of hypertension history could possibly contribute to the endothelial disorders and vessel wall plaque enhancement to some degree in this study. Moreover, plaque enhancement is dynamic. Studies about the time course of plaque enhancement have suggested that plaque enhancement after stroke may persist for several months [20], but the impact remains unknown.

Our results about plaque enhancement and stroke recurrence are quite similar to a previous study [21], which also confirmed the positive relationship between plaque

Table 2 Cox proportional hazard regression of factors associated with stroke recurrence

Variables	Stroke recurrence			
	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age (years)	1.03 (0.97, 1.10)	0.33	1.01 (0.96, 1.07)	0.61
Sex (M)	1.09 (0.33, 3.61)	0.89	1.36 (0.36, 5.19)	0.65
Hypertension	1.77 (0.48, 6.55)	0.39	0.83 (0.17, 4.01)	0.81
Diabetes	0.85 (0.26, 2.81)	0.79	0.42 (0.11, 1.59)	0.20
Hyperlipidemia	2.17 (0.65, 7.20)	0.21	4.77 (1.00, 22.83)	0.05
Blood pressure(mmHg)				
SBP	1.01 (0.98, 1.04)	0.51		
DBP	1.01 (0.95, 1.07)	0.80		
Blood tests (mmol/L)				
TC	0.82 (0.49, 1.34)	0.44		
LDL-C	0.43 (0.06, 3.27)	0.41		
HDL-C	0.68 (0.35, 1.34)	0.27		
Imaging findings				
Infarct patterns (border zone vs non-border zone)	3.02 (0.97, 9.37)	0.06	3.80 (1.04, 13.80)	0.04
Collateral (2–3 vs 0–1)	0.41 (0.13, 1.38)	0.15	0.25 (0.06, 1.08)	0.06
Stenosis (grade 2, 3 vs 0, 1)	3.84 (0.50, 29.79)	0.20	0.57 (0.05, 6.93)	0.66
Max WT (mm)	1.33 (0.64, 2.76)	0.40		
IPH	1.38 (0.65, 2.94)	0.58		
Plaque enhancement	0.15 (0.02, 1.20)	0.07	14.24 (1.21, 168.11)	0.04
Medication				
Statin (statin + antioxidant vs statin alone)	0.83 (0.18, 3.77)	0.80		
Antiplatelet (dual vs single)	1.64 (0.52, 5.16)	0.40		

Adjusted for age, gender, hypertension, diabetes, hyperlipidemia, infarction patterns, collateral, stenosis, and plaque enhancement in multivariate regression analysis

SBP systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Max WT* maximum wall thickness, *IPH* intraplaque hemorrhage

enhancement and stroke recurrence. However, compared with their studies, we focused on middle cerebral artery atherosclerosis stroke patients, and only symptomatic plaques were included. Furthermore, other imaging markers were used in our study to compare the predictive value in identifying stroke recurrence.

Hemodynamic biomarkers in predicting stroke recurrence

Hemodynamic factors as a contributing factor of stroke recurrence have often been emphasized in previous studies, especially in subjects with severe intracranial atherosclerosis stenosis. Large artery stenosis results in distal hypoperfusion, with artery-to-artery embolism secondary to vulnerable plaque rupture or a combination of factors implicated as the most commonly cited mechanisms. Infarction distributions and collateral status have been recognized as critical predictors of recurrent stroke in subjects with intracranial artery stenosis [11], with data from post hoc analysis of SAMMPRIS that established the contributory roles of compromised hemodynamic factors in stroke recurrence [6]. However, hemodynamic factors may only explain part of recurrent stroke etiology; stroke caused by vulnerable plaque is not uncommon [22]. Moreover, a prior study indicated that symptomatic intracranial atherosclerosis caused by plaque destabilization may be more responsive to aggressive medical therapy [23]. Our results reaffirmed the critical contribution of hemodynamic compromise in identifying stroke recurrence for anterior circulation stroke but also provide novel insight on the incremental role of vessel wall imaging in predicting stroke recurrence.

