Progression of Plaque Burden of Intracranial Atherosclerotic Plaque Predicts Recurrent Stroke/Transient Ischemic Attack: A Pilot Follow-Up Study Using Higher-Resolution MRI

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Background: Patients with intracranial atherosclerotic disease (ICAD) have a high frequency of stroke recurrence. However, there has been little investigation into the prognostic value of higher-resolution magnetic resonance imaging (HR-MRI).
Purpose: To investigate the use of intracranial atherosclerotic plaques features in predicting risk of recurrent cerebrovascular ischemic events using HR-MRI.
Study Type: Prospective.
Population: Fifty-eight patients with acute/subacute stroke (N = 46) or transient ischemic attack (N = 12).
Field Strength/Sequence: A 3.0 T, 3D time-of-flight gradient echo sequence and T1- and T2-weighted fast spin echo sequences with 0.31 x 0.39 mm^2 in-plane resolution, twice (with >3 months between scans) following the initial event.
Assessment: Patients were also followed clinically for recurrent ischemic events for up to 48 months or until a subsequent event occurred. The degree of stenosis, plaque burden (PB), minimal lumen area (MLA), and contrast enhancement ratio were assessed at each scanning session and the percentage change of each over time was calculated.
Statistical Tests: Univariable and multivariable Cox regression analyses were used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for predicting recurrent events.
Results: The mean time interval between baseline and follow-up MRI scans was 6.2 ± 4.1 months. After the second MRI scan, 20.7% of patients (N = 12) had experienced ipsilateral recurrent TIA/stroke within 10.9 ± 9.2 months. Univariable analyses showed that baseline triglyceride, percentage change of PB, and progression of PB were significantly associated with recurrent events (all $P < 0.05$). Multivariable Cox regression indicated that progression of PB (HR, 6.293; 95% CI, 1.620–24.444; $P < 0.05$) was a significant independent imaging feature for recurrent ischemic events.
Data Conclusion: Progression of PB was independently associated with recurrent ischemic cerebrovascular events. HR-MRI may help risk stratification of patients at risk of recurrent stroke.
Level of Evidence: 2
Technical Efficacy: Stage 4

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Stroke is the second leading cause of death in the world and the leading cause of death in Asia.[1] Ischemic stroke accounts for approximately 70% of all incident stroke cases.[2] Intracranial atherosclerotic disease (ICAD) is a major cause of ischemic stroke in China, whereas in high-income countries, extracranial carotid atherosclerosis is a more common etiology.[3] In addition, the risk of stroke recurrence is high (10%–50% per year) in stroke patients with ICAD.[4] Therefore, accurate risk assessment of intracranial plaque is helpful in guiding patient-specific treatment to prevent future stroke.[5]

Higher-resolution magnetic resonance imaging (HR-MRI) of intracranial vessel walls is a reliable and noninvasive technique, which can provide visualization of high-risk plaque features including intraplaque hemorrhage, contrast enhancement, and outward remodeling.[6, 7] Previous studies have shown that these plaque features can provide additional value to the measured degree of stenosis in differentiating stroke from asymptomatic patients.[5-9] However, most of these studies were cross sectional and there has been little investigation into the prognostic value of HR-MRI.[10,11] In addition, a previous study investigating changes in plaque features over time and their relationship to recurrent stroke was limited by small sample size ($N < 15$).[12]

Thus, the aim of this study was 1) to investigate the prognostic value of intracranial atherosclerotic plaque features in predicting recurrent cerebrovascular ischemic events using HR-MRI in acute stroke patients and 2) to evaluate the temporal changes of plaque features and study their relationship to recurrent ischemic events.

Materials and Methods

Study Population

This study was approved by the Institutional Review Board of Changhai Hospital of Shanghai and written informed consent was obtained from all patients. This prospective study included patients presenting with acute/subacute stroke or transient ischemic attack (TIA). Baseline extracranial artery Doppler ultrasonography or computed tomography angiography (CTA) examination and intracranial artery HR-MRI was performed within 8 weeks of the onset of ischemic events and repeated more than 3 months later. Studies were performed between January 2013 and December 2017. The inclusion criteria were as follows: 1) acute and subacute stroke/TIA (imaging within 8 weeks of ischemic events), 2) with intracranial artery stenosis (≥30%), and 3) ≥1 atherosclerotic risk factor, including hypertension, diabetes mellitus, hypercholesterolemia, or cigarette smoking. Patients with the following conditions were excluded: 1) presence of significant stenosis of the extracranial carotid arteries (stenosis >70%) as assessed on carotid Doppler ultrasound with peak blood flow velocity more than 125 cm/seconds; (2) presence of ascending aortic arch atheroma as identified on MRA (defined as plaque thickness > 4 mm), which may be a potential source of embolic stroke[13]; (3) nonatherosclerotic intracranial arterial disease including aneurysms with intervention therapy, vasculitis, moyamoya disease, dissection, reversible cerebral vasoconstriction syndrome, and intracranial dolichoectasia (a dilative arteriopathy primarily involving rarefaction of the elastic tissue of the tunica media and fragmentation of the internal elastic lamina)[14]; (4) suspected cardiogenic thrombosis as assessed on cardiac Doppler ultrasound or cardiac CTA; (5) known coagulopathy; (6) heart failure or respiratory failure; (7) renal dysfunction (serum creatinine >133 μmol/liter); (8) serious disturbance of consciousness; (9) intracranial hemorrhage; and (10) clinical contraindications to MRI, such as patients with pacemakers, certain types of metallic implants, or severe claustrophobia.

