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Quantitative score of the vessel morphology in middle cerebral artery atherosclerosis

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ABSTRACT

Background: We aimed to quantitatively assess the vessel morphology of middle cerebral artery (MCA) atherosclerosis and explore its value in discriminating plaque types.
Methods: Patients were selected from a high-resolution magnetic resonance imaging (HRMRI) study from January 2007 to December 2015. One hundred and three patients with acute cerebral infarcts due to MCA stenosis (> 50%) and eighty-nine patients with asymptomatic MCA stenosis (> 50%) were included. Quantitative measurements of MCA morphology, including lumen area, outer-wall and wall area at stenotic site and reference site, stenotic degree, plaque length, remodeling index and plaque eccentricity, were performed on HRMRI with observers blinded to clinical presentations. Firth's penalized logistic regression analysis was used to construct a symptomatic plaque score (SPS) model. Then, the HRMRI data of 39 patients prospectively enrolled from January 2016 to January 2017 were used to validate the SPS model.
Results: The HRMRI data of 103 patients with symptomatic MCA stenosis and 89 patients with asymptomatic MCA stenosis in the construction cohort were analyzed. Four main factors were found to be associated with symptomatic plaques: stenotic lumen area ≥ 2.28 mm^2, stenotic wall area ≥ 8.88 mm^2, plaque length and presence of an eccentric plaque. Summation of each logistic regression coefficient multiplying the corresponding score produced the SPS with an area under curve (AUC) of 0.890 on receiver operating characteristics analysis. Validation of the score of 39 plaques (19 symptomatic and 20 asymptomatic) revealed an AUC of 0.862, confirming the continued diagnostic ability. When the data were pooled in all 235 plaques, the optimal cutoff score of discriminating symptomatic and asymptomatic plaques was 2.79 (SPS ≥ 2.79 indicating a symptomatic plaque) with AUC = 0.886, sensitivity 81.1% and specificity 80.5%.
Conclusions: The quantitative analysis of MCA morphology can independently and accurately discriminate plaque types, suggesting its close association with the underlying pathophysiology. Further prospective studies are required to verify whether the SPS model is clinically valuable in monitoring plaque progression and assessing the vulnerability.

1. Introduction

Middle cerebral artery (MCA) atherosclerosis is a common disease in patients of Asian, Hispanic, and African American ancestry with vascular risk factors [1,2]. The manifestations of MCA atherosclerosis are heterogeneous. It can be asymptomatic for a long time, or it can cause severe cerebral infarcts [3]. Currently, no reliable diagnostic technique has been available to accurately predict the outcome of MCA atherosclerosis, although stenosis degree and plaque composition are important in defining culprit vessel lesions [4].

High-resolution magnetic resonance imaging (HRMRI) is a technique that can visualize intracranial vessel wall in vivo. Different vessel wall properties on HRMRI, including plaque morphology and components, are observed between symptomatic and asymptomatic MCA plaques [5–7]. It is assumed that these vessel wall properties may be useful for predicting plaque vulnerability [8]. However, the parameters of plaque components such as intra-plaque hemorrhage [6] and vessel wall enhancement [7] have limited translational clinical value. The occurrence rate of intra-plaque hemorrhage is too low to sensitively stratify stroke risk [6], while vessel wall enhancement is recently reported in healthy subjects, making its specificity questionable [9].Comparatively, quantitative measurements of plaque morphology are available for each plaque and are promising to discriminate plaque types [10]. Symptomatic MCA plaques tend to have larger wall area,

