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Characteristics of intracranial plaque in patients with non-cardioembolic stroke and intracranial large vessel occlusion

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ABSTRACT

Objective To determine the characteristics of intracranial plaque proximal to large vessel occlusion (LVO) in stroke patients without major-risk cardioembolic source using 3.0 T high-resolution MRI (HR-MRI).

Methods We retrospectively enrolled eligible patients from January 2015 to July 2021. The multidimensional parameters of plaque such as remodelling index (RI), plaque burden (PB), percentage lipid-rich necrotic core (%LRNC), presence of discontinuity of plaque surface (DPS), fibrous cap rupture, intraplaque haemorrhage and complicated plaque were evaluated by HR-MRI.

Results Among 279 stroke patients, intracranial plaque proximal to LVO was more prevalent in the ipsilateral versus contralateral side to stroke (75.6% vs 58.8%, p<0.001). The larger PB (p<0.001), RI (p<0.001) and %LRNC (p=0.001), the higher prevalence of DPS (61.1% vs 50.6%, p=0.041) and complicated plaque (63.0% vs 50.6%, p=0.016) were observed in the plaque ipsilateral versus contralateral to stroke. Logistic analysis showed that RI and PB were positively associated with an ischaemic stroke (RI: crude OR: 1.303, 95% CI 1.072 to 1.584, p=0.008; PB: crude OR: 1.677, 95% CI 1.381 to 2.037, p<0.001). In subgroup with <50% stenotic plaque, the greater PB, RI, %LRNC and the presence of complicated plaque were more closely related to stroke, which was not evident in subgroup with ≥50% stenotic plaque.

Conclusion This is the first study to report the characteristics of intracranial plaque proximal to LVO in non-cardioembolic stroke. It provides potential evidence to support different aetiological roles of <50% stenotic vs ≥50% stenotic intracranial plaque in this population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The characteristics of intracranial plaque proximal to large vessel occlusion (LVO) in stroke patients without major-risk cardioembolic source are not clear.
⇒ Unravelling the plaque characteristics will be helpful to understand the aetiology of LVO stroke.

WHAT THIS STUDY ADDS

⇒ Intracranial plaque proximal to LVO was more prevalent in the ipsilateral versus contralateral side to stroke.
⇒ In subgroup with <50% stenotic plaque, vulnerable characteristics of the plaque were more closely related to stroke.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings provide potential evidence to support different aetiological roles of <50% stenotic versus ≥50% stenotic intracranial plaque in this population.

INTRODUCTION

As a major cause of stroke, intracranial atherosclerosis (ICAS) is more prevalent in the Asian population.[1] Large vessel occlusion (LVO) due to ICAS may be due to embolism from plaque rupture or in situ thrombosis, or their mixture.[2] Therefore, it is sometimes hard to identify the cause of LVO based on the clinical and auxiliary examination information in clinical practice, while identifying the definite cause could be important for secondary prevention. As high-resolution MRI (HR-MRI) evolves, accumulating studies have investigated the characteristics of extracranial or intracranial artery plaques and their association with stroke[3–5] and found different risks of ICAS in races, for example, there was 9%–65% ICAS in Asia, followed by 39% in Brazil, then 10–16% in Europe and USA.[1] However, there is no study to determine the characteristics of intracranial plaque proximal to LVO, which may be helpful to clarify the cause of LVO. Several studies have suggested a close relationship between atherosclerotic plaques causing <50% stenosis and stroke because the intracranial plaque was more prevalent in the ipsilateral than the contralateral side to stroke[4 5] and <50% stenotic vulnerable plaque was causally associated with stroke.[6] In addition, thrombi forming on the surface of fibrous-rich plaque without rupture (plaque erosion) were common, especially in severe stenosis lumen.[7 8]

In this context, we evaluated the intracranial plaque in patients with non-cardioembolic stroke and acute intracranial LVO using 3.0 T HR-MRI to verify the hypotheses that: (1) the intracranial plaque proximal to LVO is more prevalent in the ipsilateral versus contralateral

side to stroke and (2) <50% stenotic plaque proximal to LVO is more vulnerable in the ipsilateral versus contralateral side to stroke.

METHODS

Between January 2015 to July 2021, we retrospectively enrolled patients who were ≥18 years, had an acute unilateral anterior circulation ischaemic stroke with intracranial LVO (identified by diffusion-weighted imaging (DWI) and magnetic resonance angiography (MRA)) and performed HR-MRI examination. Inclusion criteria included: (1) a non-lacunar stroke confirmed by DWI (lacunar defined as a subcortical infarct of maximum size ≤2 cm on DWI); (2) intracranial LVO within 7 days of onset and presence of extracranial atherosclerosis with <50% stenosis detected by computed tomographic arteriography (CTA) imaging or Doppler ultrasonography; (3) absence of atrial fibrillation (AF) with duration >6 min,[9] as detected by cardiac monitoring for ≥20 hour; (4) no evidence of intracardiac thrombus by transthoracic echocardiography or transoesophageal echocardiography (TEE); (5) intracranial HR-MRI (including three-dimensional (3D) T1-weighted and two-dimensional (2D) T2-weighted imaging sequences) within 2 weeks of stroke onset.

Exclusion criteria included: (1) bilateral infarcts on DWI; (2) non-stenotic carotid plaque with ≥3 mm thickness detected by CTA or carotid ultrasonography[10]; (3) aortic arch atherosclerotic ulcered plaque or plaque with ≥4 mm thickness on CTA or TEE[11]; (4) emboli of major cardiac origin including the history of AF, intracardiac thrombi, prosthetic cardiac valve (mitral or aortic, bioprosthetic or mechanical), cardiac myxoma or other cardiac tumours, moderate or severe mitral stenosis, myocardial infarction within 4 weeks, valvular vegetations or infective endocarditis; (5) stroke caused by other specific aetiology such as cerebral arteritis or dissection, migraine/vasospasm, drug abuse; (6) patients who received intravenous thrombolysis or mechanical thrombectomy; (7) patients who received endovascular treatment such as balloon dilatation or/and stent to avoid the possible effects on plaques; (8) previous radiotherapy to head or neck; (9) malignancy; (10) poor image of intracranial HR-MRI due to motion artefact or incomplete MRI sequences. This study was approved by the Institutional Review Board of XXX, which exempted informed consent.

