Neurology Asia 2025; 30(1) : 1 – 8

ORIGINAL ARTICLES

The characteristics of atherosclerotic plaque associated with onset of acute ischemic stroke: a high-resolution magnetic resonance imaging study

[1]Dongsen Zhang, [2]Wansong Li, [1]Yongqiu Li, [1]Haifeng Gao, [1]Hongying Ma

[1]Department of Neurology, Tangshan GongRen Hospital, Tangshan, China; [2]Hebei Medical University, Shijiazhuang, China

Abstract

Background & Objective: The onset of cerebrovascular events is closely related to status of atherosclerotic plaque, especially vulnerable plaques, but the majority of vulnerable plaques remain clinically silent. This study aimed to investigate the characteristics of high-risk vulnerable plaque that correlate with the onset of acute ischemic stroke. *Methods:* In this retrospective study. Patients were recruited if they conformed to acute unilateral internal carotid artery or middle cerebral artery territory infarction identified as artery to artery embolization with conjugated vulnerable plaque of bilateral internal carotid artery siphon or middle cerebral artery M1segment vulnerable plaques by 3.0-T high-resolution magnetic resonance imaging examination. Characteristics of vulnerable plaques were compared between culprit plaque and non-culprit plaque of the same patient. *Results:* A total of 78 patients (64 males; mean age = 58.49 ± 10.38 years) were included. There were statistically significant difference in irregular surface, degree of stenosis, eccentricity index between culprit plaque and non-culprit plaque (P <0.05). Multivariate analysis showed that irregular surface (OR 5.897, 95%CI, 2.355-14.767, P <0.001), moderate stenosis (OR 3.163, 95%CI, 1.208 -8.283, P =0.019), and plaque enhancement (OR 2.551, 95%CI, 1.028 -6.328, P =0.043) were associated with culprit plaque. The area under the curve of plaque enhancement of irregular surface combined with moderate stenosis was 0.816 (95% CI 0.748-0.884, p =0.000). Plaque enhancement of irregular surface combined with moderate stenosis was associated with END (OR 2.131, 95% CI 1.224-3.712, p=0.008).
Conclusions: Plaque enhancement of irregular surface combined with moderate stenosis may be potential imaging markers for predicting the occurrence of thromboembolic strokes caused by intracranial large artery atherosclerosis and early neurologic deterioration.

Keywords: High-resolution magnetic resonance imaging, acute ischemic stroke, vulnerable plaque, intracranial artery, early neurologic deterioration

INTRODUCTION

Stroke is the second most common cause of death and the leading cause of death in Asia, the most common cause of disability worldwide.[1] Ischemic stroke accounts for 70%, which most results from atherosclerosis in intracranial arteries.[2] The Chinese Intracranial Atherosclerosis (CICAS) study showed 46% of patients with acute ischemic stroke result from intracranial atherosclerosis.[3]

The onset of cerebrovascular events is closely related to status of atherosclerotic plaque[4], so it is feasible to predict ischemic stroke by assessment of the atherosclerotic plaque itself. Atherosclerosis presents as stable plaque or unstable plaque which is also called vulnerable plaque. Plaque vulnerability depends on its composition. The morphological characteristics of vulnerable plaques mainly include rupture of the plaque surface, calcification, thin fibrous cap, large lipid-rich necrotic core, formation of neovascularization, intraplaque hemorrhage (IPH) and secondary thrombus.[5-7] The majority of vulnerable plaques remain clinically silent[8], but the vulnerable plaques can lead to the occurrence of ischemic cerebrovascular event. It is still unclear which characteristics of vulnerable

Address correspondence to: Hongying Ma, PhD, Tangshan GongRen Hospital, Tangshan, 063000, China. E-mail: wangwf2004@163.com
Date of Submission: 16 October 2024; Date of Acceptance: 22 October 2024
https://doi.org/10.54029/2025hfk

plaque are the most critical factors in resulting in ischemic stroke.

The purpose of this study was to explore the characteristics of high-risk intracranial cerebral artery vulnerable plaques that correlate with the onset of acute ischemic stroke using high-resolution magnetic resonance imaging (HR-MRI), to make an early assessment and effective intervention in time to prevent the occurrence of vascular events.

