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Review article

Culprit intracranial plaque without substantial stenosis in acute ischemic stroke on vessel wall MRI: A systematic review

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HIGHLIGHTS

- About half of acute ischemic strokes patients with non-stenotic intracranial MRA have identified plaques on vessel wall MRI.
- About half of acute ischemic stroke patients with clinical intracranial atherosclerosis present < 50% stenosis on MRA.
- Intracranial high-risk plaque with zero or mild stenosis is associated with ischemic stroke and unfavorable outcome.
- Vessel wall MRI can identify the high-risk plaque features and better risk stratify stroke patients.

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ABSTRACT

Background and aims: Intracranial atherosclerotic plaque is associated with ischemic strokes without substantial stenosis, and needs better characterization. We aim to investigate the clinical significance of intracranial plaque without substantial stenosis by high resolution vessel wall MRI (vwMRI) through a systematic review of existing studies.

Methods: Studies investigating intracranial arterial atherosclerotic plaques without substantial stenosis in acute ischemic stroke patients using vwMRI were systematically identified by searching the PubMed and Medline database and article reference lists. Study characteristics were recorded, the methodological quality of eligible studies was assessed, relevant clinical data were extracted, and collective data was analyzed.

Results: Twenty-one studies were identified as eligible. 463 patients were included without stenosis of the intracranial arteries, and 651 patients were included with stenosis < 50%. The prevalence of intracranial plaque revealed by vwMRI among acute/subacute ischemic stroke patients with non-stenotic Magnetic Resonance Angiography (MRA) was 50.6% (95% confidence interval (CI), 46.1%–55.1%). The prevalence of < 50% MRA stenotic culprit plaque among acute/subacute ischemic stroke patients with a clinical diagnosis of intracranial atherosclerosis was 51.2% (95% CI, 38.4%–64.0%). Plaques features, including wall enhancement, positive remodeling, intraplaque hemorrhage, plaque location and eccentricity, were associated with acute stroke, progressive motor deficits and unfavorable overall functional outcomes.

Conclusions: Intracranial high-risk plaque with zero or mild degree of stenosis is more prevalent than previously acknowledged, and is associated with ischemic stroke and unfavorable outcome. VwMRI can identify the high-risk plaque features, which may act as a promising tool to better risk stratify these patients.

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1. Introduction

Accurate identification of stroke etiology is crucial in guiding clinical treatment and improving outcomes [1]. Intracranial atherosclerotic stenosis is a major cause of ischemic stroke, accounting for 40% of stroke in Asian, 29% in African-American, and 15% in Caucasian populations [2,3]. Luminal stenosis, often assessed by noninvasive methods such as computed tomographic angiographic (CTA) and magnetic resonance angiography (MRA), has been independently associated with increased risk of acute ischemic strokes, and current practice guidelines rely mainly on the degree of stenosis (often ≥ 50%) within major intracranial arteries to decide treatment strategies [4–7]. However, many authors have argued that such vascular assessment is limited in evaluating only the vessel lumen, while atherosclerotic plaque originates in the vessel wall, and may cause ischemic stroke in the absence of luminal stenosis [8–10].

