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Baseline vessel wall magnetic resonance imaging characteristics associated with in-stent restenosis for intracranial atherosclerotic stenosis

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ABSTRACT

Background Imaging factors, specifically baseline plaque features on high-resolution magnetic resonance vessel wall imaging (HR-VWI) that could be associated with in-stent restenosis (ISR), are still unknown. We aimed to investigate the presenting clinical and plaque features on HR-VWI associated with ISR.

Methods Sixty-four patients with intracranial stent placement for intracranial atherosclerotic stenosis who had pre- and post-contrast T1-weighted HR-VWI on 3.0T prior to stenting were included in this analysis. Student's t-test, Mann–Whitney U test, $\chi 2$ test, or the Cochran–Mantel–Haenszel (CMH) test were used to compare clinical and baseline HR-VWI characteristics of the patients between the ISR and non-ISR groups. Univariable and multivariable logistic analysis were used to test the clinical and imaging factors associated with ISR.

Results Among the 64 patients, 9 patients (14.06%) developed ISR during the 2-year follow-up period. Plaque burden (median 0.89 vs 0.92, P=0.04), minimum lumen area (0.009 cm^2 vs 0.006 cm^2, P=0.04), plaque eccentricity (55.6% vs 89.1%, P < 0.01), enhancement ratio (1.36 vs 0.84, P < 0.01), and enhancement involvement (type 2 represents ≥50% cross-sectional wall involvement; 100% vs 63.6%, P=0.03) all significantly differed between patients with and without ISR. Multivariable analysis revealed that lower frequency of plaque eccentricity (OR 0.18, 95% CI 0.04 to 0.96, P=0.04) and higher enhancement ratio (OR 3.57, 95% CI 1.02 to 12.48, P=0.04) were independently associated with ISR.

Conclusions Preliminary findings showed that ISR was independently associated with plaque concentricity and higher enhancement ratios on pre-stenting HR-VWI for patients with symptomatic intracranial atherosclerotic stenosis.

INTRODUCTION

Intracranial atherosclerosis is one of the most common etiologies of ischemic stroke.[1] For patients who are refractory to aggressive medical management, stent placement can reduce the stroke recurrence rate.[2–4] However, about 5%–30% of stented patients experience in-stent restenosis (ISR), which is an important risk factor for long-term stroke recurrence.[5] A previous study showed that compared with patients without ISR, patients with ISR had nearly three times higher risk of recurrent ischemic events (HR 2.79).[6]

Several clinical risk factors have been reported to be associated with pronounced ISR including younger patient age, vertebrobasilar junction location, and residual stenosis post-stent placement.[7] High-resolution magnetic resonance vessel wall imaging (HR-VWI) can image beyond the lumen to visualize high-risk plaque features including plaque burden, intraplaque hemorrhage, contrast enhancement, and other plaque characteristics, which are associated with ischemic stroke.[8 9] To our knowledge, whether plaque features can be used in predicting ISR has not been established. The hypothesis of this study was that clinical factors and plaque features on HR-VWI can predict ISR development in stroke/transient ischemic attack (TIA) patients who undergo intracranial stenting.

METHODS

Patients

This was a retrospective study of a prospectively maintained patient database. The study protocol was approved by the local institutional review board with all patients providing written informed consent.

Between July 2011 and October 2020, patients with atherosclerotic intracranial artery stenosis who underwent intracranial stenting were recruited for this study. The indications for stenting included: (1) patients with symptomatic intracranial atherosclerotic stenosis ≥70%; (2) no response after 4–6 weeks of intensive medical therapy; and (3) tissue hypoperfusion downstream from the target arterial segment. Inclusion criteria were: (1) underwent pre-stenting HR-VWI including both pre- and post-contrast T1WI sequences; (2) ≤3-day interval between pre-stenting HR-VWI and stenting; (3) sufficient image quality of HR-VWI for evaluation; (4) regular post-stenting imaging follow-up at around 3, 6, 12, 18, and 24 months, including computed tomography angiography (CTA), contrast enhancement-magnetic resonance angiography (CE-MRA), and/or HR-VWI; (5) ischemic stroke or transient TIA before stenting; and (6) at least one risk factor for atherosclerosis at baseline evaluation. Exclusion criteria were: (1) clinical evidence of non-atherosclerotic intracranial arterial disease, including inflammatory arteritis, Moyamoya vasculopathy, reversible vasospastic process, recent

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(1-year) history of subarachnoid hemorrhage, cranial radiation therapy, head trauma, or dissection; (2) previous stenting in the target artery before HR-VWI; (3) insufficient image quality due to motion or other artifact degradation, or low signal-to-noise ratio; and (4) no post-contrast HR-VWI included. Patients were included if they met the inclusion/exclusion criteria.