METHODS

Study population

This study was a retrospective observational study. Patients were enrolled from January 2018 to December 2022, if they converted to acute internal carotid artery (ICA) or middle cerebral artery territory (MCA) infarction and underwent 3.0-T HR-MRI. Inclusion criteria were as follows: (1) acute ischemic strokes (AIS) in the ICA/MCA territory confirmed by diffusion weighted imaging (DWI); (2) within 24 hours of onset; (3) the etiology of cerebral infarction was considered as artery to artery embolism based on clinical evidence. (4) conjugated vulnerable plaque of bilateral ICA/MCA M1 segment were identified by HR-MRI. Exclusion criteria were as follows: (1) nonatherosclerotic vasculopathy such as vasculitis, Moyamoya disease, artery dissection or arteriovenous malformation; (2) ICA/MCA occlusion ipsilateral to the infarction; (3) unstable plaques (presence of two or more of the following characteristics: hemorrhage, fibrous cap thin or ruptured, superficial irregularity, ulcer plaque, thrombus, and heterogeneous hypoechoic mixed echo) of the ipsilateral proximal carotid artery detected by imaging (ultrasound, HR-MRI, or DSA); (4) suspected cardiogenic or aortic arch stroke (embolism in different arterial areas; history of recent myocardial infarction, atrial fibrillation or flutter, rheumatic hearts valve, infective endocarditis; evidence of cardiac or valvular thrombus on cardiac imaging and cardiac rhythm monitoring); (5) undergoing emergent thrombolysis or interventional treatments; (6) contraindication to MRI examination; (7) poor-quality images of HR-MRI.

The clinical data of each patient were recorded such as age, gender, medical history (hypertension, diabetes mellitus, coronary artery disease, alcohol consumption, cigarette smoking). This study was approved by the institution's ethics committee (GRYY-LL-KJ2022-006).

Imaging scanning

All patients received a 3.0-T Siemens Trio magnetic resonance scanner (Siemens Healthcare, Ehrlangen, Germany) with a 12-channel head coil within 1 week from onset. Scanning sequences DWI: voxel size: layer thickness 6mm, B1000s/m, TR4800ms, TE101ms, interlayer spacing 1mm, FOV240×240mm, matrix 256×256. Scan sequence and parameters of HR-MRI: ① Three dimensional time of flight magnetic resonance angiography (3D-TOF-MRA): TR20.0ms, TE4.9ms, layer thickness 2.0mm, FOV160mm×160mm, Matrix 400×246. ② T1weighted imaging (T1WI): TE33.0ms, TR600.0ms, layer thickness 2.0mm, FOV160mm×160mm, Matrix 332×301. ③ T2 weighted imaging (T2WI): TE333.0ms, TR2500.0ms, layer thickness 2.0mm, FOV160mm ×1 60mm, Matrix 260×201. ④ Hyper_T1: TR9.6ms, TE4.8ms, layer thickness 2.0mm, FOV 160mm×160mm, Matrix 200×196.

Imaging assessment

The image quality is classified into four grade[9]: Grade 1: Vascular wall and vascular lumen are not clearly displayed; Grade 2: lumen is clear, plaque is not clear; Grade 3: a small amount of motion artifacts in the lumen, with clear display in vascular wall and plaque; Grade 4: plaque structure is clear without motion artifacts. It was excluded if its grade under level 2.

Vulnerable plaque was defined as the plaque with presence of at least two of the following features: plaque burden >40%, intra-plaque hemorrhage, positive remodeling, irregular surface, moderate or severe stenosis of vascular. Culprit plaque was defined as vulnerable plaque on the middle cerebral artery on the same side as the infarct, non-culprit plaque as vulnerable plaque in contralateral middle cerebral artery of the same patient.