The demographic and clinical characteristics, including age, sex, body mass index, hypertension, hyperlipidemia, diabetes mellitus, smoking, and medication, were collected from the clinical record. According to these clinical features, $ABCD^2$ scale (age, blood pressure, clinical findings, duration of symptoms, and presence or absence of diabetes) could be calculated (range, 0– 7, with higher scores indicating a greater risk of stroke), and the National Institutes of Health Stroke Scale (NIHSS) was evaluated on admission.

MRI Acquisition

Imaging was performed using a 3.0-T whole-body MRI system (GE Signa 3.0 T HDxt, GE Healthcare, WI, USA) using an eight-channel phased-array head coil. After an initial multiplane localizer sequence, axial 3D time-of-flight (TOF) MRI angiography was performed to identify the location of the middle cerebral artery (MCA) or basilar artery (BA) stenosis. T_1- and T_2-weighted FSE sequences were then prescribed with slices perpendicular to the artery of interest based on the maximal intensity projection of the TOF images. A saturation band was prescribed parallel to the slice direction and proximal to the inlet of MCA or BA to suppress the blood signal. Following a dose of 0.2 mmol/kg Gd-DTPA injected by power injector at a rate of 2 mL/seconds followed by 15 mL of physiological saline, contrast enhancement MRA, and post-contrast T_1-weighted FSE were acquired. To assist reproducibility of image plane selection between baseline and follow-up HR-MRI scans, the baseline imaging position selection image was saved as a screenshot and viewed during the follow-up scan to assist the technician with scan positioning. Two experienced technicians with more than 3 years' experience (one with 5 years' experience and the other with 8 years' experience) in intracranial vessel wall MRI performed all studies.

The scan parameters were as follows: 1) 3D TOF MRA: TR/TE = 29/3.4 msec, field of view (FOV) $=24 \times 21$ cm^2, slice thickness = 1.2 mm, NEX = 1, matrix = 384×192, sequence duration = 4.78 minutes; 2) diffusion-weighted imaging (DWI): TR/TE = 5300.0/74.3 msec, FOV = 240×240 mm^2, matrix = 160×160, slice thickness = 5 mm, gap = 1.5 mm, slices = 40, b-values = 0 and 1000 seconds/mm^2, three orthogonal diffusion directions, NEX = 2, TA = 42 seconds; (3) T2 FLAIR: TR/TE = 8000/97.0 msec, FOV = 220×220 mm^2, slice thickness = 5 mm, slice gaps = 1.5, flip angle = 150.0, ETL = 19, matrix = 320×420; (4) T2-weighted FSE: TR/TE = 2883/50 msec, FOV $=10 \times 10$ cm^2, NEX = 3, matrix = 320×256, echo-train length (ETL) = 20, slice thickness = 2 mm, and sequence duration = 111 seconds, no-phase-wrap option (acquiring a larger FOV and cut the edges) was used to avoid wrapping artifacts; and (5) the parameters for T1-weighted images were as follows: TR/TE = 567/16 msec, FOV = 10×10 cm^2, NEX = 2, matrix = 320×256, ETL = 6, slice thickness = 2 mm, and sequence

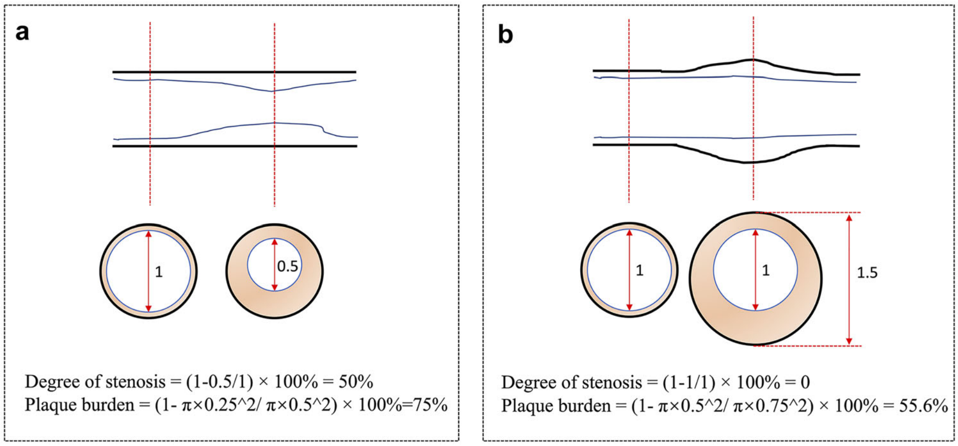

FIGURE 1: Schematic diagram showing the difference between plaque burden and traditional degree of stenosis. (a) Illustrating negative remodeling of the plaque with 50% luminal stenosis and (b) showing the nonstenotic lumen with a positive remodeling plaque.

duration = 48.4 seconds. No-phase-wrap option (acquiring a larger FOV and cut the edges) was used to avoid wrapping artifacts. Twelve slices were acquired for T1-, T2-, and contrast enhanced T1-weighted sequences with 0.31×0.39 mm^2 in-plane resolution.

Plaque Classification

All of the baseline MR images were analyzed by three experienced radiologists in vessel wall imaging (Z.S. with 5 years' experience, J.L. with 8 years' experience, and X.Z. with 10 years' experience). Each plaque was independently classified as a culprit plaque if the lesion was found on conventional MR neuroimaging (i.e. if T2 FLAIR and DWI showed infarct) after an acute ischemic stroke/TIA with accompanying clinical symptoms. When multiple stenoses were present along the artery, the classification was based on the plaque at the location of the greatest stenosis. Any disagreement was resolved by consensus.