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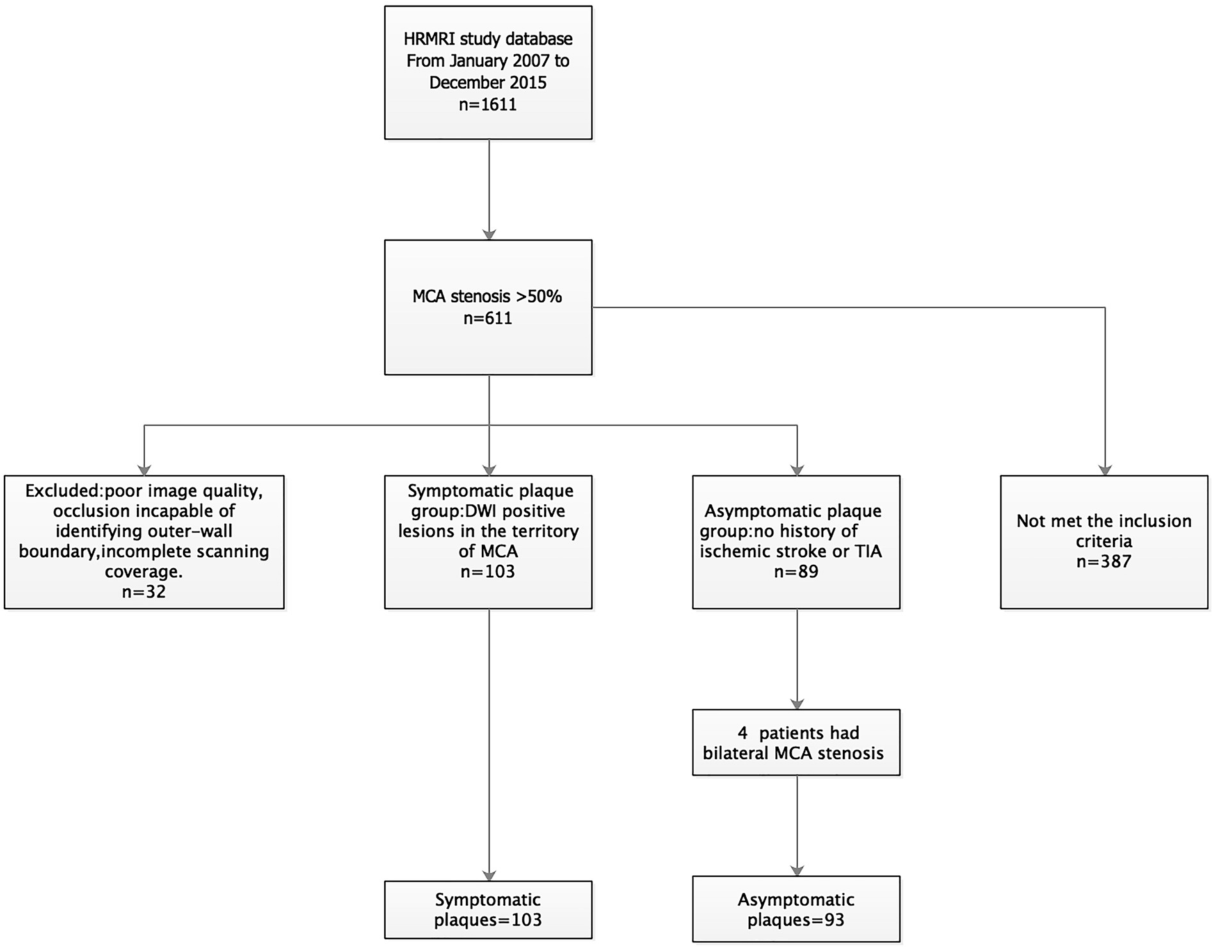

Fig. 1. An overview of patient selection and patient groups in the construction cohort.

Table 1
Plaque features of symptomatic and asymptomatic plaques.

	Symptomatic (*n* = 103)	Asymptomatic (*n* = 93)	*P* value
MCA stenotic rate (M ± SD, %)	65.27 (21.84)	63.39 (17.12)	0.503
Stenotic lumen area (IQR25–75, mm^2)	2.328 (0.919–3.300)	2.224 (1.019–3.060)	0.719
Stenotic outer wall area (M ± SD, mm^2)	13.751 (4.196)	9.269 (3.116)	< 0.001
Stenotic wall area (M ± SD, mm^2)	11.353 (3.704)	7.089 (2.700)	< 0.001
Plaque length (M ± SD, slice number)	4.84 (1.87)	3.25 (1.33)	< 0.001
Remodeling index (M ± SD)	0.975 (0.197)	0.793 (0.231)	< 0.001
Plaque geometry, n (%)			
Eccentric plaque	94 (91.3)	47 (50.5)	
Concentric plaque	9 (8.7)	46 (49.5)	< 0.001

M ± SD, mean ± standard deviation; IQR, interquartile range.

more eccentric plaque and higher remodeling ratio than asymptomatic plaques [5]. In this study, we aimed to explore the value of quantitative measurements on HRMRI in discriminating MCA plaque types.

2. Methods

2.1. Patients

The enrolled patients included two parts: the construction cohort and the validation cohort. The construction cohort was used to construct the symptomatic plaques score (SPS) and the validation cohort was to test the discrimination ability of the SPS.

2.1.1. Patients in the construction cohort

Patients were selected from an ongoing clinical study in which all patients with intracranial artery diseases from January 2007 to December 2015 in Peking Union Medical College Hospital are enrolled for HRMRI [5,6,11–14]. Inclusion criteria for the current analyses were described as following: 1) patients with symptomatic MCA atherosclerotic stenosis (> 50%) on three-dimensional time-of-flight magnetic resonance angiography (3D TOF MRA) [15],which is responsible for an acute ischemic stroke confirmed by diffusion-weighted imaging; 2) patients with asymptomatic MCA atherosclerotic stenosis (> 50%) on 3D TOF MRA, which has no history of ischemic stroke or transient ischemic attack. In addition, if a patient had bilateral asymptomatic MCA atherosclerotic stenosis (> 50%), both stenotic MCA sides were included. All patients included in the study underwent comprehensive clinical and neuroimaging evaluations, including medical history, routine blood test, electrocardiography, echocardiogram, carotid artery ultrasound and conventional cranial MRI and HRMRI of intracranial

Table 2
Firth's penalized logistic regression analysis for the symptomatic plaque score.