Depending on the presence of plaque and the stenosis degree caused by the plaque proximal to LVO, patients were categorised into three groups: no ipsilateral plaque group, ipsilateral plaque causing <50% stenosis group and ipsilateral plaque causing ≥50% stenosis group. Stenosis was defined as (1-luminal area at maximal lumen narrowing (MLN) site/luminal area at reference site)×100%.[12 13]

Imaging protocol

All participants underwent HR-MRI within 2 weeks of symptom onset. As described previously,[4] all MRI scans including DWI, T1-weighted and T2-weighted imaging, T2-weighted fluid attenuation inversion recovery imaging, 3D time-of-flight MRA, gradient echo sequences (susceptibility-weighted imaging or T2*-weighted imaging), 3D T1-weighted HR-MRI and 2D T2-weighted HR-MRI were performed with the standardised acquisition protocols on 3.0 Tesla MRI scanners (GE discovery MR750, Milwaukee, Wisconsin) by an eight-channel head coil. Fat suppression, blood flow suppression and CSF signal suppression were used to reduce fat signals from the scalp, accurately measure plaque and better delineate the outer edge of the vessel,[14] respectively. To reduce pixel size, Zero-filled Fourier transform (ZIP 512, ZIP2) was used, and the finial displaying resolution was 0.3–0.4 mm^3. In this study, the target regions were: (1) the supraclinoid and terminal internal carotid artery; (2) the proximal M1 segment of middle cerebral artery (MCA); (3) the M1-M2 junction or the proximal M2 segment of MCA.

Definition of plaque and thrombus

On 3D T1-weighted fat-suppressed/T2-weighted HR-MRI, a plaque was identified as having significant eccentric or focal wall thickness, with the thickest wall thickness ≥50% of the thinnest portion by visual inspection.[15] Intraluminal thrombus was identified if isointense, hyperintense signals on T1-weighted fat-suppressed HR-MRI or mixed signals on T2 HR-MRI were observed within the occluded artery, consistent with the signal loss on MRA (figure 1).[3 16 17] Intracranial thrombus was identified if the thrombus was located in supraclinoid and terminal ICA, proximal M1 segment of MCA, the M1–M2 junction or the proximal M2 segment of MCA ipsilateral to an ischaemic stroke. The presence/absence of plaque proximal to LVO and with >40% plaque burden (PB) was recorded and analysed, while the contralateral vessel was used as a reference and the contralateral plaque was assessed when the PB> 40% (figure 1).

Plaque parameters in morphology and composition

MRI's quality was analysed by two trained raters (DW and Z-YS) who were blinded to the clinical data and had >2 years of experience in reviewing intracranial MRIs. Poor quality images were excluded from our analysis. Image J (V.1.49, National Institutes of Health, Bethesda, Maryland) and RadiAnt DICOM Viewer (V.5.0.2, Medixant, Poznan-Poland) were used for qualitative and quantitative analysis and for 3D volume rendering by the appropriate magnification, respectively. The conspicuity of vessel contour was optimised by adjusting the window width and level. Plaque morphology and composition were included in the multidimensional parameters (presence/absence of bilateral plaque, remodelling index (RI), PB, percentage lipid-rich necrotic core (%LRNC), presence/absence of discontinuity of plaque surface (DPS), fibrous

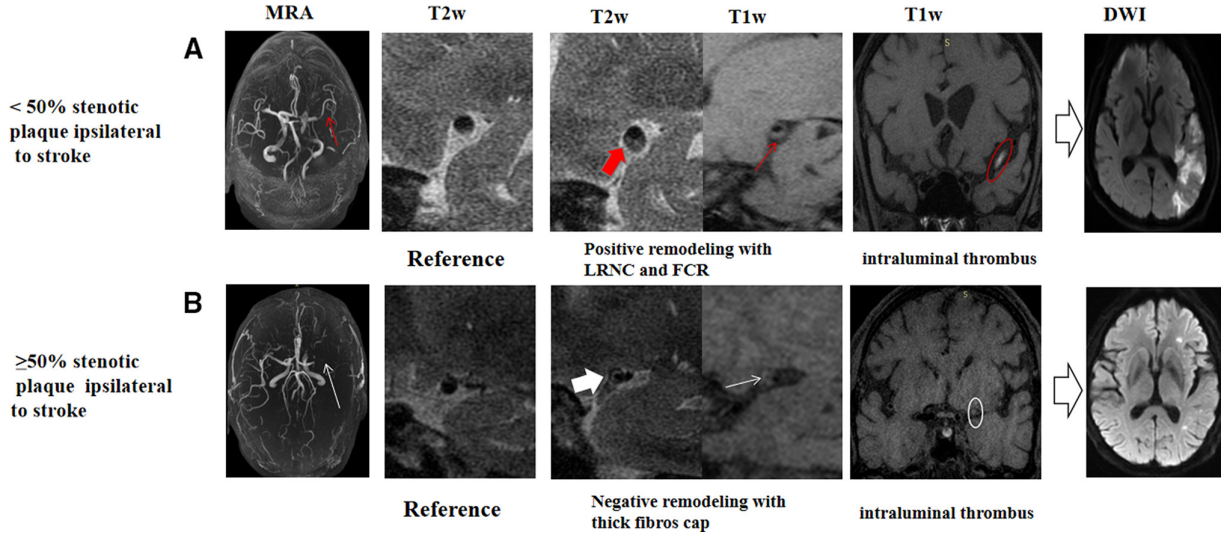

Figure 1 Brain HR-MRI images of plaque in subgroups (A) showing <50% stenotic plaque ipsilateral to stroke, left hemisphere infarct lesions on DWI and corresponding left middle cerebral artery occlusion (lower limb missing) on MRA (thin red arrow), a positive remodelling with <50% stenotic plaque with LRNC, and thin, FCR (thick red arrow on T2, thin red arrow on T1) and intraluminal thrombus (red circle) ipsilateral to stroke. (B) Showing stenotic plaque ipsilateral to stroke, left hemisphere infarct lesions on DWI and corresponding left middle cerebral artery occlusion on MRA (thin white arrow), a negative remodelling with ≥50% stenotic plaque with thick fibrous cap (thick white arrow on T2, thin white arrow on T1), and intraluminal thrombus (white circle) ipsilateral to stroke. DWI, diffusion-weighted imaging; FCR, fibrous cap rupture; HR-MRI, high-resolution-MRI; MRA, magnetic resonance angiography; LRNC, lipid-rich necrotic core.

cap rupture (FCR), intraplaque haemorrhage (IPH) and complicated American Heart Association (AHA) type VI plaque at MLN site).