Plaque characteristics including plaque distribution, irregular surface, plaque burden, remodeling index (RI), eccentricity index (EI), IPH, plaque enhancement and degree of stenosis of vascular were measured. Plaque distribution was recorded: plaques that were distributed across at least three quadrants of the vessel wall were defined as diffuse, and those across less than two were defined as local. Plaque burden is equal to plaque area/narrowest vessel area ×100%. Remodeling index was calculated as the ratio of outer wall area (OWA) at the site of maximal lumen narrowing to that at the reference site (RI =OWA lesion/OWA reference). The reference

site was selected based on the WASID method.[10] A remodelling index ⩾1.05 was defined as positive remodelling, 0.95-1.05 as intermediate remodelling, ⩽0.95 as negative remodelling.[11] Eccentricity index was calculated [(the thickest wall diameter)-(the thinnest wall diameter)]/the thickest wall diameter. Intraplaque haemorrhage was defined as a signal intensity greater than 150% of T1 signal of adjacent muscle.[12] Degree of stenosis = (1-Luminal Area at the maximal lumen narrowing site/reference luminal area)*100%.

HR-MRI was assessed by two experienced neuroradiologist together, who was blinded to the patients clinical information.

Outcomes

We have defined early neurologic deterioration (END) at least one of the following criteria within 7 days: (1) an increase of ≥ 2 points on the NIHSS score; (2) an increase of ≥ 1 points on the consciousness score; (3) an increase of ≥ 1 points on the motor score of ≥ 1 point; (4) any new neurological deficits that would be unmeasurable by NIHSS scores. The cranial computed tomography was performed to exclude intracranial hemorrhage.

Statistical analysis

Continuous variables were presented as means and standard deviations or median (interquartile range). Categorical variables were presented as counts or percentages. We compared datas from plaque composition between culprit plaque and non-culprit plaque. Between-group comparisons were performed using Paired Student's T test if normally distributed, using nonparametric test of two paired samples (Wilcoxon test) if not. We compared categorical variables between groups with (Wilcoxon test or McNemar's test). Multiple logistic regression was used to investigate independent risk factors of culprit plaque. We evaluated the predictor efficiency of culprit plaques by the independent risk factors, which was equivalent to the area under the curve (AUC) of the receiver operating characteristic curve (ROC) curve. An AUC of 0.5 indicates no discrimination whereas AUC of 1.0 indicates perfect discrimination. The relationship between independent risk factors and END was discussed by regression analysis. P values were two-sided, and values of <0.05 were considered statistically significant. All data were analyzed using SPSS software (version 22.0).

RESULTS

Patient demographics

The patient selection flowchart was shown in Figure 1. A total of 225 patients with AIS in the ICA/MCA territory were recruited and performed HR-MRI 147 of them were excluded. Seventy eight patients with vulnerable plaques conjugated

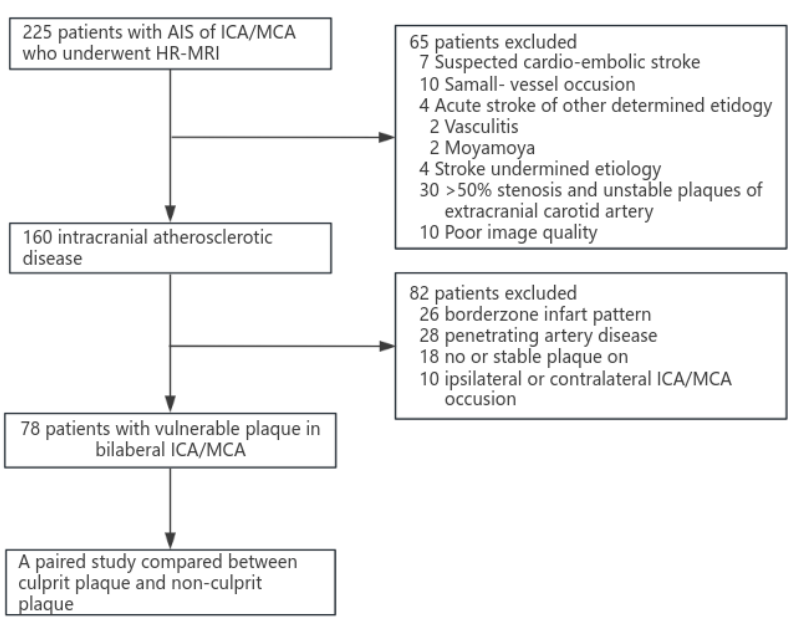

Figure 1. Flow chart of this study

in bilateral ICA/MCA who only had unilateral stroke were enrolled in the study eventually. In total, 64 (82.05%) were men, and the mean age was 58.49 ± 10.38 years. 49 patients (62.82%) had a history of hypertension, 18 (23.08%) had diabetes mellitus, 6 (7.69%) had coronary artery disease, 20 (25.64%) had a history of cigarette smoking, and 15 (19.23%) alcohol consumption.