	Regression coefficient	95% Confidence interval	Score	*P* value
Stenotic lumen area	1.174	0.336–2.012		0.005
Stenotic lumen area < 2.28 mm^2[a]			1	
Stenotic lumen area ≥ 2.28 mm^2[a]			2	
Stenotic wall area	1.445	0.590–2.301		0.001
Stenotic wall area < 8.88 mm^2[b]			1	
Stenotic wall area ≥ 8.88 mm^2[b]			2	
Plaque length	0.913	0.594–1.231	slices	< 0.001
Plaque eccentricity	2.008	0.922–3.095		< 0.001
Concentric plaque			0	
Eccentric plaque			1	
Intercept	-6.249	−8.189–-4.309		< 0.001

Stenotic lumen area and stenotic wall area are analyzed as dichotomized variables by the median of the construction cohort.
[a] 2.28mm^2 is the median of stenotic lumen area.
[b] 8.88mm^2 is the median of stenotic wall area. Symptomatic plaque score equals to the summation of each score multiplying the corresponding coefficient.

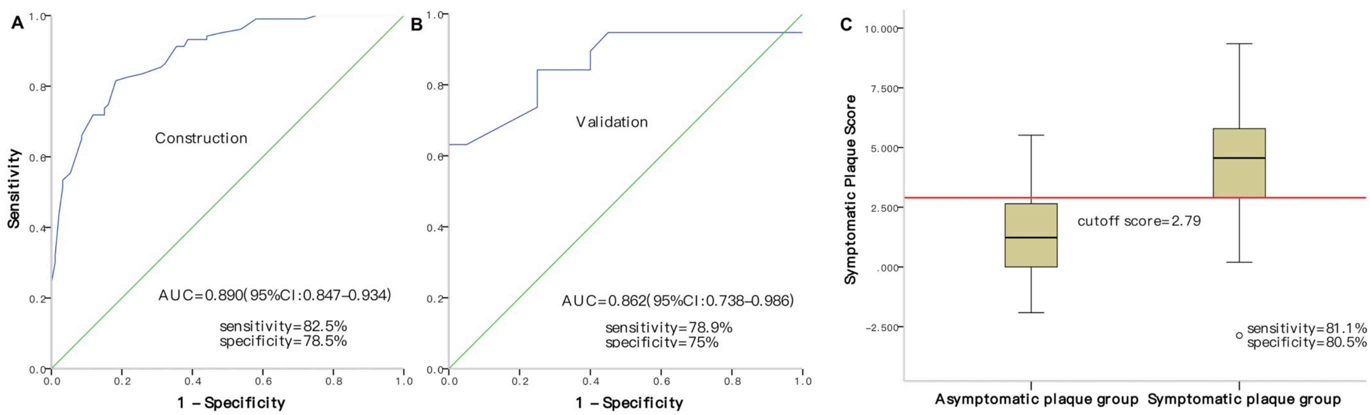

Fig. 2. The receiver operating characteristics analysis for symptomatic plaque score in the construction cohort(A) , validation cohort(B) and the pooled data of all patients(C).

arteries. The exclusion criteria were: (1) patients with coexisting > 50% ipsilateral intracranial or extracranial internal carotid artery stenosis; (2) patients with cardio-embolism diseases, such as atrial fibrillation and recent myocardial infarction within 3 weeks; (3) patients with other diseases which can cause stroke, such as vasculitis, artery dissection and moyamoya disease; (4) patients with poor image quality that cannot delineate the outer wall boundary. Patients screening process were detailed in Fig. 1. All subjects or their relatives signed written informed consent. This study was approved by Peking Union Medical College Hospital Ethics Committee.

2.1.2. Patients in the validation cohort

From January 2016 to January 2017, we prospectively enrolled patients who met the inclusion criteria for symptomatic and asymptomatic MCA stenosis in the validation cohort. The exclusion criteria were the same as that for the construction cohort.