Remodelling index and PB

We measured the vessel area and luminal area by manually tracing the contour of the outer wall and lumen at the MLN site and reference site in the cross-section images of major intracranial arteries. The cross-section with the thickest plaque was defined as the MLN site, while the neighbouring plaque-free or minimum lesion segment proximal and distal to the MLN site were selected as the reference sites. We calculated the average of the proximal and distal luminal area as the reference vessel area because of vessel tapering. The other side would be chosen as a reference site when one-side vessel had long-segment plaque or angled significantly. RI was calculated by vessel area at MLN site/reference vessel area, and positive remodelling (outward expansion of the wall), intermediate and negative remodelling (vessel wall shrinkage) was defined as an RI >1.05, 0.95 ≤RI ≤1.05 and RI <0.95, respectively. The PB was defined as (vessel area−luminal area/vessel area at MLN site)×100%, the percentage of PB was used to correct for varying with vessel size in which intracranial larger vessels usually had larger plaques. The %LRNC was defined as 100%×(LRNC area/vessel area−luminal area at MLN site), which was described in detail previously.[4 18]

Plaque components

As the layered appearance of intracranial atherosclerotic plaque is associated with the vascular wall high-resolution imaging appearance of carotid atherosclerotic plaque,[19] the signal characteristics of intracranial plaque components were defined as follows: (1) a continuous band of high signal on T2 adjacent to lumen was classified as presence of thick fibrous cap[20–22]; (2) LRNC underlying fibrous cap was featured as isointense to hyperintense on T1 and hypotense to isointense on T2 by visualisation[20–22]; (3) presence of IPH was featured as a bright signal on T1 and ≥150% of the adjacent muscle intensity[23 24]; (4) DPS was featured as irregularity of plaque luminal surface, such as FCR or formation of overlying mural thrombus[25]; (5) a complicated plaque was defined as any or both of DPS and IPH, referring to the definition of a complicated AHA type VI plaque.[26]

Definition of infarct patterns

Infarct patterns on DWI were categorised as four types[27]: (1) cortical infarct, single or multiple lesions (separated in space or discrete) located in the cortex supplied by MCA; (2) subcortical-deep infarct, located in the basal ganglion supplied by perforating artery; (3) territory infarct, massive cerebral infarct (≥one-third ipsilateral MCA distribution) or an infarct due to occlusion of an initial M2 branch (corresponding to the insula lobe, central sulcus or temporal–parietal lobe infarct); (4) watershed infarct, which included internal watershed infarct occurred between the deep and superficial perforators of the MCA, anterior watershed infarct between the anterior cerebral artery and MCA territories or posterior watershed infarct between the MCA and posterior cerebral artery territories. Also, we further classified the infarct

patterns as the large-territory infarct (territory infarct) and non-large-territory infarct (cortical, subcortical-deep or watershed infarct).

Measurement reproducibility

To determine interobserver and intraobserver variability, the RI, PB, %LRNC, presence of DPS, FCR and IPH were individually assessed by two raters in all patients, and to assess intraobserver variability, one rater (DW) reassessed these characteristics from the initial 100 consecutive patients 1–2 month later.

Statistical analysis

Continuous variables were described as mean±SD, or median and IQR, while categorical variables were expressed as absolute and relative frequencies. We used multiple imputation for missing data in categorical variables and continuous variables. McNemar test was used to compare the incidence of bilateral intracranial plaque in the whole patients with non-cardioembolic stroke. Multiple test was performed to compare the baseline characteristics in patients with ipsilateral plaque causing <50% vs ≥50% stenosis versus plaque free, which was further corrected by the Bonferroni test with an adjusted significance level of 0.017 (0.05/3). To compare the morphology and composition characteristics of plaque ipsilateral versus contralateral to ischaemic stroke, we used the t test or Wilcoxon rank-sum test (not normally distributed) for continuous data and χ^2 test for categorical data. A similar method was conducted to compare the differences in plaque characteristics and infarct patterns between patients with ipsilateral plaque causing <50% and ≥50% stenosis. In patients with both ipsilateral and contralateral plaque, paired t test or Wilcoxon signed-rank test (not normally distributed) was used for continuous variables and McNemar test for categorical variables.

Logistic regression analysis was performed to evaluate independent predictors for an index stroke by comparing the plaques ipsilateral versus contralateral to stroke. The three logistic regression models were established with model 1 serving as a crude model, model 2 adjusting for general covariates and model 3 additionally adjusting for lumen stenosis. Conditional logistic regression analysis was performed to evaluate independent predictors for an index ischaemic stroke based on the comparison of plaques ipsilateral versus contralateral to stroke in patients with both ipsilateral and contralateral plaque.

Given luminal stenosis as a potential confounder, subgroup analysis was stratified by the luminal stenosis at a threshold of 50% to investigate whether the two subgroups harbouring the distinct plaque characteristics both were correlated with stroke. In addition, logistic regression analysis including infarct patterns and plaque characteristics was used to investigate the potential mechanisms underlying LVO. Interobserver and intraobserver variability was tested with the intraclass correlation coefficient (ICC). All analyses were conducted using SPSS V.22 and R statistical package V.4, and p<0.05 were considered statistically significant.

RESULTS

Patient characteristics

We retrospectively screened 1728 patients with ischaemic stroke who underwent head HR-MRI. After excluding cases with major-risk cardioembolism (n=342), cases with extracranial atherosclerosis causing ≥50% stenosis (n=298), cases with lacunar stroke (n=381) and cases with specific aetiology stroke (n=35), 672 patients were initially identified. Additionally, after excluding 149 with acute posterior circulation ischaemic stroke and 78 with acute bilateral ischaemic stroke, 445 with unilateral anterior circulation ischaemic stroke with intracranial LVO on MRA within 2 weeks from onset to HR-MRI were identified. Finally, 279 eligible patients specific to intracranial LVO were included in the study (figure 2), after further excluding cases without culprit luminal thrombus detected by HR-MRI (n=11), cases with carotid plaque ≥3 mm thickness (n=76), cases with ulcered plaque or plaque with ≥4 mm in thickness in aortic arch (n=20), cases with balloon dilatation or sent (n=25), cases with malignant tumour and severe organ failure/disfunction (n=8), cases with poor image quality or incomplete data (n=26).

Among 279 patients, 211 patients had intracranial plaque ipsilateral to stroke. For these ipsilateral plaques, 31 (14.7%) plaques were located in terminal ICA, 150 (71.1%) in proximal M1 segment of MCA, and 30 (14.2%) in the proximal M2 segment of MCA. The LVO locations of these patients were: 5 (5/211, 2.4%) in terminal ICA, 123 (123/211, 58.3%) in proximal M1 segment of MCA and 83 (83/211, 39.3%) in the proximal M2 segment of MCA.

The comparison between ipsilateral versus contralateral plaque

Among 279 patients, 220 (78.9%) had any intracranial plaque including 56 (20.1%) with ipsilateral plaque, 9 (3.2%) with contralateral plaque and 155 (55.6%) with bilateral coexisting plaque. No plaques were found in 59 (21.1%) patients. Intracranial plaque was more prevalent in ipsilateral versus contralateral to the infarct (75.6% vs 58.8%, respectively, OR: 6.22, 95% CI 3.08 to 12.58, p<0.001). Their baseline characteristics are shown in table 1. There were significant differences in hypertension, coronary artery disease and baseline National Institute of Health Stroke Scale (NIHSS) among groups.