Culprit plaque and non-culprit plaque composition comparison

Culprit plaques had higher plaque irregular surface than non-culprit plaques (58.97% vs. 15.38%, P <0.001). The degree of stenosis was significantly different between culprit plaques and non-culprit plaques (no and mild stenosis, 34.62% vs. 60.26%; moderate stenosis, 34.62% vs. 14.10%; severe stenosis, 30.80% vs. 25.64%, respectively. P =0.027). The eccentricity index of culprit plaques [0.66, (0.59, 0.74)] was more obvious than that of non-culprit plaques [0.60, (0.52, 0.70)] (P =0.034). The proportion of plaque enhancement of culprit plaques was higher than that of non-responsible plaque (39.74% vs.14.10%, P <0.001). However, there was no association with plaque distribution, arterial remodeling, IPH (P >0.05) (Table 1).

Multivariate analyses showed irregular surface (OR 5.897, 95%CI, 2.355-14.767, P <0.001), moderate stenosis (OR 3.163, 95%CI, 1.208 -8.283, P =0.019), and plaque enhancement (OR 2.551, 95%CI, 1.028 -6.328, P =0.043) were independent characteristics of vulnerable plaque significantly associated with acute ischemic stroke (Table 2). Representative case was shown in Figure 2.

Characteristics of plaque and acute ischemic stroke

Plaque enhancement of irregular surface combined with moderate stenosis were associated with acute ischemic stroke (OR 3.026, 95% CI 2.139-4.280, P<0.001). We compared the accuracy of irregular surface and moderate stenosis for distincting culprit plaque using ROC curve analysis. The AUC of irregular surface, moderate stenosis and plaque enhancement was 0.718 (95%CI 0.636-0.800, P <0.001), 0.603 (95%CI 0.514-0.692, P =0.027), and 0.679 (95%CI 0.595-0.764, P <0.001) respectively. The AUC of plaque enhancement of irregular surface combined with moderate stenosis was 0.816 (95% CI 0.748-0.884, P <0.001). (Figure 3).

Relationship between characteristics of culprit plaque and END

Among the enrolled, 20 (25.64%) patients developed END. Plaque enhancement of irregular surface combined with moderate stenosis was associated with END (OR 2.131, 95% CI 1.224-3.712, P=0.008).

DISCUSSION

The ischemic stroke represents an etiologically

Table 1: Compared composition with responsible plaque and non-responsible plaque

Variable	Culprit plaque	Non-culprit plaque	P-value
Plaque distribution			0.700
Diffuse[n(%)]	37(47.44)	34(43.59)	
Irregular surface[n(%)]	46(58.97)	12(15.38)	<0.001
Arterial remodeling			0.832
Negative remodelling[n(%)]	22(28.21)	23(29.49)	
Intermediate remodelling[n(%)]	15(19.23)	19(24.36)	
Positive remodelling[n(%)]	41(52.56)	36(46.15)	
Remodelling index	1.12±0.36	1.09±0.32	0.609
Degree of stenosis			0.027
No and Mild stenosis[n(%)]	27(34.62)	47(60.26)	
Moderate stenosis[n(%)]	27(34.62)	11(14.10)	
Severe stenosis[n(%)]	24(30.80)	20(25.64)	
Eccentricity index	0.66(0.59,0.74)	0.60(0.52,0.70)	0.034
Plaque enhancement[n(%)]	39(50.00)	11(14.10)	<0.001
Plaque burden(%)	43.82(28.23,67.95)	43.01(25.66,56.25)	0.284
Intraplaque haemorrhage[n(%)]	6(7.69)	4(5.13)	0.688