2.2. Neuroimaging protocol

All patients were imaged by a 3-T (T) magnetic resonance scanner (Signa VH/I, GE Medical Systems, from January 2007 to June 2013; GE Discovery MR750, from June 2013 to January 2017) with a standard 8-channel head coil. The imaging protocol in detail was described previously, including conventional T2-weighted imaging, diffusion weighted imaging, 3D TOF MRA, and T2-weighted HRMRI of the MCA [11,12]. T2-weighted HRMRI was obtained on the stenotic side of the MCA shown on 3D TOF MRA. Cross-section images were perpendicular to the stenotic M1 segment of the MCA by 3D MRA localizer (choosing maximum intensity projection images and sources images of 3D TOF MRA as topogram). Imaging parameters for T2-weighted HRMRI were described as follows: TR/TE = 3000/50 ms; FOV, 13 cm × 13 cm; matrix size, 256 × 256; slice thickness, 2 mm; slice gap, 0.5 mm; 4 signal averages, echo train length (ETL) 22. Briefly, the final display resolution was 0.25 × 0.25 × 2 mm.

2.3. Quantitative measurements of MCA atherosclerosis on HRMRI

Quantitative measurements of M1 segment of the stenotic MCA was performed on T2-weighted HRMRI sequence. We manually measured lumen area and outer wall area at the maximal stenotic site and reference site of the M1 segment of MCA. Wall area was calculated as outer wall area minus lumen area [5]. The MCA stenotic degree measured on HRMRI was calculated by the following formula [5]: MCA stenotic degree = (1 − stenotic lumen area/reference lumen area) × 100%. The reference site was defined using the MCA segment of normal appearance proximal to the stenotic segment. If a proximal reference site was not available, the neighboring distal site was used instead [5]. The remodeling index of MCA was calculated by dividing the outer wall area at the maximal stenotic site to that at the reference site [5]. A lesion was defined as an eccentric plaque if the minimum wall thickness was smaller than half of the maximum wall thickness at the maximal stenotic site, and as a concentric plaque if the minimum wall thickness was larger than half of the maximum wall thickness at the maximal stenotic site [16]. We counted the total number of images of eccentric or concentric plaque as the plaque length.

Image analysis was performed on a software (Osirix MD, v.9.02). All images were reviewed by two experienced readers (YM and YNY) who were blinded to clinical details and diffusion weighted imaging. The differences between two observers were solved by consensus.