Table 2 shows that in plaque causing any stenosis group, the larger PB (median, IQR: 79.13 (73.04–85.19) vs 72.83 (61.51–83.43), p<0.001), RI (median, IQR: 1.06 (0.95–1.14) vs 1.02 (0.97–1.06), p<0.001) and %LRNC (mean±SD: 23.32±10.98 vs 19.76±9.66, p=0.001), the higher prevalence of DPS (61.1% vs 50.6%, p=0.041) and complicated plaque (63.0% vs 50.6%, p=0.016) were observed in the plaque ipsilateral versus contralateral

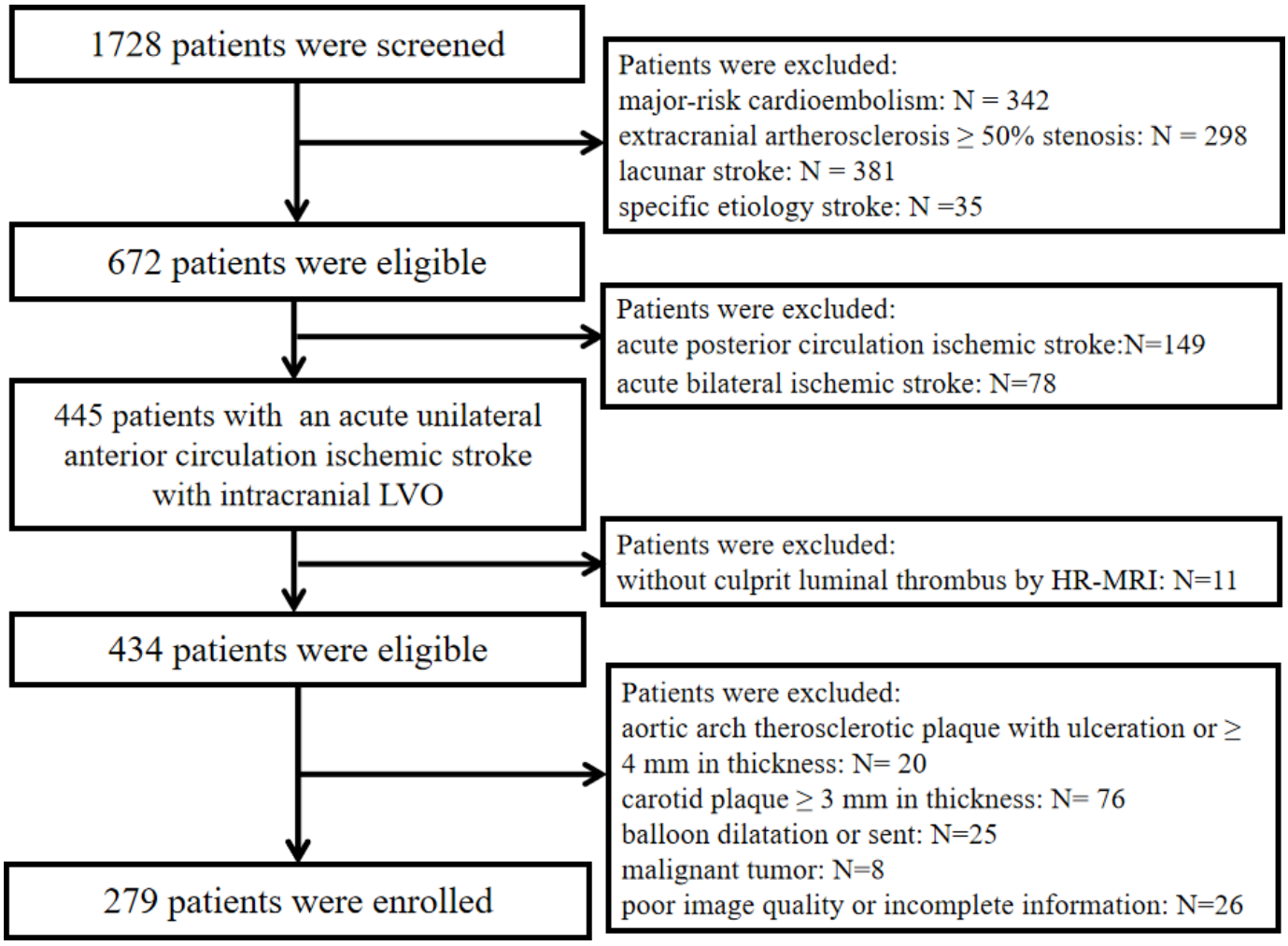

Figure 2 Flowchart of the stroke imaging study. HR-MRI, high-resolution-MRI; LVO, large vessel occlusion.

to stroke but not in FCR and IPH. Similar findings were also seen in group with plaque causing luminal stenosis of <50%, but the association was not identified in group with plaque causing luminal stenosis of ≥50% (table 2). Furthermore, paired comparison of the ipsilateral versus contralateral plaque among the 155 patients with both ipsilateral and contralateral plaque was also performed. The results showed that there were the significant differences in plaque morphology but not plaque composition (online supplemental tables 1 and 2).

Logistic regression analysis of an index event

As shown in table 3, for model 1, logistic regression analysis showed that PB (crude OR: 1.677, 95% CI 1.381 to 2.037, p<0.001) and RI (crude OR: 1.303, 95% CI 1.072 to 1.584, p=0.008) were positively associated with an index ischaemic stroke. For model 2, no obvious change of ORs was found in the four variables when adjusted for general covariates. For model 3, evident changes of OR were observed in PB towards an inverse direction to stroke (adjusted OR (aOR): 0.670, 95% CI 0.467 to 0.960), and RI with an increased OR (aOR: 1.986, 95% CI 1.529 to 2.579), when additionally adjusting for luminal stenosis.

ROC analysis

Figure 3 showed that the discrimination of plaque biomarkers for an index ischaemic stroke was significantly improved after excluding plaques with ≥50% lumen stenosis. Of these biomarkers, we found that RI had the most evident increase of AUC when excluding stenotic plaques (AUC (95% CI) from 62.5% (56.8%–68.2%) to 79.1% (71.6%–86.6%), absolute difference between areas: 16.6%), followed by %LRNC (AUC (95% CI) from 61.0% (55.3%–66.7%) to 75.6% (67.8%–83.5%), absolute difference between areas: 14.6%), PB (AUC (95% CI) from 62.8% (56.9%–68.6%) to 72.8% (65.0%–80.5%), absolute difference between areas: 10.0%) and complicated plaque (AUC (95% CI) from 56.2% (50.3%–62.1%) to 64.4% (55.8%–73.1%), absolute difference between areas: 8.2%), respectively.