Table 2: Multiariable logistic regression analysis

Variable	Coefficients ts	S.E	χ^2	P	OR	95% CI lower	upper
Irregular surface	1.774	0.468	14.351	<0.001	5.897	2.355	14.767
Degree of stenosis			5.941	0.051			
Moderate stenosis	1.152	0.491	5.498	0.019	3.163	1.208	8.283
Severe stenosis	0.025	0.473	0.003	0.958	1.025	0.406	2.592
Plaque enhancement	0.936	0.464	4.081	0.043	2.551	1.028	6.328
Eccentricity index	0.658	1.175	0.314	0.575	1.932	0.193	19.333
Constant	-1.589	0.770	4.261	0.039	0.204	-	-

heterogeneous group and may be caused by various potential sources of thromboembolism, so that the effective therapeutic methods and intensity are individual. Intracranial atherosclerotic disease is a common cause of ischemic stroke. Atherosclerotic sources of embolism, particularly non-stenotic plaques (unstable plaque causing <50% stenosis) are now recognized as a major contributor to stroke.[13-15] It is critical and challenging to assess accurately the association between the

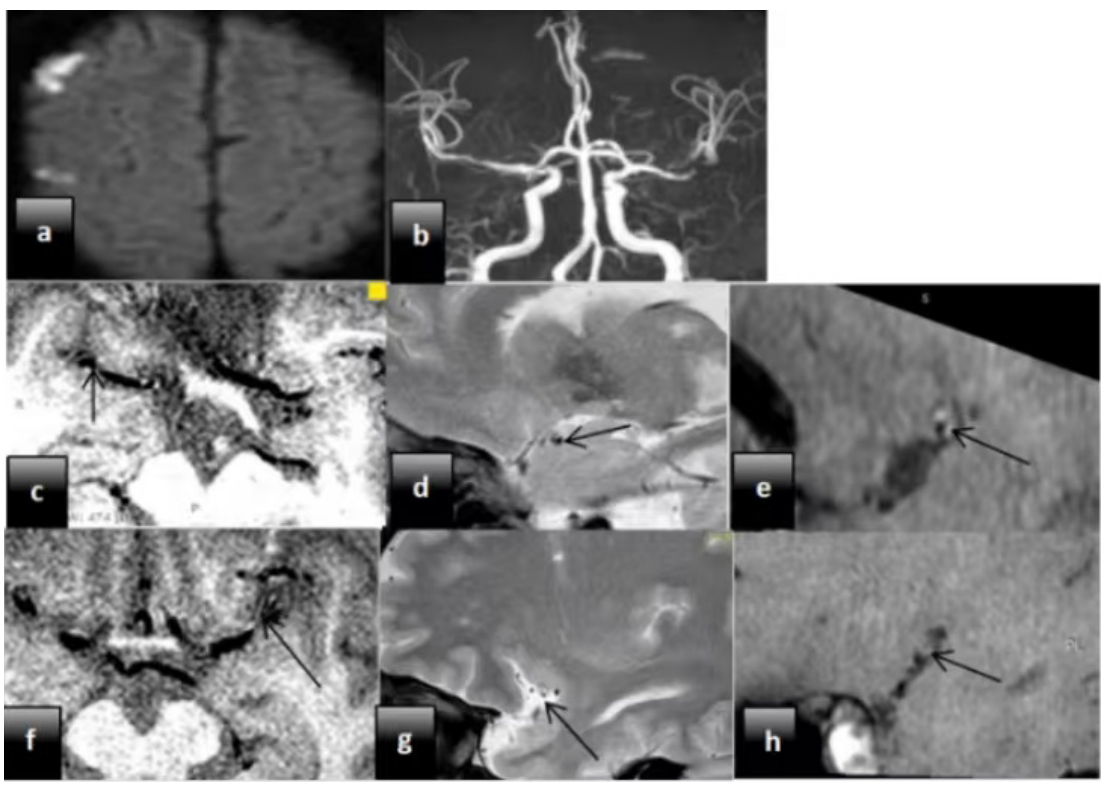

Figure 2. Representative cases: A 68-year-old man with acute left middle cerebral artery territory infarction with vulnerable plaque of bilateral middle cerebral arteries on HR-MRI.
a: diffusion-weighted images: with the black arrow pointing to acute ischemic strokes;
b: 3-dimensional time-of-flight magnetic resonance angiography: with the black arrow pointing to bilateral middle cerebral arteries;
c, d, e: the right middle cerebral artery on HR-MRI: with the black arrow pointing to culprit plaque: moderate stenosis,irregular surface and enhancement.
f, g, h: the left middle cerebral artery on HR-MRI: with the black arrow pointing to non-culprit plaque: severe stenosis, regular surface and non-enhancement.
The figures a – h notation cannot be seen. The arrows of a and b cannot be seen.