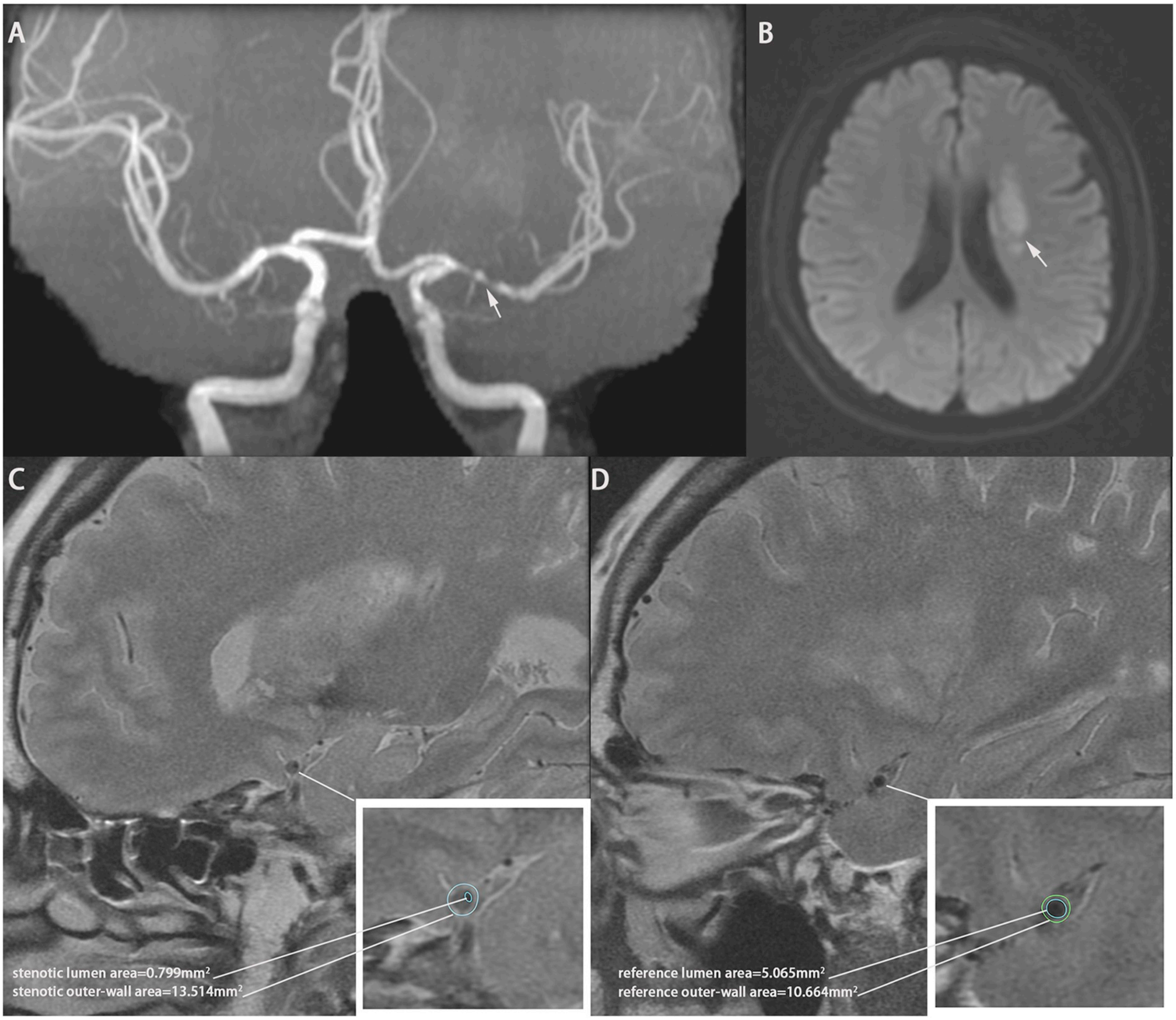

Fig. 3. An example of the quantitative measurements of an eccentric symptomatic plaque. A 61 years old man with left MCA stenosis(A) had an acute cerebral infarction on diffusion weighted imaging(B). (C) and (D) show the quantitative measurements of the symptomatic eccentric plaque at the maximal stenotic site(C) and the reference site(D) on high-resolution T2-weighted imaging sequence, respectively. Plaque length = 5 slices. SPS = 4.388(> 2.79)indicates a symptomatic plaque.

2.4. Statistical analysis

We used statistical package for the social sciences (SPSS 23) and statistical analysis system (SAS 9.4) to conduct statistical analysis. For continuous and category variables, intra-class correlation coefficient and Cohen's κ coefficient were used to assess intra-reader and inter-reader agreement respectively. We compared clinical, HRMRI features of symptomatic and asymptomatic plaques using χ^2 test , student-*t*-test , Mann-Whitney *U* test as appropriate. Multivariate Firth's penalized likelihood logistic regression with stepwise selection method was used to constitute the symptomatic plaque score (SPS) model, because the proportion of concentric plaques of symptomatic plaques group was only 8.7% ($n = 9$) [17].Independent variables reaching significance at the $P < 0.05$ level on univariate logistic analysis entered the multivariate logistic analysis. Based on the results of previous study [18], stenotic lumen area and stenotic wall area were directly entered the multivariate logistic analysis and analyzed as dichotomous variables categorizing by the median of the construction cohort. Variance inflation factor was used to perform multicollinearity diagnosis between independent variables. To assess model fit and performance, Hosmer-Lemeshow goodness of fit test and receiver operating characteristics (ROC) analysis were examined [19].

Following construction of the SPS, the diagnostic equation was applied to the validation cohort. Each score was initially calculated on HRMRI with the observer blinded to the clinical features, until the ROC curve was calculated. To increase precision, we calculated cutoff score for discriminating plaque types in the combined construction and validation cohorts.

3. Results

3.1. Patient demographics

From January 2007 to December 2015, a total of 103 symptomatic plaques and 93 asymptomatic plaques were analyzed in the construction cohort. Patients screening process were detailed in Fig. 1. Patients with symptomatic plaques were older ($p < 0.001$) and more likely to be male ($p = 0.043$) than patients with asymptomatic plaques (Supplement Table 1, online only). From January 2016 to January 2017, 39 patients, including 19 symptomatic and 20 asymptomatic plaques, were prospectively independently enrolled in the validation cohort.

3.2. Symptomatic and asymptomatic plaque features on HRMRI

The intra-reader and inter-reader agreement for quantitative measurements parameters were good (Supplement Table 2, online only). MCA stenotic degree and stenotic lumen area were similar between