Subgroup analysis stratified by luminal stenosis

As shown in figure 4, in subgroup with <50% stenotic plaque, the greater PB (aOR:2.438, 95% CI 1.407 to 4.225, p=0.001), RI (aOR: 2.014, 95% CI 1.229 to 3.300, p=0.005), %LRNC (aOR: 2.036, 95% CI 1.069 to 3.881, p=0.031) and more prevalent complicated plaque (aOR:

Table 1 Baseline characteristics of patients with non-cardioembolic stroke

	Ipsilateral plaque causing <50% stenosis (N=68)	Ipsilateral plaque causing ≥50% stenosis (N=143)	No ipsilateral plaque (N=68)	P value
Age, years, (median, IQR)	61 (53–69)	60 (51–66)	59 (51–68)	0.457
Male, n, %	50/68 (73.5)	102/143 (71.3)	43/68 (63.2)	0.368
Hypertension, n, %	45/67 (67.2)	97/135 (71.1)	33/66 (50.0)[c*]	0.027
Diabetes mellitus, n, %	17/66 (25.8)	42/132 (31.8)	9/65 (13.8)	0.154
Coronary artery disease, n, %	5/66 (7.6)	15/131 (11.5)	15/64 (23.4)[b*]	0.032
Prior stroke or TIA, n, %	18/48 (37.5)	34/107 (31.8)	6/50 (12.0)	0.229*
Drinking, n, %	24/48 (50.0)	50/107 (46.7)	19/50 (38.0)	0.985*
Smoking, n, %	35/67 (52.2)	76/134 (56.7)	28/66 (42.4)	0.314
TC, mmol/L (median, IQR)	3.60 (2.78–4.92)	4.35 (3.73–5.66)	4.54 (3.91–5.54)	0.185
HDL-C, mmol/L (median, IQR)	0.99 (0.89–1.18)	0.99 (0.90–1.14)	1.09 (0.87–1.45)	0.410
LDL-C, mmol/L (mean±SD)	2.53±0.75	2.66±0.90	2.79±0.77	0.545
Triglyceride, mmol/L (median, IQR)	1.33 (1.04–2.02)	1.54 (1.06–2.21)	1.34 (0.99–1.98)	0.388
Homocysteine, umol/L (median, IQR)	12.31 (9.99–18.20)	11.88 (9.30–15.78)	12.88 (10.50–16.64)	0.497*
GLU, mmol/L (median, IQR)	5.81 (4.92–7.50)	5.78 (5.18–7.16)	5.74 (5.05–6.99)	0.884*
Baseline NIHSS (median, IQR)	3 (1-6)	3 (1-7)	7 (3-13)[b,c*]	0.000
NIHSS at discharge (median, IQR)	1 (0–7)	2 (0–5)	2 (0–10)	0.120
Onset to HR-MRI time, h (median, IQR)	72 (48–100)	72 (48–120)	58 (38–96)	0.204

A significant difference exists if there is a superscript letter among subgroups, including a, ipsilateral plaque causing <50% stenosis versus ipsilateral plaque causing ≥50% stenosis; b, ipsilateral plaque causing <50% stenosis versus no ipsilateral plaque; c, ipsilateral plaque causing ≥50% stenosis versus no ipsilateral plaque. Values are mean ± SD, median (interquartile range), or n (%). *Indicates P value with multiple imputation.
*p<0.017 (Bonferroni significance threshold 0.05/3=0.017).
GLU, glucose; HDL, high-density lipoprotein; HR-MRI, high-resolution MRI; LDL, low-density lipoprotein; NIHSS, National Institute of Health Stroke Scale; TC, total cholesterol; TIA, transient ischaemic attack.

3.562, 95% CI 1.200 to 10.576, p=0.022) were closely related to an index ischaemic stroke (aOR for ipsilateral vs contralateral side), a finding that was not evident in the subgroup with ≥50% stenotic plaque. P values for interaction between plaque vulnerability (PB, RI, %LRNC and complicated plaque) and luminal stenosis were <0.001, <0.001, 0.031 and 0.048, respectively.

The comparison between patients with ipsilateral plaque causing <50% vs ≥50% stenosis

As shown in table 4, greater RI (1.15 (1.06–1.21) vs 1.04 (0.91–1.10), p<0.001), %LRNC (25.24±9.64 vs 22.41±11.48, p=0.080) and more prevalent FCR (66.2% vs 50.3%, p=0.031), DPS (73.5% vs 55.2%, p=0.011), IPH (16.2% vs 7.0%, p=0.037) and complicated plaque (79.4% vs 55.2%, p=0.001) but with smaller PB (68.55 (62.95–76.58) vs 82.37 (77.43–87.13), p<0.001) were found in patients with ipsilateral plaque <50% stenosis versus ≥50% stenosis. In addition, heterogeneous compositions of infarct pattern were also seen between the two groups (for those at <50% vs ≥50% stenosis: 25.0% vs 25.2% in cortical infarct, 19.1% vs 16.1% in subcortical-deep infarct, 42.6% vs 17.5% in territory infarct and 13.2% vs 41.2% in watershed infarct, p<0.001).

Reproducibility

The intraobserver and interobserver reproducibility was high for the measurements of RI, PB, %LRNC, presence of DPS, FCR and IPH. For intraobserver, ICC (95% CI) was as follows: RI: 0.829 (0.763 to 0.877), PB: 0.823 (0.756 to 0.873), %LRNC: 0.866 (0.814 to 0.905), presence of DPS: 0.885 (0.839 to 0.918), FCR: 0.806 (0.733 to 0.860) and IPH: 0.908 (0.889 to 0.924), respectively; while for interobserver, RI: 0.842 (0.782 to 0.887), PB: 0.830 (0.764 to 0.878), %LRNC: 0.819 (0.751 to 0.870), presence of DPS: 0.788 (0.710 to 0.847), FCR: 0.786 (0.707 to 0.845) and IPH: 0.871 (0.845 to 0.894), respectively.

DISCUSSION

This is the first report to determine the characteristics of intracranial plaque proximal to LVO in non-cardioembolic stroke by HR-MRI, which has been demonstrated to have high agreement of plaque signal features

Table 2 Comparison of characteristics of plaque ipsilateral versus contralateral to stroke

	Plaque causing any stenosis (N=375)			Plaque causing <50% stenosis (N=157)			Plaque causing ≥50% stenosis (N=218)		
	Ipsilateral plaque (n=211)	Contralateral plaque (n=164)	P value*	Ipsilateral plaque (n=68)	Contralateral plaque (n=89)	P value†	Ipsilateral plaque (n=143)	Contralateral plaque (n=75)	P value‡
Plaque morphology									
PB (%, median, IQR)	79.13 (73.04–85.19)	72.83 (61.51–83.43)	<0.001	68.55 (62.95–76.58)	62.54 (52.18–68.40)	<0.001	82.37 (77.43–87.13)	84.08 (80.16–86.42)	0.037
RI (median, IQR)	1.06 (0.95–1.14)	1.02 (0.97–1.06)	<0.001	1.15 (1.06–1.21)	1.02 (0.98–1.06)	<0.001	1.04 (0.91–1.10)	1.01 (0.93–1.05)	0.087
%LRNC (mean±SD)	23.32±10.98	19.76±9.66	0.001	25.24±9.64	17.05±7.29	<0.001	22.41±11.48	22.97±11.09	0.729
Stenosis (%, median, IQR)	68.31 (48.02–77.75)	47.55 (37.02–69.10)	<0.001	45.83 (38.38–47.90)	38.47 (30.49–44.06)	<0.001	73.72 (68.01–82.05)	69.95 (64.18–76.86)	0.002
Plaque composition									
FCR (n, %)	117 (55.5)	75 (45.7)	0.062	45 (66.2)	38 (42.7)	0.004	72 (50.3)	37 (49.3)	0.887
DPS (n, %)	129 (61.1)	83 (50.6)	0.041	50 (73.5)	45 (50.6)	0.004	79 (55.2)	38 (50.7)	0.520
IPH (n, %)	21 (9.9)	9 (5.5)	0.114	11 (16.2)	7 (7.9)	0.112	10 (7.0)	2 (2.7)	0.226§
Complicated plaque (n, %)	133 (63.0)	83 (50.6)	0.016	54 (79.4)	45 (50.6)	< 0.001	79 (55.2)	38 (50.7)	0.520