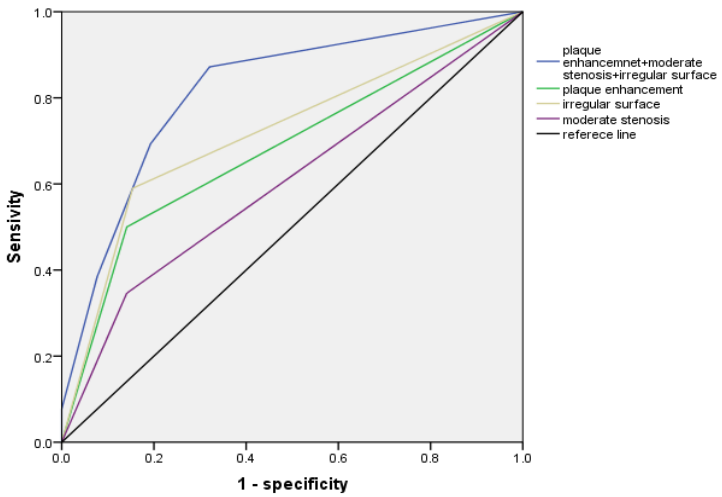

Figure 3. ROC curve of irregular surface, moderate stenosis, plaque enhancement, and plaque enhancement of irregular surface combined with moderate stenosis for disincting? culprit plaque. Plaque enhancement of irregular surface combined with moderate stenosis has the best diagnostic value on culprit plaque.

vulnerability of intracranial artery plaque and the occurrence of ischemic cerebrovascular disease. Knowledge of characteristics of high-risk vulnerable atherosclerotic plaque may change the current management strategies of ischemic stroke based merely on the degree of stenosis. In this study, the intracranial large artery atherosclerotic plaque resulting in thromboembolic stroke was investigated through 3.0-T high-resolution magnetic resonance imaging examination.

A self-paired design was conducted to explore the differences between vulnerable plaques of ICA siphon or MCA M1 segment on the infarct side and one on the contralateral side, to identify the characteristics of high-risk vulnerable plaques associated with artery to artery cerebral embolism, betterly eliminating interference from other factors. We found that the irregular surface and enhancement of plaques and moderate stenosis were independent risk factors for onset of ischemic stroke. Plaque enhancement of irregular surface combined with moderate stenosis can well predict the occurrence of thromboembolic strokes caused by intracranial large artery atherosclerosis and END.

It is reported that intracranial severe stenosis (≥70%) of the major cerebral arteries is an important cause of ischemic stroke.[16,17] Currently, the screening of patients at high-risk suffering from ischemic cerebrovascular events is mainly based on morphological evaluation of cerebrovascular stenosis degree by imaging. The presence of symptomatic 50-99% intracranial stenosis was independently associated with an increased risk of ischemic stroke which was more higher for the 70–99% intracranial stenosis subgroup.[18] This study showed the proportion of 50–99% intracranial stenosis on infarction side accounted for up to 65%. The result of our study revealed that moderate stenosis (50-70%) was an independent risk factor for AIS, but not mild stenosis (<50%) or severe stenosis (70-99%). Severe stenosis often brings about watershed infarction even if it does not form thrombosis in-situ causing artery occlusion, but this study shows that moderate stenosis with plaque surface rupture is more likely causing artery-to-artery embolism because of the ulcer surface formed fresh thrombosis and strong blood erosion force, in the condition of plaque surface ulcer the possibility of vessel occlusion resulting from thrombosis in situ between moderate stenosis and severe stenosis is not involved in this study due to the limitation of equipment. More than one-half of ischemic events arise from patients without obstructive disease, even the majority of lesions are located in vessel segments without significant stenosis prior to the event.[19,20] We found that about 70% of culprit plaques that did not cause haemodynamically stenosis can trigger AIS. The occurrence of ischemic cerebrovascular disease was mainly caused by vulnerable plaque itself, rather than indirect luminal stenosis by plaque. On the basis of atherosclerosis, surface ulcer of vulnerable plaque leading to platelet aggregation and thrombosis may be an important pathogenesis of ischemic cerebrovascular disease.