Imaging Analysis

The image quality and qualitative features including intraplaque hemorrhage and eccentricity were assessed by three experienced radiologists in vessel wall imaging (Z.S. with 5 years' experience, J.L. with 8 years' experience, and X.Z. with 10 years' experience). The quantitative factors, such as stenosis ratio, enhancement ratio, plaque volume, plaque burden (PB), minimum luminal area (MLA), and remodeling ratio, were measured independently on HR-MRI images by two experienced readers (Z.S. with 5 years' experience and J.L. with 8 years' experience).[15] The image quality was assessed with a method described previously: each slice was graded on a 4-point scale (1 = poor; 4 = excellent) based on the overall signal-to-noise ratio and the contrast between the vessel wall and surrounding tissues.[16, 17] Images with image-quality grade ≥ 3 were included in this analysis. If an imaging slice had insufficient image quality in either baseline or follow-up scans, the patient was excluded in the analysis. Outer wall boundaries were manually segmented on T2-weighted images at the slice with maximum plaque area using CMR Tools software (Cardiovascular Imaging Solutions Ltd, UK). The reproducibility of this area measurement method has been previously reported to be excellent.[7] The degree of luminal stenosis was measured based on TOF maximum intensity projection (MIP) using the WASID criterion.[18] The contrast enhancement ratio was measured at the slice of greatest enhancement using adjacent gray matter (in a region of $\sim$15 mm^2 at the cerebral cortex or hippocampus) to normalize the signal intensity. The contrast enhancement ratio was calculated as [signal of plaque (postcontrast)/signal of gray matter (postcontrast)]/[signal of plaque (precontrast)/signal of gray matter (precontrast)] $\times$ 100%. Fresh intraplaque hemorrhage was identified as an area with >150% intensity of the signal of the adjacent muscle on precontrast T_1-weighted images by the two radiologists independently, blinded to patient clinical information.[8] MLA was the lumen area at the site of maximal stenosis. Plaque burden (PB) was defined as [1 − MLA/outer area (maximal stenosis)] $\times$ 100%, as defined in previous studies[5, 19–22]; PB represents the plaque area percentage at the most stenotic site. It has also been called normalized wall index in previous studies.[23-25] A schematic diagram showing an example of plaque burden definition (with and without positive remodeling) and how it differs from conventional lumen-diameter-based analysis of degree of stenosis is shown in Fig. 1. The arterial remodeling ratio (RR) was assessed as follows[26]: RR = Outer area $_{\text{lesion}}$/(Outer area $_{\text{reference}}$ + $S \times D$) $\times$ 100% (where S is the slope of the lumen tapering and D is the distance between the lesion and reference site). Positive remodeling was defined as RR > 1.05 and negative remodeling as RR < 0.95. Eccentricity was defined as the plaque distribution less than 50% wall involvement.[27]

The percentage change of plaque volume, enhancement ratio, MLA, stenosis, and PB were calculated as (1 − value at second scan/value at first scan) $\times$ 100%. Progression of each parameter was defined in binary fashion (Yes/No) with progression defined as a percentage change greater than the measurement error as defined in the reproducibility substudy (in the Reproducibility section). For example, if the measurement error of plaque burden was around 12.5% and plaque burden increased more than 12.5% on follow-up, then progression of plaque burden was defined as "Yes."

Assessment of Outcomes

Patients were followed for up to 48 months to record the recurrence of TIA/stroke after the follow-up MRI scan. Face-to-face or

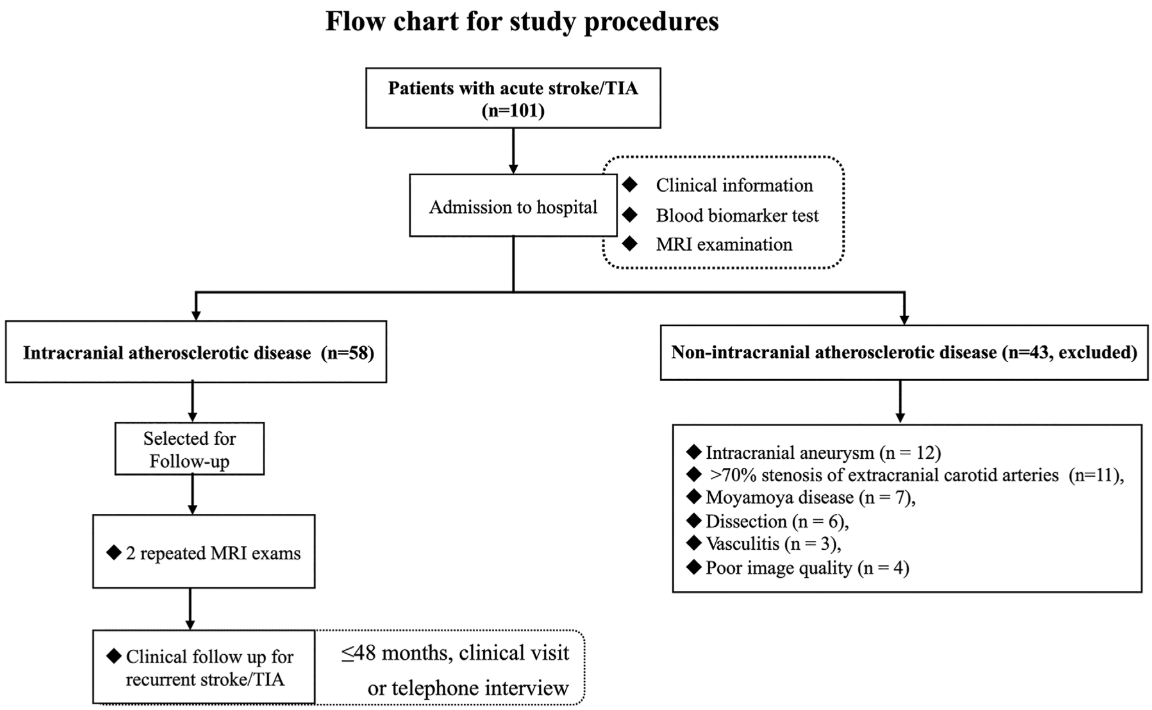

FIGURE 2: Flow chart for study procedures.