Stenosis at the site of the thickest plaque proximal to thrombus was calculated.
*P value = comparison of plaque causing any stenosis ipsilateral versus contralateral to stroke
†P value = comparison of plaque causing <50% stenosis ipsilateral versus contralateral to stroke
‡P value = comparison of plaque causing ≥50% stenosis ipsilateral versus contralateral to stroke
§Fisher's exact test
DPS, discontinuity of plaque surface; FCR, fibrous cap rupture; IPH, intraplaque haemorrhage; LRNC, lipid rich necrotic core; PB, plaque burden; RI, remodelling index.

Table 3 Multivariate logistic regression analysis for an index ischaemic stroke

	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
PB (per 10% increase)	1.677 (1.381 to 2.037)	< 0.001	1.726 (1.411 to 2.111)	< 0.001	0.670 (0.467 to 0.960)	0.029
RI (per 0.1 increase)	1.303 (1.072 to 1.584)	0.008	1.312 (1.071 to 1.607)	0.009	1.986 (1.529 to 2.579)	< 0.001
%LRNC (per 10% increase)	1.068 (0.837 to 1.364)	0.596	1.043 (0.805 to 1.350)	0.751	0.910 (0.692 to 1.196)	0.093
Complicated plaque	1.352 (0.821 to 2.226)	0.236	1.399 (0.840 to 2.329)	0.197	1.598 (0.925 to 2.759)	0.057

Model 1=a crude model; Model 2=adjusted for general covariates (including age, sex, hypertension, diabetes mellitus, coronary artery disease, prior stroke or transient ischaemic attack, drinking, smoking, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglyceride, homocysteine, glucose, Baseline National Institute of Health Stroke Scale and time from onset to HR-MRI); Model 3=additionally adjusted luminal stenosis.
HR-MRI, high-resolution-MRI; LRNC, lipid-rich necrotic core; PB, plaque burden; RI, remodelling index.

with histology.[20 28] We found that intracranial plaque was more prevalent in the ipsilateral versus contralateral side. Importantly, in subgroup with <50% stenotic plaque, the high-risk feature of ipsilateral plaque was more likely to be closely related to an ischaemic stroke, a finding that was not identified in the subgroup with ≥50% stenotic plaque.

The relationship between plaque and acute ischaemic stroke had been proved previously.[1] As a specific subtype, ICAS-LVO has been widely studied about early diagnosis and treatment, but the underlying mechanisms were seldom investigated.[29] Previous studies showed histological evidence of FCR, IPH and subintimal dissection of the involved vessel segment in autopsy patients.[30 31] In the current study, we found that the morphological characteristics of ipsilateral plaque proximal to LVO such as PB and RI were independent predictors for an index ischaemic stroke in the population of non-cardiogenic stroke with intracranial LVO, which was in line with prior studies finding that RI and PB were closely related with stroke.[32 33] We also found that stenosis also interacted with plaque morphology such as RI and PB. These results suggest that the correlation between events and high-risk plaque may be dynamic at different stages of plaque formation, indicating potentially different mechanisms underlying acute LVO (figure 5).

In <50% stenotic subgroup, we found that the high-risk morphological components of plaque were more closely related to stroke events, suggesting that an important role of adaptive positive remodelling in the early stage of plaque formation. In coronary disease studies, positive remodelling occurs in response to plaque formation by releasing matric metalloproteinases from a LRNC.[34 35] Before reaching the maximum of remodelling

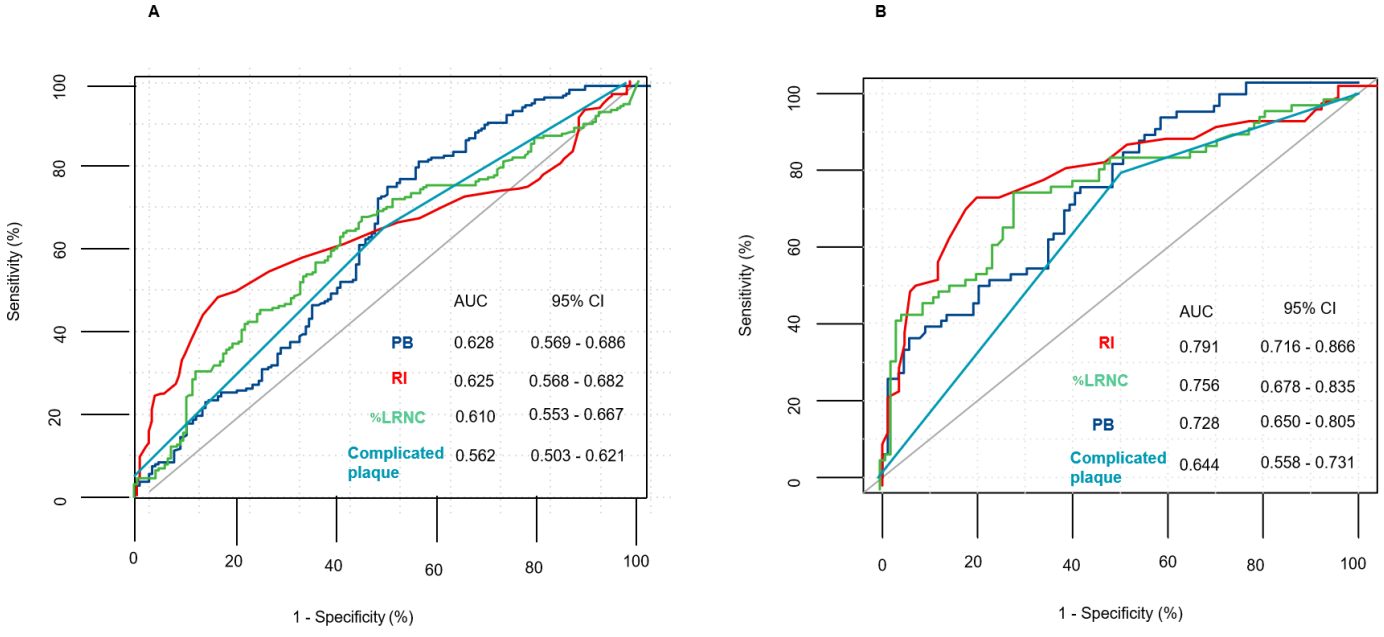

Figure 3 Receiver operating characteristics (ROC) analysis before and after excluding plaques with ≥50% lumen stenosis showing the changes of diagnostic performances of plaque biomarkers for predicting an index ischaemic stroke, before (A) and after (B) excluding plaques causing at least 50% lumen stenosis. AUC, area under curve; LRNC, lipid-rich necrotic core; PB, plaque burden; RI, remodelling index.