Unstable atherosclerotic plaque formation and

plaque rupture are important reasons to lead to the occurrence and progress of ischemic stroke. The rupture of atherosclerotic plaque is considered to be the principal mechanism that accounts for stroke.[21] Plaque rupture is responsible for the majority (73%) of all acute coronary events.[22,23] The results of this study showed that about 60% of culprit plaques has irregular surface of plaque. As a result of plaque rupture, the necrotic core containing collagen fibers becomes exposed to the vessel lumen, leading to the formation of thrombus, which leads to early neurological deterioration. Thin neovascularization walls in plaque and invasion of inflammatory cells lead to plaque strengthening, which can reflect plaque stability and predict stroke occurrence.

In conclusion, plaque enhancement, irregular surface, and moderate stenosis are independent characteristics of vulnerable plaque significantly associated with ischemic stroke. Plaque enhancement of irregular surface combined with moderate stenosis may be potential imaging markers for predicting END and the occurrence of thromboembolic strokes caused by intracranial large artery atherosclerosis.

Atherosclerosis is a chronic condition. It is very important to have accurate diagnosis of high risk vulnerable atherosclerotic plaques prior to clinical manifestations that would help the risk stratification, to develop personalized treatment strategy.

There are some limitations in this study. First, this is a cross-sectional study. HR-MRI was performed after the ischemic stroke event. The statistical results might be inevitably biased due to the small sample size. Our results should be validated with future larger-scale longitudinal studies. Second, we studied atherosclerotic embolic stroke in large arteries. Patients frequently have two or more co-existing potential embolic sources, making identification of the underlying cause difficult and often inconclusive, which may lead to errors in the results.

DISCLOSURE

Data availability: Data are available on reasonable request.