Stenosis was measured and calculated according to the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) method as (1–Dstenosis/Dnormal) × 100%.[10] From a prospectively maintained database, the baseline clinical and imaging data of all the patients that met the inclusion/exclusion criteria were retrospectively analyzed. Clinical data including sex, age, hypertension, diabetes, hyperlipidemia, current smoking status, and pre-stenting symptoms were recorded. The stent was placed at the location of maximal stenosis. Stenosis pre-stenting, the stent type (Wingspan or Enterprise), and the location of stent placement were all recorded.

If stenosis greater than 30% was identified on follow-up CE-MRA or CTA, digital subtraction angiogram (DSA) was then performed to confirm whether the patient had ISR. ISR was defined as >50% stenosis within or immediately adjacent (within 5 mm) of the implanted stent.[7] Symptomatic ISR was defined as the presence of ISR with new ischemic stroke or TIA. The degree of stenosis and the presence of ISR were identified on DSA by three radiologists (BT, XT, and QK, with 12, 9 and 9 years of experience in neuroradiology, respectively), blinded to the patient's clinical information.

MRI protocol

All patients were scanned on a 3.0T whole-body MRI system (HDx; GE Healthcare, Waukesha, WI, USA or Skyra, Siemens Healthineers, Erlangen, Germany). Diffusion-weighted images (DWI) were acquired for the identification of acute ischemic infracts and 3D time-of-flight (TOF) magnetic resonance angiography (MRA) was performed for identifying the location of stenosis.

The HDx system used an eight-channel phased array brain coil. Based on the MRA, the HR-VWI scan plane was angled to be perpendicular to the plane of the diseased arterial segment. Black blood 2D fast spin-echo (FSE) T1-weighted (T1WI) pre-contrast and post-contrast (CE-T1) were acquired with the following parameters: TR/TE=581/20 ms, FOV=10×10 cm^2, NEX=4, matrix=320×256, ETL=6, slice thickness=2 mm, gap=0.5 mm, slices=12, and sequence duration=5 min. Gadopentetate dimeglumine (Beilu Pharmaceutical, Beijing, China) contrast agent was injected intravenously at a dose of 0.2 mmol/kg and a flow rate of 2 mL/s followed by 15 mL of saline solution immediately prior to post-contrast imaging.

The Skyra system used a 20-channel head/neck coil. 3D T1WI FSE HR-VWI was acquired in the sagittal plane with a spatially nonselective excitation including pre-contrast and post-contrast with the following parameters: 0.6 mm isotropic resolution, 180×180 mm FOV, 360×360 matrix, 240 slices, echo train length 60, TR/TE=900/5.6 ms, 5/8 partial Fourier in the slice direction, generalized autocalibrating partial parallel acquisiton (GRAPPA) factor 2 in the phase-encoding direction, and scan time 7 min. The same 3D HR-VWI sequence was repeated immediately after intravenous administration of gadopentetate dimeglumine at a dose of 0.2 mmol/kg and a flow rate of 2 mL/s followed by 15 mL of saline solution.

HR-VWI image analysis

Lumen and outer wall boundaries were manually segmented in each MR image in which plaque was present using VesselMass (Leiden University Medical Center, Leiden, The Netherlands).[11] All images were measured independently by three experienced radiologists who were blinded to patient identifiers and clinical data. The raters measured plaque characteristics, including the minimum lumen area, plaque burden, and enhancement ratio.

The minimum lumen area was measured in square centimeters (cm^2). Plaque burden was measured at the maximal stenosis site and was defined as (1–(lumen area/total wall area)) × 100%. The contrast enhancement ratio was measured at the slice of greatest enhancement, using adjacent gray matter (in a region of ~15 mm^2) to normalize signal intensity. The contrast enhancement ratio was calculated as (((signal of plaque (post-contrast)/signal of gray matter (post-contrast))/(signal of plaque (pre-contrast)/signal of gray matter (pre-contrast)))−1 × 100%. The enhancement involvement was also visually categorized as type 1 (<50% cross-sectional wall involvement) or type 2 (≥50% cross-sectional wall involvement).[12]

The presence of intraplaque hemorrhage (IPH) was defined as >150% signal relative to nearby medial pterygoid muscles on pre-contrast T1WI.[13] Plaque eccentricity was defined as a localized plaque surrounding less than 75% of the vessel wall or its thickest part was more than twice the thinnest part.[14] If a plaque involved 100% of the vessel wall but the thickest portion was twice as thick as the thinnest portion, the plaque was classified as an eccentric plaque.