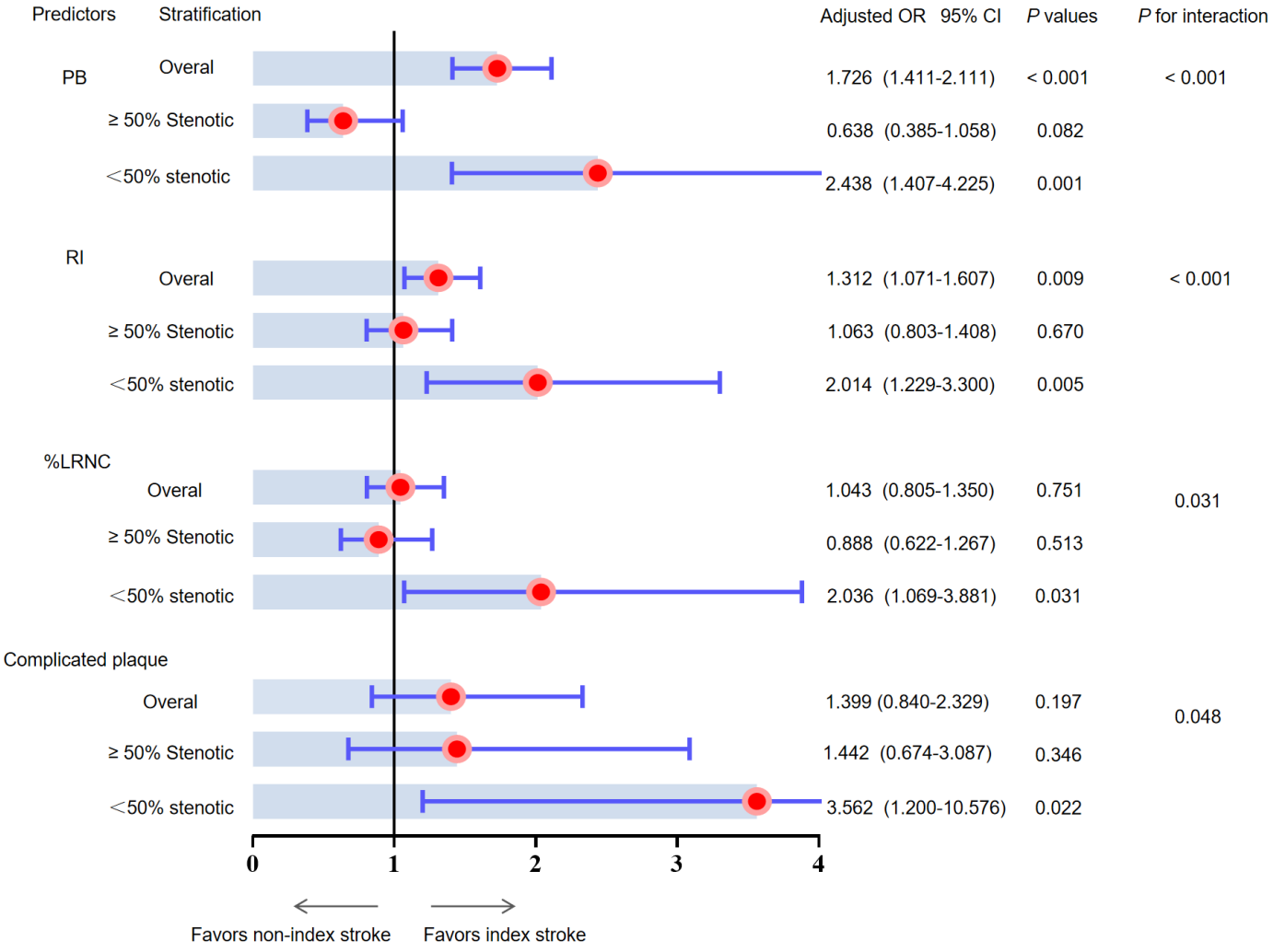

Figure 4 Subgroup analysis stratified by stenosis at the threshold of 50% caused by plaque showing the distinct characteristics of plaque ipsilateral vs contralateral to stroke in subgroup with ≥50% stenosis or <50% stenosis. The circles (red) and shadows (light blue) represented the points estimation and strengths of OR, respectively. The error bars (blue lines) represented DPS, discontinuity of plaque surface, LRNC, lipid rich necrotic core, PB, plaque burden, RI, remodelling index.

and causing stenosis, the lumen stenosis can be adjusted, but there is a greater PB coupled with the vessel wall outward enlargement, which eventually led to the rupture of fibrous cap and the formation of thrombosis.[36] Collectively, these results suggest that embolism or local thrombosis secondary to proximal plaque rupture may be the main cause of LVO in patients with <50% stenotic plaque (figure 5).

In ≥50% stenotic subgroup, we found no correlation between high-risk plaque and stroke events. Prior findings showed that the vessel wall would stop expanding outwardly when reaching a maximum cut-off of PB, and at this time the lumen began to narrow,[36] and the remodelling was no longer positive but negative. This could explain why there was no difference in plaque morphology between the ipsilateral and contralateral sides, while the remodelling is intermediate in ≥50% stenotic subgroup. As to the component of plaques, as the plaques advanced, they experienced self-repair and healing, when the fibrous components of the plaque gradually increased, so the plaque may become relatively mature and stable despite significant retractive stenosis,[8 37] which may explain no difference of plaque components in ipsilateral versus contralateral side. In this condition, there were more fibrous components in ≥50% stenotic versus <50% stenotic plaques. Due to more fibrous components on the surface of stenotic plaques, glycoproteins were easily eroded by metalloproteinases, which may lead to mural thrombus although the plaques do not rupture.[8 34] Therefore, local thrombosis formation secondary to plaque erosion may be involved in stroke with stenotic plaque proximal to LVO (figure 5).