During the past two decades, intracranial atherosclerotic disease (ICAD) imaging has shifted from an indirect assessment of atherosclerosis by measuring luminal stenosis toward a more direct assessment of atherosclerotic plaque itself, with increasing acknowledgment of the role of vascular remodeling patterns and the clinical significance of atherosclerotic plaque features [11–13]. Positive remodeling results in compensatory enlargement of the arterial outer wall with plaque growth, increasing the luminal diameter, thereby resulting in underestimation of the atherosclerotic plaque burden by traditional luminal angiographic techniques (CTA, MRA and Digital Subtraction Angiography (DSA)) [14–16]. Previous studies have shown positive remodeling to precede detectable stenosis, and its association with high risk of acute ischemic stroke [17–19]. Conventional luminal imaging techniques cannot characterize or differentiate features of atherosclerotic plaques pathologies, including thrombotic occlusion, occlusion of perforating arteries and plaque rupture, leading to distal embolization [7,20]. There has been increasing use of high-resolution vessel wall magnetic resonance imaging (vwMRI) to study intracranial plaques, and a recent meta-analysis identified characteristics of intracranial plaques on vwMRI that were significantly associated with plaque vulnerability and increased risk of stroke, with odds ratios between 1.22 and 10.09[12]. It is even argued that some, if not all, treatment failure may arise from limited awareness of high-risk intracranial arterial lesion properties [9]. However, most studies have focused only on intracranial arteries with high-grade stenosis (at least > 50% stenosis). While up to 27% of fatal ischemic strokes could be attributed to an intracranial plaque with mild to moderate (30–75%) stenosis in autopsy studies [20–22], such atheromatous plaques are most often neglected in clinical setting. The clinical prevalence, characteristics and significance of atherosclerotic plaques of intracranial arteries with mild or no stenosis have been historically under-reported. For those individual studies that had included non-stenotic intracranial arteries, results were often based on small samples, aggregated with severely stenotic plaque, and varied widely between studies, limiting the appreciation of their significance.

Therefore, this study aimed to systematically review existing literature evidence to report (1) the relative prevalence, characteristics and clinical significance of non-stenotic atherosclerotic plaque by vwMRI and (2) the prevalence of culprit plaques with < 50% stenosis in acute/subacute stroke patients. This information would define the clinical benefit and appropriate application of intracranial vwMRI in non-stenotic intracranial arteries both for clinical use and future prospective studies.

2. Materials and methods

This systematic review was performed with a standardized written protocol with reference to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

2.1. Search strategy

A senior researcher performed a comprehensive search of the PubMed and MEDLINE database from inception through January 31st, 2019. To identify eligible studies, the following keywords were used in combination with the Boolean operators OR and AND: “intracranial atherosclerosis” or “plaque” and “stroke” or “cerebral ischemia”; “high resolution magnetic resonance imaging” or “vessel wall imaging”; “stenosis” or “stenotic” or “angiogram” or “MRA”. Scoping searches were performed and an iterative process was used to translate and refine the searches. The key articles were used to validate the success of the searches. The list of articles was supplemented with extensive cross-checking of reference lists within the included articles. The search strategies were peer-reviewed by a second researcher, and discrepancies in judgment were resolved by consensus.

2.2. Eligibility criteria and study selection

Specific inclusion criteria were: (1) English language articles; (2) investigations of patients with clinical suspicion of acute cerebral ischemia or infarction; (3) all patients in each study underwent intracranial vwMRI to assess arterial abnormalities; (4) studies that included patients with < 50% (including 0%) stenosis of intracranial arteries shown on MRA (usually considered without substantial stenosis [23]); (5) studies with total sample sizes greater than 10 patients; (6) manuscripts reported necessary study data to calculate the prevalence of atherosclerotic plaque. Attempts were made to contact the corresponding author for additional details to collect data when necessary. If multiple studies were thought to contain overlapping patient cohorts, only the study with the largest sample size was retained. Review articles, abstracts, letters, comments, and case reports were excluded. This selection strategy was prospectively chosen to provide a detailed systematic review collecting sufficient and accurate information.

2.3. Quality assessment of studies

Methodological quality of included studies was independently assessed by two researchers using the “Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies,” provided by the National Institutes of Health [24].

2.4. Data extraction and analysis

Two reviewers independently extracted data from included studies, and disagreements were resolved by consensus. The following study characteristics were extracted: (1) demographics of study participants such as sample size, major stroke-related risk factors; (2) study properties including major inclusion and exclusion criteria, stenosis degree of included patients, and definition of relevant plaques; (3) specific MRI protocols employed; (4) additional methodological design details of each study according to the above-mentioned quality assessment tool; and (5) clinical data regarding the prevalence of intracranial atherosclerotic plaque. The percentage of patients with intracranial plaque