Statistical analysis

All analyses were performed using MedCalc software (Version 20.009). Clinical and imaging characteristics of the patients were compared between the ISR and non-ISR groups. Quantitative data with a normal distribution were analyzed and compared between groups using a t-test. Otherwise, the data were analyzed using the Mann–Whitney U test. The enumerated data were analyzed using the $\chi 2$ test or the Cochran–Mantel–Haenszel (CMH) test. Inter-reader agreement was determined using the interclass correlation coefficient (ICC) for ISR and the HR-VWI parameters among three readers.

A univariable analysis of all the clinical and imaging factors was performed with a value of $P<0.15$. Variables with $P<0.15$ in univariate analysis were considered as candidates for the stepwise logistic regression analysis in which the entry level probability was set at 0.05 and the removal level at 0.1. Multivariable logistic analysis was used to test the clinical and imaging factors associated with ISR, with non-ISR as the reference. The diagnostic performance was described using receiver operating characteristic (ROC) curves and area under curve (AUC) values. ROC curves were compared using the method developed by DeLong *et al*.[15] Youden's J-statistics were used to calculate the optimal sensitivity, specificity, and accuracy for predicting ISR.

RESULTS

Between January 2011 and December 2020, a total of 80 patients with symptomatic intracranial artery atherosclerotic stenosis who underwent pre-stenting HR-VWI and intracranial stenting were eligible for our study based on the inclusion criteria. Fourteen patients were excluded due to too long an interval between HR-VWI and stenting. Two patients were excluded because of poor image quality. Sixty-four patients (60 stroke and 4 TIA patients) were included in this analysis, and 57 patients had improvement of clinical symptoms after stenting. The median patient age was 58 (IQR 51–65) years and 46 patients (71.9%) were men. Forty-three patients were scanned on a GE HDx scanner and 21 patients were scanned on the Siemens Skyrra system. Wingspan stents were placed in

19 patients (29.7%), while an Enterprise stent was placed in 45 patients (70.3%) (online supplemental figure S1). The location of the stenosis/stenting included middle cerebral artery (MCA) (53 patients) for anterior circulation and basilar artery (BA) (11 patients) for posterior circulation. Residual stenosis was present in 18 patients, and the average degree of residual stenosis was 10%±12% for all patients.

Among the 64 patients, 9 patients (14.06%) had ISR, and 3 patients (4.68%) had symptomatic ISR (with recurrent stroke). The average interval from stenting to ISR was 7.1 (range 4–17) months, and the average follow-up interval for patients without ISR was 19.2 (range 11–25) months. Baseline clinical and imaging characteristics of patients with and without ISR can be found in online supplemental table S1. There was no significant difference between patients with and without ISR for all clinical baseline characteristics. Plaque burden (median 0.89 vs 0.92, P=0.04), minimum lumen area (0.009 cm^2 vs 0.006 cm^2, P=0.04), plaque eccentricity (55.6% vs 89.1%, P < 0.01), enhancement ratio (1.36 vs 0.84, P < 0.01), and enhancement involvement (type 2 represents ≥50% cross-sectional wall involvement; 100% vs 63.6%, P=0.03) all significantly differed between patients with and without ISR (online supplemental figures S2 and S3).

Agreement among the three readers was excellent for measurements of ISR, acute infarct, residual stenosis, IPH, plaque eccentricity, enhancement involvement, minimum lumen area, plaque burden, and enhancement (ICC ranged from 0.9085 to 0.9588, details in online supplemental table S2).

The results of the multivariable logistic analysis revealed that only lower frequency of plaque eccentricity (odds ratio (OR) 0.18, 95% confidence interval (CI) 0.04–0.96, P=0.04) and higher enhancement ratio (OR 3.57, 95%CI 1.02 to 12.48, P=0.04) were significantly associated with ISR (table 1). The AUCs were 0.668 (95% CI 0.539 to 0.780) and 0.787 (95% CI 0.667 to 0.879), respectively. When combined, the AUC increased to 0.802 (95% CI 0.684 to 0.891) with optimal accuracy, sensitivity, and specificity being 0.875, 0.778, 0.764, and 0.653, respectively (figure 1).