The main strength of the current study is the first report of a high proportion of intracranial plaques proximal to LVO ipsilateral to non-cardioembolic stroke, suggesting that the plaque may play an aetiological role in this specific subtype. In addition, significant differences in ipsilateral plaque characteristics and infarct pattern were observed in the plaque ipsilateral in <50% vs ≥50% stenotic subgroups. Collectively, there may be two

Table 4 Comparison of characteristics of patients with <50% stenotic versus ≥50% stenotic plaque proximal to LVO

	Ipsilateral plaque causing <50% stenosis (N=68)	Ipsilateral plaque causing ≥50% stenosis (N=143)	P value
Plaque morphology			
PB (%, median, IQR)	68.55 (62.95–76.58)	82.37 (77.43–87.13)	<0.001
RI (median, IQR)	1.15 (1.06–1.21)	1.04 (0.91–1.10)	<0.001
%LRNC (mean±SD)	25.24±9.64	22.41±11.48	0.080
Stenosis (%, median, IQR)	45.83 (38.38–47.90)	73.72 (68.01–82.05)	<0.001
Plaque composition			
FCR (n, %)	45 (66.2)	72 (50.3)	0.031
DPS (n, %)	50 (73.5)	79 (55.2)	0.011
IPH (n, %)	11 (16.2)	10 (7.0)	0.037
Complicated plaque (n, %)	54 (79.4)	79 (55.2)	0.001
Infarct patterns (polytomous variables)			
Cortical	17 (25.0)	36 (25.2)	
Subcortical deep	13 (19.1)	23 (16.1)	
Territory	29 (42.6)	25 (17.5)	
Watershed	9 (13.2)	59 (41.2)	<0.001
Infarct patterns (dichotomous variables)			
Large-territory	29 (42.6)	25 (17.5)	<0.001

Values are mean±SD, median (IQR) or n (%).
DPS, discontinuity of plaque surface; FCR, fibrous cap rupture; IPH, intraplaque haemorrhage; LRNC, lipid rich necrotic core; LVO, large vessel occlusion; PB, plaque burden; RI, remodelling index.

potential mechanisms underlying LVO at different stages of plaque, that is, local thrombosis or embolism secondary to <50% stenotic plaque rupture versus mural thrombus secondary to ≥50% stenotic plaque erosion. These findings could inform future studies of secondary prevention in this population.

On the other hand, the retrospective nature and the sample size are limitations of our study, although current rigorous inclusion/exclusion criteria may restrict this effect. Second, the low resolution of intracranial HR-MRI was an intrinsic limitation for evaluating the nature of the vessel wall thickening, which would make it difficult to

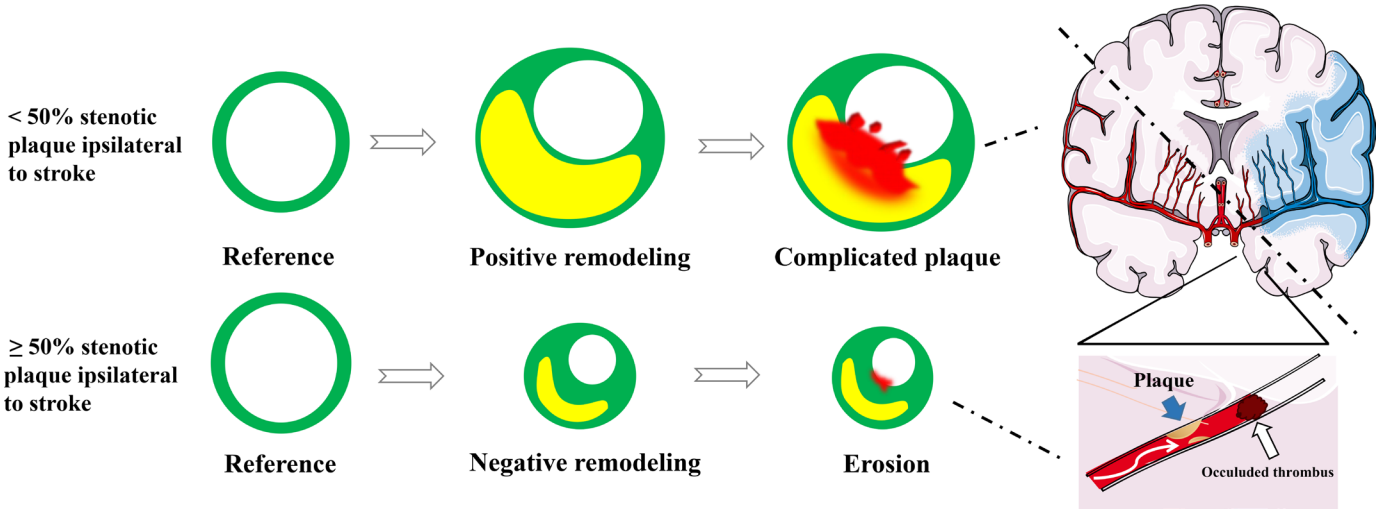

Figure 5 The possible underlying aetiology of LVO in <50% stenosis versus ≥50% stenosis group In <50% stenosis group, a positive remodelling plaque was highly associated with increased vulnerability (disrupted fibrous cap, IPH or mural thrombus) and the index stroke, while in ≥50% stenosis group, a negative remodelling plaque with thick fibrous cap erosion to index stroke. Upper: showed a positive remodelling plaque with IPH and thin, ruptured fibrous cap ipsilateral to stroke. Lower: showed a negative remodelling plaque with thick fibrous cap erosion ipsilateral to stroke. **Green**=vessel wall/fibrous tissue, **yellow**=LRNC, **red**=IPH/mural thrombus. IPH, intraplaque haemorrage; LVO, large vessel occlusion

accurately distinguish an embolus, especially at the initiation site of occlusive thrombus from a plaque, or lipid core from IPH in some cases. Third, RI might be underrated because the remodelling status at the reference location may respond to early phases of atherosclerosis. Additionally, an overestimation of PB margin may be unavoidable due to a partial volume averaging effect, although we used 3D-rendering technology to minimise the obliquity and tortuous curvature of intracranial vessels, especially in angled lesions.[38] Unfortunately, we did not include plaque enhancement in the analysis, but suppression of MRI signal in blood and CSF was used for accurate measurement of plaque and better delineation of the outer edge of the vessel.[14 19] Fourth, there were missing data which might have confounded our results: (1) no long-term ECG monitoring was performed, which may mix some patients with occult AF; (2) aortic arch atherosclerosis was not estimated; (3) due to lack of follow-up, the relationship between following recurrent events and plaque with high-risk characteristics is unknown. Fifth, the patients with severe NIHSS were not included in the current study based on the tolerance and safety concerns, which may result in selection bias with overestimate of the patients in ≥50% stenosis group. Sixth, it is hard to differentiate between acute LVO versus acute on chronic LVO cases, which was an important concern. Taken together with previous studies in coronary artery,[39 40] we contend that acute LVO may be more likely to occur in <50% stenosis cases while acute on chronic LVO more likely in ≥50% stenosis cases. Finally, our findings in non-Chinese population would need to be further confirmed.

In conclusion, this is the first study to report the features of intracranial plaque proximal to LVO in non-cardioembolic stroke and provided some potential evidence for different aetiological roles of <50% stenotic versus ≥50% stenotic intracranial plaque in these population.

Contributors DW and Z-YS contributed equally. DW and Z-YS acquired the data and did the literature search. DW wrote the first draft of the paper. DW and Z-YS analysed imaging data and made the figures. YC analysed the data. B-QY acquired the imaging data. GN critically revised the manuscript. H-SC designed the study and critically revised the manuscript and is responsible for the overall content as the guarantor.

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