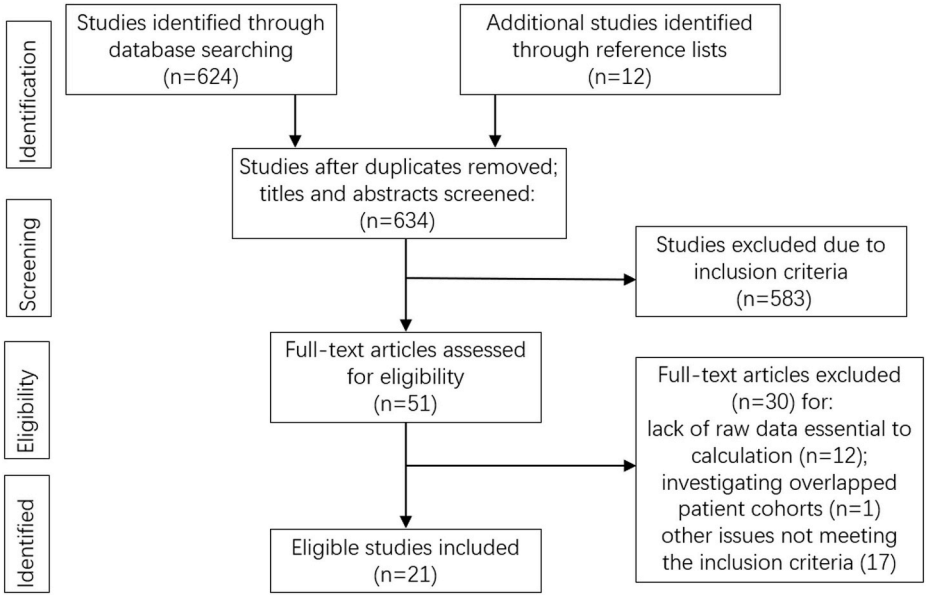

Fig. 1. Flow diagram of literature screening and selection process.

detected by vwMRI among symptomatic patients without stenosis on MRA, and the percentage of patients with < 50% stenosis on MRA among all ischemic stroke patients with a clinical diagnosis of ICAD were calculated with 95% confidence interval (CI) by data pooled from corresponding included studies. *Q* statistics were employed to examine the heterogeneity among the included studies. I^2 can be calculated from *Q* statistics. A random-effects model was applicable with an I^2 value of over 50%, while a fixed-effects model was applicable with an I^2 value of less than 50% [25]. Graphs of study results were produced with RStudio (R Foundation for Statistical Computing) [26]. Proportions of two groups were compared using the Fisher exact test.

3. Result

3.1. Search results

The detailed study selection process is shown in Fig. 1. A total of 634 articles were identified after the removal of duplicates. After screening of titles and abstract, 583 were excluded, as not investigating intracranial plaques by high resolution vwMRI. Thirty studies were excluded after full-text examination due to reporting of patients with stenosis degree of > 50% only, or lack of sufficient data to allow specific analysis on arteries with < 50% stenosis. Finally, 21 studies were identified as eligible, including 11 studies reporting data of non-stenotic atherosclerotic plaques, 13 studies reporting the prevalence of low-degree stenosis in acute/subacute ischemic stroke patients with ICAD, and 3 overlapping studies reporting both.

3.2. Characteristics of included studies and quality assessment

The basic demographics and prevalence of ischemic stroke-related risk factors of the included 21 studies are summarized (Table 1). The sample sizes ranged from 15 to 219. Twelve studies (n = 610) exclusively enrolled middle cerebral artery (MCA) lesions, six studies (n = 537) exclusively enrolled basilar artery (BA) lesions, one study included both MCA and BA (n = 15) and only two studies (n = 195) included MCA/BA and other intracranial arteries (vertebral arteries, posterior cerebral artery, internal carotid artery and so on), however MCA and BA were still the majority (more than 50%). Of the 12 MCA studies, 5 studies focused on M1 segment, 1 included both M1 (92%) and M2 (8%) segment, and the remaining did not clarify specific segments investigated.