Table 1 Univariable and multivariable effect of baseline factors on in-stent restenosis

	Univariable analysis		Multivariable analysis	
Factor	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Clinical				
Median age	0.99 (0.93 to 1.06)	0.71		
Male	0.43 (0.10 to 1.82)	0.26		
Hypertension	0.71 (0.17 to 2.97)	0.64		
Hyperlipidemia	0.64 (0.12 to 3.40)	0.60		
Diabetes	1.79 (0.43 to 7.50)	0.43		
Smoking	0.84 (0.16 to 4.51)	0.84		
Pre-stenting symptoms		0.26		
Stroke	NA			
TIA	Reference			
Stenting				
Stenosis pre-stenting	8.23 (0.00 to 16.92)	0.78		
Stent location-anterior	1.46 (0.26 to 8.21)	0.67		
Stent type		0.80		
Wingspan	Reference			
Enterprise	0.82 (0.18 to 3.69)			
Residual stenosis	0.19 (0.00 to 104.26)	0.61		
Imaging				
Acute infarct	0.45 (0.10 to 1.98)	0.28		
IPH	2.20 (0.47 to 10.33)	0.33		
Plaque burden	0.00 (0.00 to 4.44)	0.10*		
Minimum lumen area	2.09 (0.02 to 188.74)	0.07*		
Plaque eccentricity	0.15 (0.03 to 0.73)	0.02*	0.18 (0.04 to 0.96)	0.04*
Enhancement ratio	4.01 (1.19 to 13.47)	0.02*	3.57 (1.02 to 12.48)	0.04*
Enhancement involvement		0.01*		
Type 1 (<50% area)	Reference			
Type 2 (≥50% area)	NA			

*P < 0.05.
CI, confidence interval; IPH, intraplaque hemorrhage; ISR, in-stent restenosis; NA, not applicable; OR, odds ratio; TIA, transient ischemic attack.

DISCUSSION

In this retrospective observational cohort study, we found that both a lower frequency of plaque eccentricity and a higher enhancement ratio were independent predictors of ISR in patients with stroke/TIA who had intracranial stenting. To the best of our knowledge, this is the first study investigating intracranial plaque features associated with ISR. If validated in future larger-scale studies, pre-contrast HR-VWI of plaque characteristics could be a potential tool for identifying patients at elevated risk of ISR.

Given that patients with ISR have much higher risk of stroke recurrence, prospectively identifying those patients who will develop ISR potentially has great clinical value.[5 6] Our preliminary results showed plaque features on HR-VWI had excellent prognostic value for ISR with AUC values >0.8. We did not find any significant differences for traditional factors between the ISR and non-ISR groups, which may in part be due to the small sample size. With further validation of these findings, closer imaging monitoring and more aggressive medical treatment may reduce ISR rate and improve outcome in patients with concentric plaque that have high enhancement ratio.

Intracranial plaque enhancement on HR-VWI may be associated with neovascularization, inflammation, and endothelial dysfunction leading to leakage of gadolinium.[16] Plaque enhancement was also found to be an independent risk factor of posterior ischemic events in patients with BA stenosis >50%.[17] Previous longitudinal studies found that plaque enhancement or changes in plaque enhancement characteristics during follow-up predicted stroke recurrence.[18] One possible explanation for our findings that increased plaque enhancement predicted ISR is that more active inflammation in the plaque persisted after stent placement, promoting subsequent plaque progression.

Plaque eccentricity has been recognized as a factor associated with intracranial plaque vulnerability but the results are mixed. Dieleman *et al* found symptomatic lesions showed both eccentric and concentric patterns, but asymptomatic lesions were frequently eccentric[19] However, a separate study indicated that eccentric morphology was associated with normal lumen preservation and improved blood supply to the distal vascular territory.[20] In our study, concentric plaque morphology had a higher risk of ISR than eccentric plaque. The mechanism of concentric plaque resulting in ISR needs to be addressed in future studies, but one possible explanation could be that in that setting biomechanical forces on the stent could more circumferentially uniform, inhibiting plaque expansion.

The rate of ISR in our analysis was similar with a systematic review and meta-analysis by Peng *et al*, which had a 14.8% ISR rate.[7] The SAMMPRIS Trial, a prospective randomized controlled