telephone interviews were conducted to ascertain ischemic event recurrence by accompanying clinical symptoms (such as glossolalia, ataxia, dizziness, ipsilateral limb weakness, or ipsilateral numbness). Recurrent ischemic events were defined as an ipsilateral TIA/stroke or intracranial plaques after the initial TIA/stroke. The interviewer collecting follow-up information was blinded to the results of the MRI.

Reproducibility

To evaluate the reproducibility of the imaging measurements, inter-reader agreement in measuring quantitative plaque morphology was evaluated on baseline images selected at random from 30 patients in the study population. Two readers (Z.S. with 5-year experience and J.L. the other with 8-year experience in vessel wall imaging) independently made measurements on the MRI.

Statistical Analysis

The calculation of sample size was based on a two sample unpaired *t*-test with 0.80 power and 0.05 significance level (two sided). The measurement error was used as the coefficient of variation for sample size determination. According to a previous scan-rescan study of intracranial vessel wall imaging,[7] the coefficients of variation of measurements are 5%–10%. Hence 7.5% was used as the estimated coefficient of variation to detect 15% difference) in the recurrent stroke group compared to stable group. The required sample size is eight in each group. Considering the recurrent stroke rate is 20% in our study cohort in 4 years, a sample size of 40 patients is needed (with eight recurrent strokes in 4 years). Measurement error between readers was quantified using 95% confidence interval (CI) (95% CI = 2*1.96*SD). Given the measurement error, plaque morphological features (plaque volume, enhancement ratio, MLA, stenosis, and PB) were considered to have progressed when the increase was larger than the 95% CI.

The mean and SD were recorded for continuous variables, and the frequency and percentage were recorded for categorical variables. Univariable analysis was first performed. Student's *t* tests were used for comparing continuous variables and chi-square tests were used for comparing categorical variables. A Kaplan–Meier survival analysis was performed to estimate the cumulative event-free rates. Univariable and multivariable Cox regression analyses were used to calculate the hazard ratio (HR) and corresponding 95% CI of the plaque features in discriminating between patients with and without recurrent events. Variables with $P < 0.20$ in univariable analysis were selected as inputs for the multivariable model and then underwent sequential backward elimination to a P value < 0.10. The diagnostic performance was described using receiver operating characteristic (ROC) curves and area under curve (AUC) values. The inter-observer reproducibility of continuous variables was evaluated using the intra-class coefficient (ICC) with a two-way random-effects model with absolute measurements, while the Kappa value was determined for the categorical variables. All statistical analyses were performed using SPSS24.0. A P value < 0.05 was considered to be statistically significant.

Results

Patients

A flow chart is shown in Figure 2. A total of 101 patients met the inclusion criteria. Of these, 43 patients were excluded due to intracranial aneurysm (N = 12), >70% stenosis of extracranial carotid arteries (N = 11), Moyamoya disease (N = 7), dissection (N = 6), vasculitis (N = 3), and poor image quality (N = 4, 2 with image quality score of 1, 2

TABLE 1. Patient Demographical Information

Clinical Characteristics	Recurrent Patients (N = 12)	Stable Patients (N = 46)	P value
Age	58.92 ± 13.27	57.11 ± 11.38	0.671
Gender			0.809
Male	9	36	
Female	3	10	
Diabetes mellitus	2	10	0.699
Hypertension	8	20	0.152
Smoking (baseline)	3	22	0.155
Smoking-keeper (follow-up)	1	6	0.187
LDL cholesterol, mmol/liter	2.46 ± 0.91	2.50 ± 0.96	0.900
HDL cholesterol, mmol/liter	1.11 ± 0.28	1.13 ± 0.23	0.802
Triglyceride, mmol/liter	2.37 ± 2.14	1.53 ± 0.71	0.028
Total cholesterol, mmol/liter	4.59 ± 1.26	4.13 ± 1.22	0.063
A/G	1.12 ± 0.59	1.53 ± 0.67	0.133
Fasting glucose	5.61 ± 1.43	5.99 ± 1.79	0.823
NIHSS (baseline)	2.00 ± 1.91	1.98 ± 2.48	0.980
$ABCD^2$ score	3.1 ± 0.9	2.5 ± 1.8	0.269
Location			0.359
MCA	11	37	
BA	1	9	
Medications on baseline			
Antiplatelets and high-intensity statin	6	30	0.853
Blood pressure control	1	13	0.196
Medications on follow-up			
Antiplatelets and statin	3	15	0.951
Blood pressure control	1	7	0.702

A/G = albumin/globulin; MCA = middle cerebral artery; BA = basilar artery; $ABCD^2$, A = age, B = Blood pressure, C = clinical findings, D = duration of symptom; diabetes.

with image quality score of 2). As a result, 58 symptomatic patients (mean age: 57.3 ± 11.4 years; 45 male patients; 41acute symptomatic patients and 17 subacute symptomatic patients) were included in the final analysis. There were only nine patients (15.5%) with a carotid stenosis <50% at baseline (two patients had a recurrent stroke/TIA and seven patients did not have a recurrent stroke/TIA) and all other patients (N = 49) did not have a carotid plaque. At the second imaging follow-up, the patients' carotids were not evaluated. The mean time interval between the two MRI scans was 6.2 ± 4.1 months.