Study characteristics are summarized in Table 2. All included studies focused on the acute or subacute phase of ischemic stroke patients. Target lesions for high resolution vwMRI were firstly assessed by 3D (time-of-flight (TOF) MRA in all included studies. Etiologies other than ICAD including cardiac embolism, extracranial carotid/vertebral artery stenosis and other arterial pathologies (e.g., dissection, vasculitis or Moyamoya disease) were all excluded in 13 studies, partly excluded in 5 studies, and not clearly stated in 3 studies. The studies defined relevant plaques as being within the ipsilateral side or specific territory of the diffusion-weighted imaging (DWI)-identified infarction (in 12 studies).

Eighteen of the twenty-one included studies employed 3.0 T MRI scanners to perform vwMRI. Twelve of the included studies specified the black-blood sequence used, which were versions of fast or turbo spin echo. Six studies used 2D techniques (Fast Spin-Echo or Turbo Spin-Echo), and six studied used 3D techniques: one study used 3D FSE, three studies used 3D Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (SPACE) sequences, and two studies used 3D Volume Isotropic Turbo spin echo Acquisition (VISTA). Tissue contrast weightings included T1, post-contrast T1 and T2-and proton density-weighted imaging.

Regarding the subtypes of ischemic stroke, two studies investigating MCA dichotomized subjects into artery-to-artery (A-to-A) embolic infarction and non-A-to-A infarction [27,28]. One study focused on

Table 1
Patient demographics.

Study, year	Country	N	Mean age (range or ± SD) (years)	Male (%)	Lesion site	HTN (%)	DM (%)	Dyslipidemia (%)	Smoking	Prior ischemic stroke or TIA
Teng, 2016	China	112	56.8 ± 10.2	67.0	MCA	68.1	34.8	N/A	32.1	N/A
Kim J, 2012	Korea	26	65.2 ± 12	61.5	MCA	65.4	30.8	38.5	N/A	N/A
Wu, 2018	China	74	54.7 ± 13.9	79.7	MCA	75.7	21.6	40.5	52.7	N/A
Zhu, 2018	China	126	61.2 ± 10.4	56.3	BA	80.2	33.3	51.6	27.8	N/A
Sui, 2015	China	45	46.6 + 12.3	73.3	MCA	N/A	N/A	N/A	N/A	N/A
Alexander, 2019	USA	54	62.8 ± 16.2	61.1	Any	N/A	N/A	N/A	N/A	N/A
Huang, 2018	China	141	61.1 ± 11.4	72.3	Any	81.6	41.1	82.3	39.0	N/A
Cho, 2018	Korea	40	67.5 (59.0–75.0)	67.5	BA	65.0	50.0	30.0	30.0	12.5
Sun, 2018	China	32	60.97 ± 11.54	68.8	MCA	68.8	25.0	62.5	31.3	9.4
Klein, 2010	France	41	66 (42–86)	82.9	BA	87.8	31.8	63.4	26.8	N/A
Klein, 2005	France	24	67.2 (40–89)	83.3	BA	70.8	20.8	25.0	50.0	N/A
Kim Y, 2012	Korea	219	67.3 ± 12.3	59.0	BA	66.7	33.3	9.6	28.8	16.9
Lim, 2015	Korea	87	66.7 ± 10.7	54.0	BA	77.0	41.4	41.4	28.7	N/A
Natori, 2014	Japan	18	69.8 (33–89)	61.1	MCA	55.6	22.2	33.3	N/A	N/A
Chung, 2012	Korea	15	69[a] (38–85)	60.0	MCA or BA	66.7	33.3	40.0	40.0	26.7
Bae, 2017	Korea	145	62.5 ± 12.6	40.0	MCA	63.4	34.5	20.0	42.8	17.2
Yoon, 2013	Korea	39	63.4 ± 10.6	48.7	MCA	59.0	15.4	17.9	15.4	17.9
Xu, 2014	China	57	60 ± 18	77	MCA	73	21	33	51	N/A
Zou, 2015	China	18	54.6[a] (40–70)	88.9	MCA	66.7	22.2	55.6	72.2	N/A
Zhang, 2017	China	15	67 ± 14	80	MCA	80	60	N/A	53	N/A
Zhao, 2015	China	29	67.6 ± 9.1	58.6	MCA	62.1	31.0	N/A	27.6	N/A