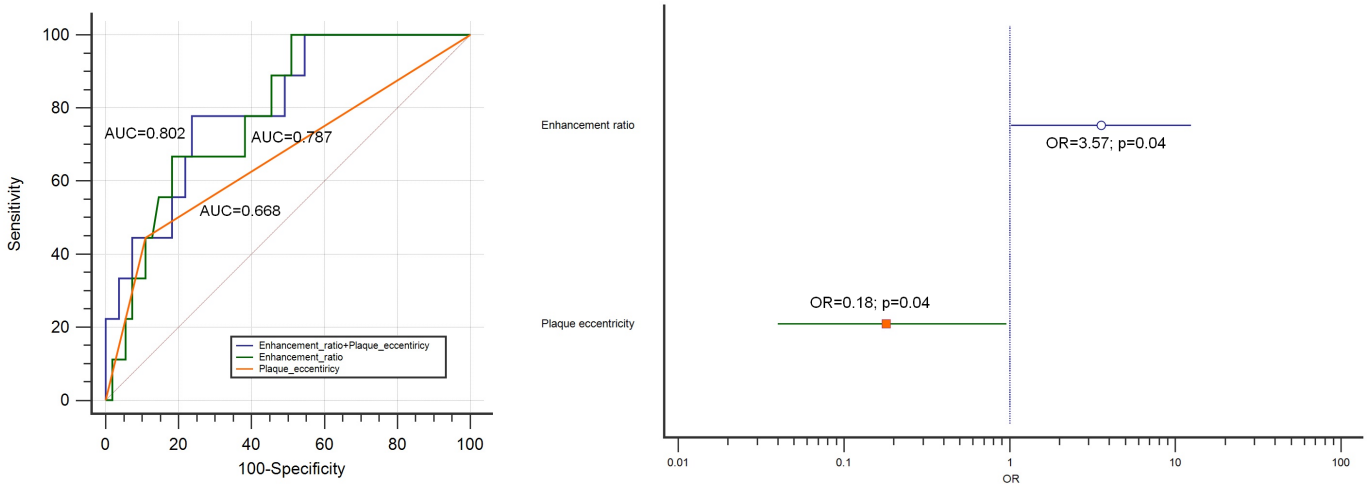

Figure 1 Receiver operating characteristic (ROC) curves, odds ratios (OR), and 95% confidence intervals based on multivariable logistic regression to predict in-stent restenosis. AUC, area under curve.

trial whose subgroup analysis of symptomatic ISR included 183 patients, had an imaging follow-up rate of 60%. The 1-, 2-, and 3-year rates for symptomatic ISR in the SAMMPRIS stent cohort were 9.6%, 11.3%, and 14.0%, respectively.[21] In our analysis, 3 patients (4.68%) had symptomatic ISR within 2 years, which was much lower than what was seen in the SAMMPRIS Trial. One potential reason for the contrasting symptomatic ISR incidence is racial differences in the cohorts. Another reason may be that only 29.7% (19/64) of patients had Wingspan stents placed in our study, with a majority receiving Enterprise stents. However, all patients were placed with Wingspan stent in the SAMMPRIS Trial. Several studies have reported that the Enterprise stent yielded a relatively lower ISR rate than with the Wingspan stent.[22] In our analysis, however, there was no difference in ISR between the Wingspan and Enterprise stents.

There are several limitations of this study. First, the number of patients included in our study was limited. Only 9 patients had ISR and 3 patients had symptomatic ISR, which limited the power of the statistical results. Besides, this was a retrospective analysis, and only patients who underwent HR-VWI were included in our analysis which introduced bias in patient selection. For this reason, only ISR was described in our analysis. Further validation of these results in larger prospective, multicenter trials could strengthen the clinical implications of our preliminary results. Second, 2D and 3D HR-VWI were both used in this study and have different resolution and imaging approaches. Spatial resolution may impact the ability to characterize plaque characteristics. However, these issues were mitigated by ensuring that 2D HR-VWI was only performed in a plane perpendicular to the targeted atherosclerotic plaque, thus reducing volume averaging and wall thickness overestimation.

CONCLUSIONS

Preliminary findings show that ISR was independently associated with plaque concentricity and higher enhancement ratios on pre-stenting HR-VWI for patients with symptomatic intracranial atherosclerotic stenosis. Future larger-sample studies evaluating plaque enhancement and morphology as a predictive marker for ISR and symptomatic ISR could validate these findings and create a prospective pre-stenting biomarker for ISR.

Contributors BT: study concepts, study design, quality control of data and algorithms, data analysis and interpretation, statistical analysis, manuscript preparation, manuscript review. CZ: study concepts, study design, quality control of data and algorithms, statistical analysis , manuscript editing. XT: quality control of data and algorithms, data analysis and interpretation. QK: quality control of data and algorithms, data analysis and interpretation. CS: study design, manuscript review. MM-B: manuscript editing. JL: study design, manuscript review, guarantor of the study. DS: study design, manuscript editing.

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Data availability statement Data are available upon reasonable request.

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