Reproducibility of Measurements

The mean-difference (lower and upper limits of agreement) for measurements were −1.7% (−8.7, 5.3) for degree of stenosis, −0.04% (−0.20, 0.11) for enhancement ratio, −2.9 mm^3 (−11.7, 5.9) for plaque volume, −0.01 mm^2 (−0.68, 0.65) for MLA, 0.02% (−0.08, 0.13) for remodeling ratio and 2.8% (−5.5, 11.1) for PB. Bland–Altman plots are shown in the Supplemental Materia Fig. I . The ICC values for the reviewers were considered excellent: image quality assessment (0.923) degree of stenosis o (0.989), enhancement ratio (0.968), plaque volume (0.988), MLA (0.968),

TABLE 2. Imaging Features of Intracranial Atherosclerotic Plaque

Imaging Characteristics	Recurrent Patients (N = 12)	Stable Patients (N = 46)	P value
Baseline			
Infarction on brain MRI	10	36	0.694
Remodeling index	0.94 ± 0.09	0.97 ± 0.17	0.510
Remodeling type			0.186
Positive remodeling	0	6	
Negative remodeling	12	40	
Plaque eccentricity	9	32	0.713
Degree of stenosis (%)	63.94 ± 27.13	62.16 ± 22.67	0.818
Enhancement ratio (%)	42.56 ± 28.85	38.21 ± 33.67	0.684
Plaque volume	68.79 ± 35.18	69.29 ± 52.25	0.970
MLA	2.63 ± 2.10	2.33 ± 1.75	0.727
Plaque burden	78.82 ± 15.77	77.63 ± 15.89	0.821
Follow-up			
Remodeling index	0.96 ± 0.10	0.97 ± 0.17	0.928
Remodeling type			0.308
Positive remodeling	4	9	
Negative remodeling	8	37	
Degree of stenosis (%)	60.18 ± 25.44	56.02 ± 28.14	0.648
Enhancement ratio (%)	39.96 ± 35.22	23.73 ± 28.15	0.160
Plaque volume	68.37 ± 37.21	68.07 ± 54.08	0.985
MLA	2.56 ± 2.25	2.69 ± 2.06	0.682
Plaque burden	83.19 ± 15.56	74.03 ± 18.04	0.095
Percentage change (PC) and progression			
PC of stenosis (%)	9.77 ± 26.36	3.72 ± 12.46	0.319
PC of enhancement ratio (%)	−7.62 ± 73.84	−36.94 ± 66.02	0.976
PC of plaque volume (%)	−2.59 ± 10.45	−2.97 ± 15.53	0.582
PC of MLA (%)	0.79 ± 24.95	15.76 ± 62.76	0.542
PC of plaque burden (%)	5.89 ± 4.93	−4.49 ± 17.33	0.046
Progression of stenosis	2	5	0.953
Progression of enhancement	2	3	0.273
Progression of plaque volume	1	5	0.797
Progression of plaque burden	4	2	0.014
Progression of MLA	0	4	0.571

MCA = middle cerebral artery; BA = basilar artery; MLA = Minimal lumen area.

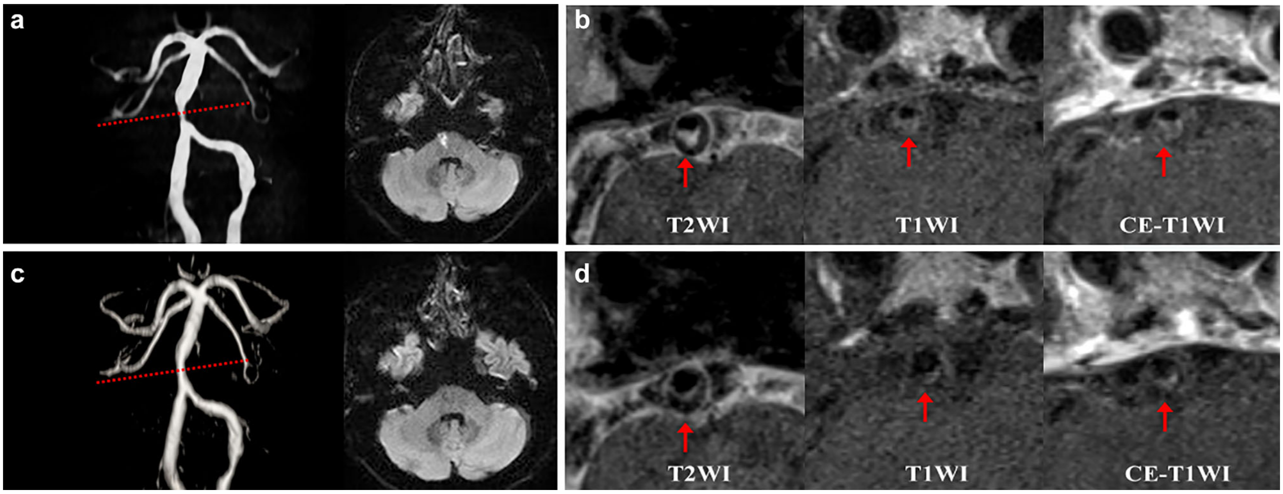

FIGURE 3: A patient without recurrent stroke during follow-up. A 59-year-old male patient with basilar artery stenosis had acute stroke and DWI images show the infarct involves the brainstem at baseline (a and b). On the second MRI 3 months later (c and d), the plaque area and burden were found to be reduced on T2-weighted images; plaque enhancement was also found to be reduced on postcontrast T1-weighted images.