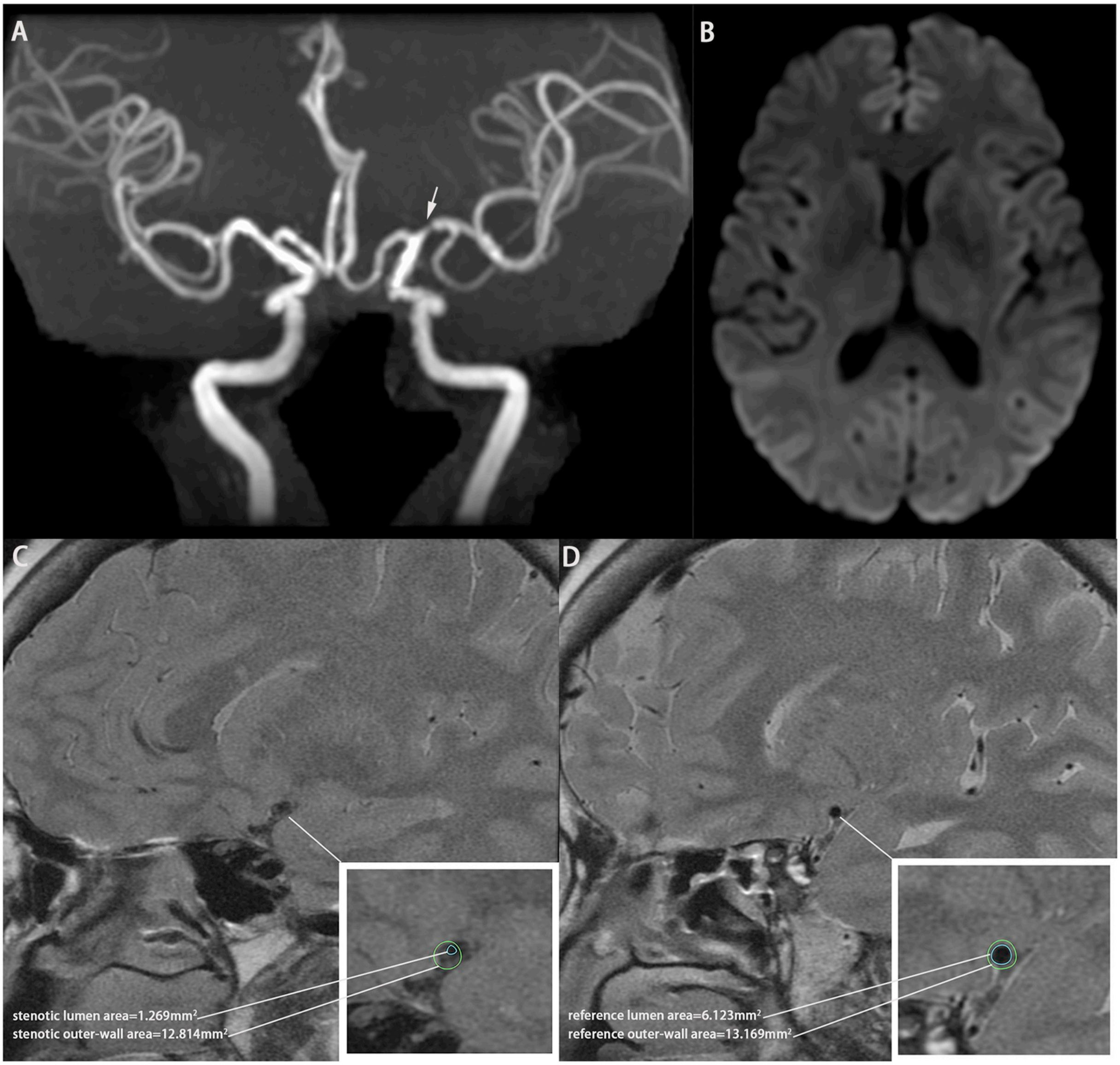

Fig. 4. An example of the quantitative measurements of an eccentric asymptomatic plaque. A 60 years old woman with hypertension, diabetes mellitus and hyperlipidemia had left MCA stenosis(A) and did not have a lesion on diffusion weighted imaging(B). (C) and (D) show the quantitative measurements of the asymptomatic eccentric plaque at the maximal stenotic site(C) and the reference site(D) on high-resolution T2-weighted imaging sequence, respectively. Plaque length = 3 slices. SPS = 2.562(< 2.79)indicates an asymptomatic plaque.

symptomatic and asymptomatic plaques. Total plaque length ($p < 0.001$) was greater in symptomatic plaques than in asymptomatic plaques, combined with a greater stenotic wall area ($p < 0.001$) and stenotic outer-wall area ($p < 0.001$). Furthermore, symptomatic plaques exhibited a greater remodeling index ($p < 0.001$). Among 103 symptomatic plaques, 94 (91.3%) were eccentric plaques, the remaining 9 (8.7%) were concentric plaques. In 93 asymptomatic plaques, 47 (50.5%) were eccentric plaques, 46 (49.5%) were concentric plaques. Eeccentric plaques occurred more frequently in symptomatic plaques than in asymptomatic plaques ($p < 0.001$) (Table 1).

3.3. Construction and validation of the symptomatic plaque score (SPS)

Table 2 showed Firth's penalized logistic regression analysis prediction model for symptomatic plaque score (SPS). SPS was equal to the summation of each score multiplying the corresponding coefficient and was calculated by the regression equation as follows: SPS = 1.174 × Stenotic lumen area(1 score for < 2.28mm^2, 2 score for ≥2.28mm^2) + 1.445 × Stenotic wall area(1 score for < 8.88mm^2, 2 score for ≥8.88mm^2) + 0.913 × Plaque length + 2.008 × Plaque eccentricity (1 score for eccentric plaques, 0 score for concentric plaques) −6.249.