N, No. of patients; SD, standard deviation; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; MCA, middle cerebral artery; BA, basilar artery; N/A, data not available.
For the studies that reported demographics of symptomatic and asymptomatic patients separately, data of the symptomatic group was recorded.
[a] Median age.

paramedian pontine infarct which was considered to be caused by penetrating branch occlusion [29]. Two studies investigating BA dichotomized subjects into paramedian pontine infarct and small deep pontine infarction, which was attributed to small vessel lipohyalinosis [30,31]. One study explored small vessel disease subtypes of deep brain infarcts and white matter lesions in MCA territory [32]. Other studies did not specifically examine different stroke subtypes.

The results of the quality assessment were satisfactory with all the studies satisfying at least 9 of the 14 domains (Supplemental table: quality assessment). A fatal flaw concerning the sample size justification was found in all studies. Eleven of twenty-one studies showed a high risk of bias by potential confounders which were not adjusted by logistic regression or other regression methods [23,29–38].

3.3. The prevalence of non-stenotic atherosclerotic plaques on high resolution vwMRI

Eleven studies reported the prevalence of non-stenotic atherosclerotic plaques on high resolution vwMRI [29–32,34–40]. As shown in the forest plot of Fig. 2A, among a total of 463 acute ischemic stroke patients who had etiologies other than ICAD excluded and nevertheless demonstrated no luminal stenosis on TOF-MRA, 233 (50.6%, 95% CI, 46.1%, 55.1%, fixed effect model) were identified with intracranial plaque on vwMRI. Fig. 3 illustrates a representative case. Prevalences of non-stenotic plaques in the anterior circulation (MCA) and the posterior circulation (BA) were 49.7% and 50.2%, respectively ($p = 1.00$).

3.4. The prevalence of culprit plaques with low-degree stenosis in acute stroke patients

Thirteen studies reported the prevalence of culprit plaques with low-degree stenosis in acute stroke patients [5–7,17,19,23,27–29,33,39–41]. The raw data of four studies were not presented in the original articles but were obtained through communication with the authors [6,17,19,28]. Four studies enrolled both symptomatic and asymptomatic patient groups, and only symptomatic patients were included in these calculations [6,7,17,19]. Bae et al. included both acute and chronic infarction patient groups, and only acute infarction patients were included for our analysis [40].

As shown in the forest plot of Fig. 2B, among the 651 acute ischemic stroke patients who had etiologies other than ICAD excluded and had intracranial plaques identified by vwMRI, 321 (51.2%, 95% CI, 38.4%, 64.0%, random effects model) had MRA results revealing < 50% stenosis. A corresponding clinical case is shown in Fig. 4. The prevalence of low-degree stenosis in the posterior circulation (BA) was significantly higher than in the anterior circulation (MCA) (63.1% and 45.4%, respectively, $p < 0.001$).

3.5. The characteristics and clinical significance of non-to-mild stenotic atherosclerotic plaques on high resolution vwMRI

Multiple characteristics and clinical significance of the identified non-stenotic plaques are reported. Studies reported gadolinium enhancement percentages, ranging from 20% to 100% (n = 10) [5–7,27,29,30,36,38,40,41]. A tendency of homogeneous or heterogeneous T2-weighted hyperintense plaque signal was observed, suggesting possible plaque compositions of hemorrhage and/or lipid (n = 3) [29,33,40]. In the study by Zhu et al., intraplaque hemorrhage (IPH) was the strongest independent marker of symptomatic status, with a remarkable odds ratio of 27.5 [7]. Included studies also analyzed the location of plaques (n = 7) [17,32,33,36–38,40], observed positive remodeling (n = 4) [17,19,32,34], noted plaque surface irregularity (n = 2) [17,28], and recorded eccentricity (n = 1) [40]. Identified plaques within non-stenosed arteries revealed on vwMRI were reported to be associated with multiple stroke risk factors [34], larger infarction lesion [31], progressive motor deficits [39] and unfavorable overall functional outcome [35].