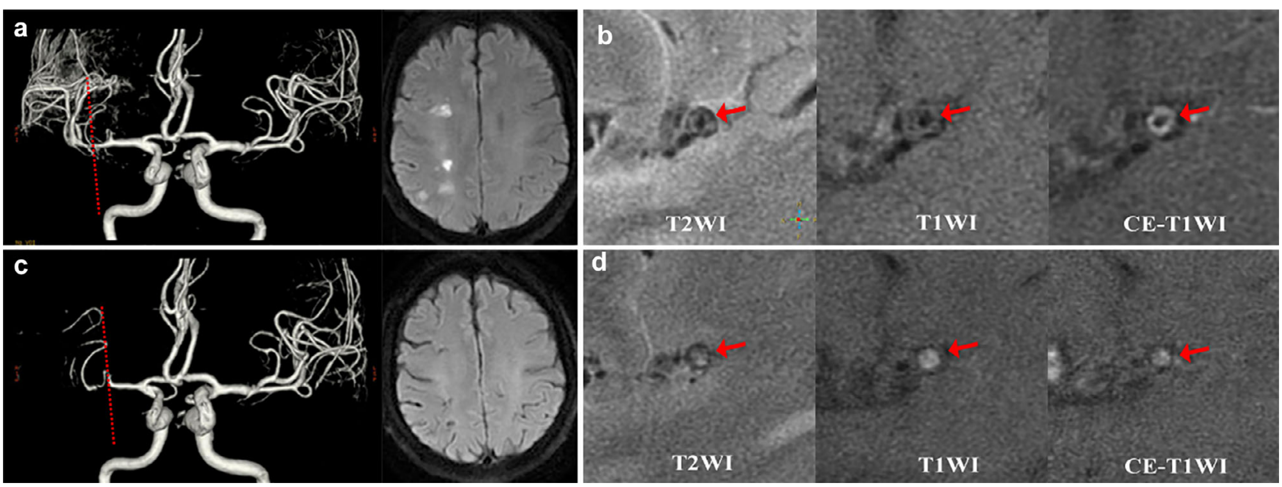

FIGURE 4: Progression of plaque burden associated with recurrent stroke. A 67-year-old male patient with middle cerebral artery (MCA) plaque experienced a recurrence of ipsilateral stroke 13 months after the second MRI scan. Baseline stenosis was 80% (a and b) and second MRI (75 days interval) showed progression of plaque to nearly occlusion (c and d). DWI at baseline MRI scan showed the scattered and multiple fresh infarcts.

remodeling ratio (0.943), and PB (0.951). The Kappa value of eccentricity was 0.791.

Clinical Features and Plaque Characteristics of Recurrent TIA/Stroke and Stable Patients

During 10.9 ± 9.2 months (range, 4–48 months) of follow-up, 20.7% of patients (N = 12) experienced recurrent ischemic events (five strokes and seven TIA) ipsilateral to the initial TIA/stroke. The clinical and radiological characteristics of the intracranial atherosclerotic plaques are summarized in Tables 1 and 2. There was no IPH identified in our population, thus it was not included in the analysis. The tables show that triglyceride ($P < 0.05$), percentage change of PB ($P < 0.05$), and progression of PB ($P < 0.05$) were associated with recurrent ischemic events. Other clinical features (such as $ABCD^2$, P = 0.269) and plaque morphological features (stenosis ratio, enhancement ratio, plaque volume and MLA) were not significantly different between recurrent TIA/stroke and stable patients (stenosis ratio, P = 0.818; enhancement ratio, P = 0.684; plaque volume, P = 0.970; and MLA, P = 0.727). The enhancement ratio decreased 36.94% in the stable group, but only decreased 7.62% in the recurrent group (P = 0.976). Within the recurrent stroke/TIA patients (N = 12), the progression group (N = 4) had more smokers than the nonprogression group (N = 8) (3/4 vs. 0/8, $P < 0.05$). For other risk factors, there was no significant differences between the two groups (Table I in the Supplemental Material). Example images of patients with and without recurrent TIA/stroke are shown in Figs. 3 and 4.

TABLE 3. Cox Regression of Risk Factors for Ipsilateral Recurrent TIA/Stroke

	Univariate Cox Regression			Multivariate Cox Regression		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Gender (Female = reference)	0.915	0.247–3.390	0.895			
Diabetes mellitus	1.402	0.128–4.687	0.493			
Hypertension	2.674	0.803–8.905	0.109	4.173	0.966–18.029	0.046
Smoking	0.475	0.127–1.772	0.268			
LDL cholesterol	1.166	0.547–2.485	0.692			
HDL cholesterol	0.564	0.056–5.661	0.627			
Triglycerides	1.511	1.107–2.063	0.009	1.278	0.825–1.981	0.023
Total cholesterol	1.268	0.808–1.990	0.301			
A/G	0.292	0.107–0.795	0.016	0.101	0.023–0.443	0.071
Fasting glucose	0.828	0.560–1.226	0.346			
Degree of stenosis (baseline)	1.002	0.978–1.032	0.827			
Progression of stenosis	1.539	0.335–7.069	0.580			
Enhancement ratio (baseline)	2.334	0.401–13.631	0.347			
Progression of enhancement	1.938	0.422–8.904	0.295			
Plaque volume (baseline)	1.007	0.997–1.018	0.186	1.001	0.984–1.011	0.728
Progression of plaque volume	0.824	0.105–6.455	0.854			
Plaque burden (baseline)	1.007	0.970–1.045	0.713			
Progression of plaque burden	5.021	1.497–16.838	0.009	6.293	1.620–24.444	0.008
MLA (baseline)	1.052	0.786–1.634	0.733			
Progression of MLA	0.046	0.015–18.303	0.612			

A/G = albumin/globulin; MLA = minimal lumen area.