The variance inflation factor values (stenotic lumen area 1.116, stenotic wall area 1.485, plaque length 1.142, plaque eccentricity1.456) showed no evidence of multicollinearity between independent variables. Hosmer-Lemeshow goodness of fit test showed no evidence of poor calibration both in the construction cohort ($p = 0.819$) and validation cohort ($p = 0.353$).

The construction cohort showed a strong discriminatory power for plaque types with an AUC = 0.890 (95%CI: 0.847–0.934, Fig. 2A). SPS maintained a good predictive ability for symptomatic plaques with an AUC = 0.862 (95%CI: 0.738–0.986, Fig. 2B) in the validation cohort. When the data were pooled in all patients (construction cohort = 196 plaques, validation cohort = 39 plaques), the optimal cutoff score of discriminating symptomatic and asymptomatic plaques was 2.79 with sensitivity = 81.1%, specificity = 80.5%, AUC = 0.886 (95%CI:0.845–0.927, Fig. 2C). SPS ≥ 2.79 was more typical of a symptomatic plaque and SPS < 2.79 was more likely to represent an asymptomatic plaque. In addition, we compared model performance between the SPS model

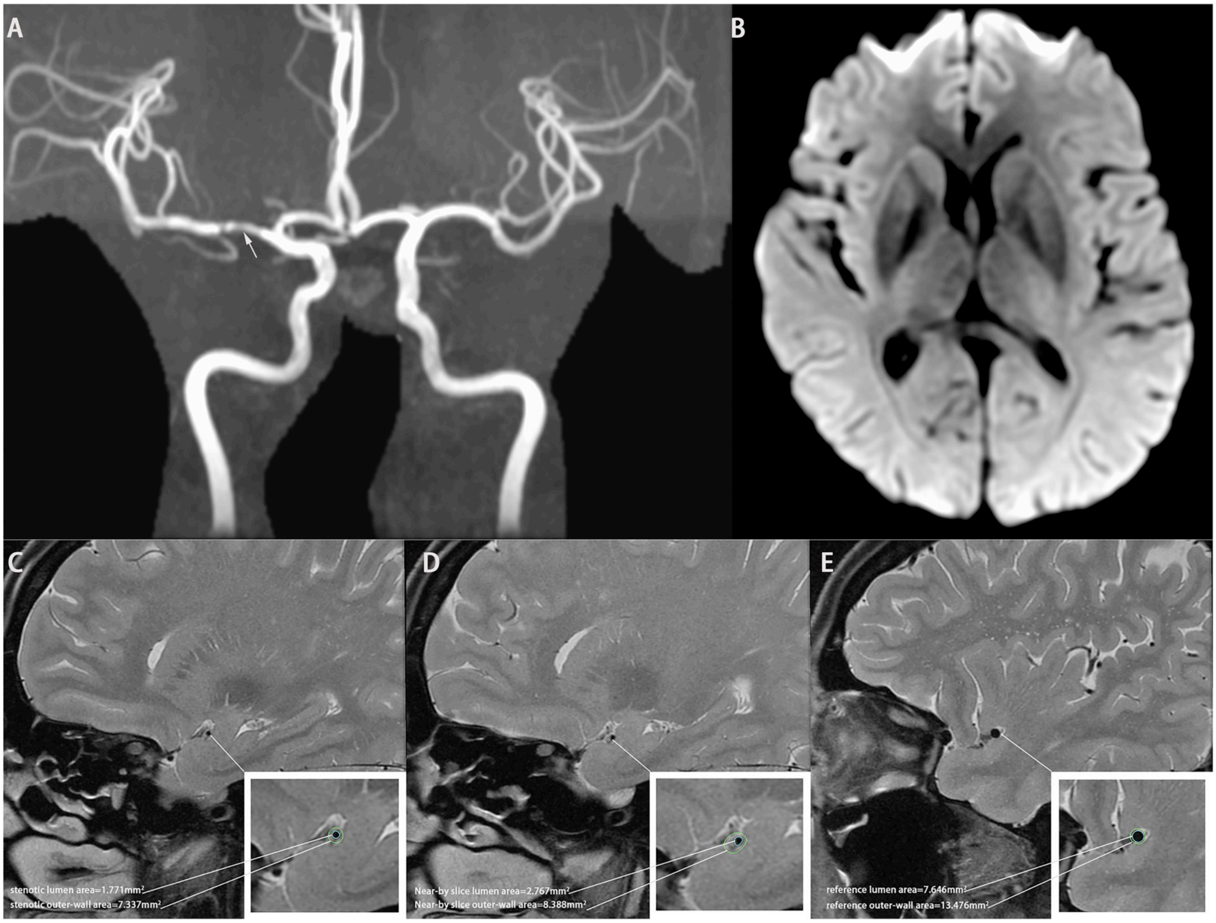

Fig. 5. An example of the quantitative measurements of a concentric asymptomatic plaque. A 51 years old woman with hypertension and hyperlipidemia had right MCA stenosis(A) without history of cerebrovascular disease. (B), (C) and (D) are three slices. Quantitative measurements were performed at the maximal stenotic site (B, concentric wall thickening) and the reference site(D) on high-resolution T2-weighted imaging, respectively. Plaque length = 4 slices. SPS = 0.022 (< 2.79) indicates an asymptomatic plaque.

and the SPS model with age and gender parameters. The AUC for SPS model and SPS model with age and gender parameters were 0.892 (95%CI: 0.852–0.932) and 0.886(95%CI:0.845–0.927) respectively. The inclusion of age and gender in the model did not change model performance significantly ($p = 0.294$).

Figs. 3–5 show examples of the application of SPS in patients with an eccentric symptomatic plaque (Fig. 3), with an eccentric asymptomatic plaque (Fig. 4) and with a concentric asymptomatic plaque (Fig. 5).

4. Discussion

In this study, quantitative measurements of symptomatic and asymptomatic MCA atherosclerosis were performed on HRMRI. Using logistic regression, four vessel morphological features were combined as an integrated score -SPS to identify plaque types. Discrimination accuracy of SPS was highly satisfying, suggesting its close association with the underlying pathophysiology.

Four plaque morphological parameters of SPS, including stenotic lumen area, stenotic wall area, plaque eccentricity and plaque length, have been shown to mainly represent plaque burden and vulnerability in coronary artery, carotid artery and MCA studies. Using intravascular ultrasound, coronary plaques associated with future acute coronary syndrome are observed to exhibit more eccentric pattern and greater plaque area than plaques without future acute events [20]. In a HRMRI study of MCA atherosclerosis, plaque burden, represented by normalized wall index (a ratio of stenotic wall area to stenotic outer wall area), is closely associated with stroke