Financial support: None

Conflict of interest: None

REFERENCES

1. Wu S, Wu B, Liu M, *et al*. Stroke in China: Advances and challenges in epidemiology, prevention, and management. *Lancet Neurol* 2019;18:394-405. doi: 10.1016/S1474-4422(18)30500-3.
2. Banerjee C, Chimowitz MI. Stroke caused by atherosclerosis of the major intracranial arteries. *Circ Res* 2017; 120:502-13. doi: 10.1161/CIRCRESAHA.116. 308441.
3. Wang Y, Zhao X, Liu L, *et al*. Prevalence and outcomes of symptomatic intracranial large artery stenoses and occlusions in China: the Chinese Intracranial Atherosclerosis (CICAS) Study. *Stroke* 2014; 45:663-9. doi: 10.1161/STROKEAHA.113.003508.
4. Yanez ND, Burke GL, Manolio T, *et al*. Sibling history of myocardial infarction or stroke and risk of cardiovascular disease in the elderly: the Cardiovascular Health Study. *Ann Epidemiol* 2009; 19:858-66. doi:10.1016/j. annepidem.2009.07.095.
5. Dai J, Xing L, Jia H, *et al*. In vivo predictors of plaque erosion in patients with ST-segment elevation myocardial infarction: a clinical, angiographical, and intravascular optical coherence tomography study. *Eur Heart J* 2018; 39:2077-85. doi: 10.1093/eurheartj/ehy101.
6. Doonan RJ, Hafiane A, Lai C, *et al*. Cholesterol efflux capacity, carotid atherosclerosis, and cerebrovascular symptomatology. *Arterioscler Thromb Vasc Biol* 2014; 34:921-26. doi: 10.1161/ATVBAHA.113.302590.
7. Chu B, Kampschulte A, Ferguson MS, *et al*. Hemorrhage in the atherosclerotic carotid plaque: A high-resolution MRI study. *Stroke* 2004; 35:1079-84. doi: 10.1161/01.STR.0000125856.25309.86.
8. Abela GS, Aziz K, Vedre A, *et al*. Effect of cholesterol crystals on plaques and intima in arteries of patients with acute coronary and cerebrovascular syndromes. *Am J Cardiol* 2009; 103:959-68. doi: 10.1016/j.amjcard.
9. Uaderhill HR, Yarnykh VL, Hatsukami TS, *et al*. Carotid plaque morphology and composition: initial comparison between 1.5 and 3.0 T magnetic feld strengths. *Radiology* 2009; 248(2): 550-60. doi: 10.1148/radiol.2482071114.
10. Samuels OB, Joseph GJ, Lynn MJ, *et al*. A standardized method for measuring intracranial arterial stenosis. *AJNR Am J Neuroradiol* 2000; 21: 643-6.
11. Ma N, Jiang WJ, Lou X, *et al*. Arterial remodeling of advanced basilar atherosclerosis: a 3-tesla MRI study. *Neurology* 2010; 75:253-8. doi: 10.1212/WNL.0b013e3181e8e714.
12. Turan TN, LeMatty T, Martin R, *et al.* Characterization of intracranial atherosclerotic stenosis using high-resolution MRI study-rationale and design. *Brain Behav* 2015; 5(12):e00397. doi: 10.1002/brb3.397.
13. Ntaios G, Perlepe K, Sirimarco G, et al. Carotid plaques and detection of atrial fibrillationin embolic stroke of undetermined source. Neurology 2019;92:e2644–2652. doi: 10.1212/WNL.0000000000007611.
14. Ntaios G, Swaminathan B, BerkowitzSD, *et al*. Efficacy and safety of rivaroxaban versus aspirin in embolic stroke of undetermined source and carotid

atherosclerosis. *Stroke* 2019; 50: 2477-85. doi: 10.1161/STROKEAHA.119.025168.
15. Ospel JM, Singh N ,Marko M, *et al*. Prevalence of ipsilateral nonstenotic carotid plaques on computed tomography angiography in embolic stroke of undetermined source. *Stroke* 2020; 51:1743 -9. doi: 10.1161/STROKEAHA. 120.029404.
16. Holmstedt CA, Turan TN, Chimowitz MI. Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. *Lancet Neurol* 2013; 12(11):1106-14. doi: 10.1016/S1474-4422(13)70195-9.
17. Amarenco P, Lavallée PC, Monteiro Tavares L, *et al*. Five-year risk of stroke after TIA or minor ischemic stroke. N Engl J Med 2018; 378 (23):2182-90. doi: 10.1056/NEJMoa1802712.
18. Hurford R, Wolters FJ, Li L, *et al*. Prevalence, predictors, and prognosis of symptomatic intracranial stenosis in patients with transient ischaemic attack or minor stroke: a population-based cohort study. *Lancet Neurol* 2020; 19(5):413-21. doi: 10.1016/S1474-4422(20)30079-X.
19. Ambrose JA, Tannenbaum MA, Alexopoulos D, *et al*. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol* 1988; 12: 56-62. doi: 10.1016/0735-1097(88)90356-7.
20. Dzaye O, Razavi AC, Blaha MJ, *et al*. Evaluation of coronary stenosis versus plaque burden for atherosclerotic cardiovascular disease risk assessment and management. *Curr Opin Cardiol* 2021; 36(6):769-75. doi: 10.1097/HCO.0000000000000911.
21. Roth GA, Johnson C, Abajobir A, *et al*. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol* 2017; 70:1-25. doi: 10.1016/j.jacc.2017.04.052.
22. Moreno PR. Pathophysiology of plaque disruption and thrombosis in acute ischemic syndromes. *J Stroke Cerebrovasc Dis* 2001; 10:2-9. doi: 10.1053/jscd.2001.24785.
23. Falk E, Nakano M, Bentzon JF, *et al*. Update on acute coronary syndromes: The pathologists' view. *Eur Heart J* 2013; 34(10):719-28. doi: 10.1093/eurheartj/ehs411.