Plaque Characteristics on HR-MRI Associated With Recurrent TIA/Stroke

Univariable Cox regression identified hypertension (HR, 2.674; 95% CI, 0.803–8.905; P = 0.109), triglyceride (HR, 1.511; 95% CI, 1.107–2.063; P = 0.009), albumin/globulin (HR, 0.292; 95% CI, 0.107–0.795; P = 0.016), plaque volume (baseline) (HR, 1.007; 95% CI, 0.997–1.018; P = 0.186) and progression of plaque burden (HR, 5.021; 95% CI, 1.49–16.838; P = 0.009) as inputs to multivariable analysis (Table 3). Multivariable Cox regression analysis revealed that hypertension (HR, 4.173; 95% CI, 0.966–18.029; $P < 0.05$), triglyceride (HR, 1.278; 95% CI, 0.825–1.981; $P < 0.05$), and progression of PB (HR, 6.293; 95% CI, 1.620–24.444; $P < 0.05$) were independent predictors of recurrent ischemic cerebrovascular events. The Kaplan–Meier curves for the recurrence of ischemic events showed that the event-free survival was significantly higher for patients without progression of PB than for those who had progression of PB ($P < 0.05$; Fig. 5a). ROC curves are shown in Fig. 5b. The AUC of the final Cox regression model (including all three independent risk factors) was 0.885, which was significantly higher than the AUC of any single factor (hypertension = 0.616, triglyceride = 0.698, and progression of PB = 0.808). Additionally, when comparing the AUC values, the classical traditional factors had lower values than the MRI parameters (AUC: $ABCD^2$ = 0.622; infarction on baseline imaging = 0.525; progression of plaque burden = 0.810) as shown in the Supplemental Material Fig. II.

Discussion

This study investigated the association between intracranial plaque features and recurrent ischemic events in acute symptomatic patients. Progression of plaque burden was a

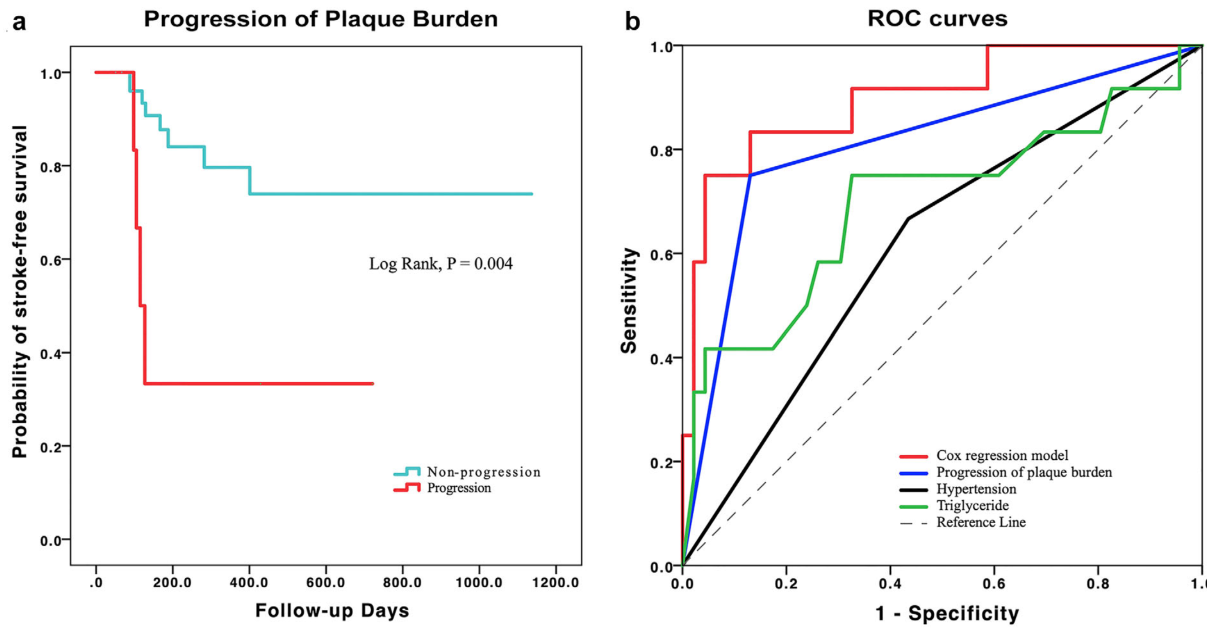

FIGURE 5: Kaplan–Meier curves and ROC analyses. (a) Kaplan–Meier curves of recurrent TIA/stroke between the nonprogression and progression of plaque burden group during the 48-month follow-up. (b) ROC curves for the risk factors identified by the Cox multivariable regression analysis (hypertension, triglyceride, and progression of plaque burden) to predict recurrent TIA/stroke.

significant independent predictor for recurrent symptomatic ischemic events. Serial MR examinations of intracranial plaque may provide additional information comparing with traditional risk factors (like ABCD^2 or presence of infarct) for risk stratification in predicting recurrent ischemic events in symptomatic patients.