severity [21]. Moreover, both normalized wall index and minimal lumen area are proposed as better indicators than stenosis degree in differentiating culprit and non-culprit MCA lesions [18]. Plaque length is viewed as another important plaque burden parameter at longitudinal level. In a study of 414 patients with symptomatic carotid stenosis, longer stenosis length is associated with increased risk of peri-procedural stroke or death after both endovascular treatment and carotid endartectomy, and with increased long-term risk of restenosis after endovascular treatment [22].

It was observed that stenotic lumen area ≥ 2.28 mm^2 was significantly associated with increased risk of ischemic stroke in patients with > 50% MCA stenosis. It may seem counterintuitive because previous cohort studies highlight the higher stroke recurrence in patients with higher stenosis degree [23,24]. There are some possibilities to explain this in-consistency. Firstly, most previous studies only included patients with symptomatic intracranial stenosis [23] , while our study included both patients with symptomatic and asymptomatic MCA stenosis. Secondly , atherosclerotic luminal narrowing is caused by the combined effects of plaque burden and arterial remodeling [25]. Artery positive remodeling is associated with unstable clinical presentations, whereas negative remodeling is more common in patients with stable clinical presentations [26].Therefore , symptomatic MCA stenosis can present with relatively large lumen area with positive remodeling [27].

Our study suffered from several limitations. Firstly, considering the dynamic changes of atherosclerotic plaques [28] which are in influenced by treatments, patients with old infarction in the MCA distribution are not included in the study. This may lead to a bias. Secondly, we used two-dimensional T2-weighted HRMRI with relatively high in-plane resolution (0.25 mm × 0.25 mm) to perform quantitative measurements. Comparing two-dimensional T1-weighted and T2-weighted HRMRI, we find that T2-weighted HRMRI has a short imaging time and relatively high signal to noise ratio, which is beneficial to the quantitative measurements of plaques [5]. However, two-dimensional images have low spatial resolution due to large slice thickness [29]. Thirdly, the SPS model is based solely on current data and large sample size studies are needed to validate it in the future.

Nevertheless, our findings have potential clinical value. Firstly, the goal of anti-atherosclerosis therapy is to improve plaque stability. It is reasonable to assume that the morphological transformation from symptomatic plaques to asymptomatic plaques may represent an improvement of plaque stability. SPS score has the potential to be used as a marker to monitor the effects of therapy. Secondly, in practice, it is important to predict the outcome in an individual patient with MCA stenosis. Because SPS shows a close association with the clinical presentations of MCA plaques, it may have a value in evaluating the vulnerability of MCA plaques once confirmed by large prospective studies.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.02.025.

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