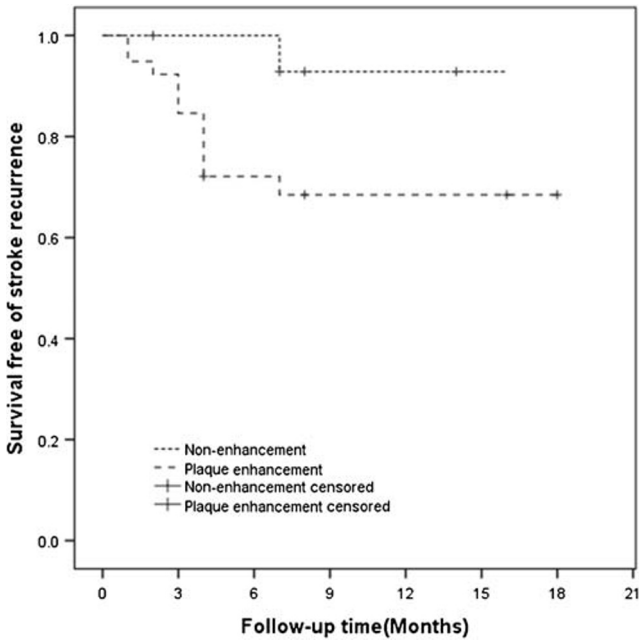

Fig. 4 Kaplan-Meier analysis of stroke recurrence in the plaque enhancement and non-enhancement group over a total of 18 months follow-up. The *x*-axis represents the time of follow-up in months, and the *y*-axis represents the proportion of patients who were free from recurrent stroke ($\chi^2 = 4.43$, $p = 0.04$)

The individual and combined roles of imaging biomarkers in identifying stroke recurrence

Despite the associations between infarct pattern, collateral status, high-risk plaque, and recurrent stroke, their individual role as predictor of stroke recurrence is limited, which is determined by the heterogeneity and complexity of stroke mechanisms. Our results also confirmed the added value of combined hemodynamic and vascular wall imaging in predicting stroke recurrence. It is acknowledged that these imaging markers are clearly not independent of each other. Patients with severe vessel stenosis and poor collateral status usually have larger infarctions, and high-risk plaques are more likely present in those with advanced atherosclerosis. Furthermore, blood flow fluctuations caused by luminal stenosis may also contribute to atherosclerosis plaque progression or be a trigger of plaque rupture. There is also a study indicating that plaque length, eccentricity, and pial collaterals are associated with hypoperfusion [12]. There is a possibility that each marker may play a different role in distinct patients.

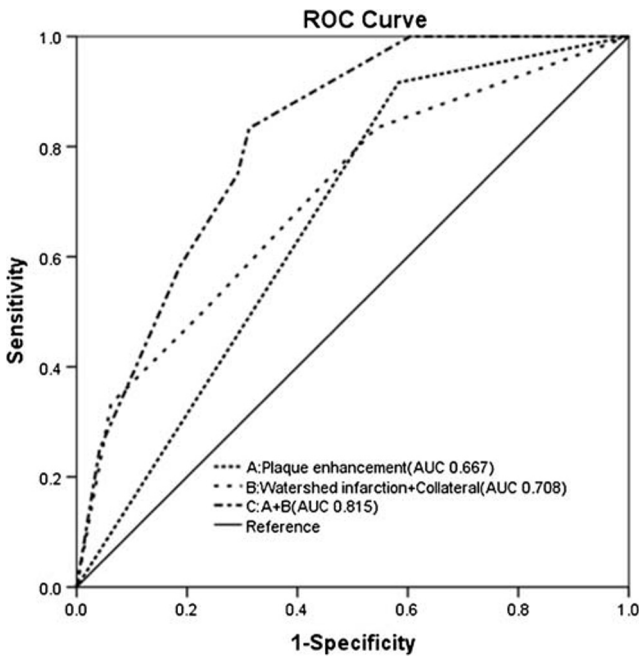

Fig. 5 ROC curves of imaging markers in predicting stroke recurrence

Strengths and limitations

The key strength of these analyses is that we conducted a prospective study to evaluate vessel wall plaque characteristic and stroke recurrence and investigated different imaging markers within one population. Previous studies about imaging markers and stroke recurrence mostly focus on infarction distribution, perfusion, collateral status, or vessel wall imaging individually whereas no comprehensive study about these various features in one population has been conducted to date. Furthermore, we used the noninvasive markers readily available from routine examinations to predict stroke risk. Future strategies to stabilize plaque and improve distal blood flow may be fueled by such insight.

There are indeed some limitations to our study. First, the sample size of this study is relatively small, which may underestimate the effects of collateral status to some degree. Second, plaque enhancement was defined by visual assessment but not a more accurate signal ratio. Finally, the heterogeneous pathology behind plaque enhancement needs further study.

Conclusion

Baseline plaque enhancement is independently associated with stroke recurrence in intracranial atherosclerosis. Combined hemodynamic markers and vessel wall imaging characteristics may better inform stroke recurrence.

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Compliance with ethical standards

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

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments; the protocol was also approved by the local ethics committee.

Informed consent Informed consent was obtained from all individual participants included in the study.

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