Most previous studies of intracranial plaque using HR-MRI have been cross-sectional studies and have focused on differentiating plaque features between symptomatic and asymptomatic patients.[6] However, there have been very few longitudinal studies investigating the prognostic value of HR-MRI to predict future recurrent ischemic events.[12] Kim et al scanned 138 acute stroke patients using HR-MRI and followed them for a median duration of 18 months.[10] They found HR-MRI plaque enhancement at baseline was independently associated with stroke recurrence with a hazard ratio of 7.42. In contrast to Kim et al, our study did not find the baseline enhancement ratio to be associated with future ischemic event risk. Such differences can be potentially explained by: 1) the use of qualitative wall enhancement grading in their study whereas we quantified the enhancement ratio; 2) the previous study did not examine plaque burden, minimal lumen area, IPH features, while we did a comprehensive multivariable analysis of all plaque features and it is possible the enhancement ratio is not an independent factor when combining other features; and 3) differences in follow-up duration. The prognostic value of baseline contrast enhancement needs to be further investigated in larger scale studies.

Kwee et al[12] included 14 symptomatic stroke/TIA patients with a heterogeneous symptomatic status (acute, sub-acute or chronic) and scanned them twice with a median interval of 3.5 months. They found the lack of enhancement at baseline or a decrease in enhancement at follow-up suggested that the plaque was not the culprit lesion.[12] Our study included a larger cohort of patients with a homogenous symptom status (all acute symptomatic patients) with longer duration of follow up imaging. In stable patients, despite we observed a decrease in the average enhancement ratio during follow-up (from 38.21 to 23.73), but it was not statistically significant. As contrast enhancement has been studied as an indicator of vasa vasorum and inflammation,[28] the decrease of enhancement possibly suggests that the plaque has stabilized, while a constant high enhancement ratio may indicate an active plaque, which might lead to recurrent ischemic events.

In our study, we did not find vulnerable plaque features such as enhancement ratio or degree of stenosis, as suggested by previous studies, to predict recurrent stroke.[10, 12, 29] However, we did find a nonsignificant trend of 1.7-fold higher enhancement ratio in recurrent stroke patients than that in stable patients at follow-up MRI. While not statistically significant, this observation might be due to the small sample size in this pilot. In addition, we did not notice a difference in stenosis values between the two groups, possibly related to vessel wall remodeling. Although stenosis has been reported as a risk factor for recurrent stroke,[30] baseline stenosis values were comparable between groups in this study. There is increasing evidence that vessel wall features provide additional value over stenosis degree alone.[12, 31, 32] Our results provide additional evidence regarding plaque features and encourage a larger sample size longitudinal study to further explore these findings.

The progression of plaque volume has been studied as a predictor of recurrent stroke in a carotid plaque study.[17] Our previous study[7] showed good scan–rescan reproducibility of plaque parameters. Consequently, in our current study, the progression results depend more on the inter-reader variability rather than on scan–rescan variability. We observed progression of plaque burden as an independent predictor of ischemic symptom recurrence, whereas changes in plaque volume, minimal lumen area or stenosis were not significant predictors. Importantly, there is a major difference between plaque burden and plaque volume: plaque burden is defined at a single location (the most stenotic location) and represents the plaque area percentage, while the plaque volume is calculated across the entire plaque length. During the evolution of the plaque, the plaque can get longer or shorter, and the changes of the plaque at different locations (upstream/downstream to the most stenotic site) can vary. However, understanding of the history of progression is limited. The MLA is defined at the same location of plaque burden. The fact that MLA did not have a significant change may implicate outward remodeling. This observation may reflect that plaque burden uniquely accounts for both the magnitude of narrowing in incorporating minimal lumen area while also providing information regarding vessel remodeling. The combination of both luminal narrowing and vessel size in plaque burden provides greater understanding as to whether a vessel has enlarged to accommodate greater plaque volume or has stayed the same size, resulting in greater stenosis.

Limitations

First, this was a single-center study performed in an Asian population which has a higher prevalence of ICAD. Hence, the sample could be affected by selection bias and may be less applicable to other populations. Therefore, further studies should be conducted on other racial and ethnic groups. Second, although this study had a sample size that was larger than previous studies, future work would benefit from a larger data set to validate our findings. Furthermore, the analysis was performed using two-dimensional imaging data and the plaque burden was only measured at the most stenotic location. It is possible that the use of three-dimensional imaging acquisitions with thinner slices may better characterize plaque features and improve the image analysis. In addition, 3D imaging could allow coverage of pituitary infundibulum to serve as a more reliable reference to quantify relative plaque enhancement. Fourth, no carotid vessel wall MRI was performed, and it is possible that carotid plaque with <50% stenosis could be an etiology of stroke. And the comprehensive evaluation of carotid vessel wall and intracranial vessel wall features may provide additional value for predicting recurrent stroke.[11]

Conclusion

Progression of plaque burden was independently associated with recurrent ischemic cerebrovascular events. Intracranial vessel wall MRI may assist in risk stratification of patients for recurrent stroke.

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AUTHORS CONTRIBUTION

Dr. Zhang Shi, Dr. Jing Li, and Dr. Ming Zhao contributed to the study concept and design, analysis and interpretation of data, drafting/revising the manuscript for content, and statistical analysis. Dr. Xuefeng Zhang and Dr. Andrew J. Degnan were involved in analysis and interpretation of data, drafting/revising the manuscript for content, and statistical analysis. Dr. Mahmud Mossa-Basha and Dr. David Saloner performed analysis and interpretation of data. Dr. Jianping Lu took part in the study concept and design, analysis, and interpretation of data. Dr. Qi Liu and Dr. Chengcheng Zhu contributed to the study concept and design, acquisition, analysis, and interpretation of data, and drafting/revising the manuscript for content.

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