Table 2
Study characteristics.

Study, year	Inclusion			Exclusion			Definition of relevant plaque	vwMRI protocol		
	Patient population	Vessel stenosis degree (modality)	Interval between symptom and MRI/ stroke phase	Cardiac embolism	Stenosis at extracranial carotid/vertebral artery	Non-atherosclerosis[a]		MRI Field Strength (tesla)	High resolution MRI sequences	Resolution (mm^3)
Teng, 2016	Suspicion with intracranial atherosclerotic diseases	Any stenosis (TOF MRA)	3.3 ± 2.5 days	✓	✓	✓	Ipsilateral to MRI confirmed infarcts	3.0	2D FSE	0.4 × 0.3 × 2
Kim J, 2012	MCA territory infarction or TIA	Any stenosis (TOF MRA)	< 7 days	✓	✓	✓	With intraplaque heterogeneous signal intensity and enhancement	3.0	Black blood sequence	0.4 × 0.3 × 2
Wu, 2018	MCA territory acute ischemic stroke	Any stenosis (CTA, MRA, or DSA)	8.3 ± 4.1 days	✓	✓	✓	Same territory with DWI confirmed lesions	3.0	3D inversion-recovery prepared sampling perfection	0.5 × 0.5 × 0.5
Zhu, 2018	Ischemic stroke or TIA in the basilar artery territory	> 30% (DSA, CTA or MRA)	< 12 weeks	✓	✓	✓	Same territory with DWI confirmed lesions	3.0	2D-FSE	0.4 × 0.3 × 2
Sui, 2015	Acute ischemic stroke	Any stenosis (TOF MRA)	2 weeks later	✓	✓	N/A	Ischemic symptoms and DWI confirmed lesions	3.0	2D-TSE	0.3 × 0.3 × 2
Alexander, 2019	New ischemic stroke	Any stenosis (TOF MRA)	< 2 weeks	✓	✓	✓	The most apparent plaque in the territory of recent symptom and/or DWI confirmed lesions	3.0	3D SPACE	0.46 × 0.46 × 0.5
Huang, 2018	All with intracranial atherosclerotic plaque identified on vwMRI	Any stenosis (TOF MRA)	< 12 weeks	✓	✓	✓	N/A	3.0	VISTA	0.55 × 0.55 × 0.55
Cho, 2018	Acute isolated pontine infarction	No stenosis (TOF MRA)	Median, 96.3 h (range, 79.4–102.2 h)	✓	✓	✓	On the dorsal side of the artery, on the ipsilateral side and the same axial slices of the ischemic lesion	3.0	2D TSE	0.3 × 0.5 × 2
Sun, 2018	Isolated lenticulostriate infarction	No stenosis (TOF MRA)	Acute phase (DWI restricted)	✓	✓	✓	Same artery territory, DWI confirmed lesion	3.0	3D VISTA	0.5 × 0.5 × 0.6
Klein, 2010	Pontine infarction	Normal, irregular, or mild stenosis (< 50%) (TOF-MRA)	Acute phase	N/A	Seven patients had a vertebral stenosis	N/A	Ischemic symptoms and MRI confirmed lesions	1.5	Black blood sequence	0.4 × 0.5 × 2
Klein, 2005	Paramedian pontine infarcts	Any stenosis (TOF MRA)	Within 3 months	Three patients had atrial fibrillation	N/A	N/A	Ischemic symptoms and MRI confirmed lesions	1.5	N/A	0.4 × 0.5 × 2
Kim Y, 2012	Acute ischemic stroke	Any stenosis (TOF MRA)	Within 7 days	21% of patients had atrial fibrillation	Statement: strokes of other determined etiologies were excluded		Ischemic symptoms and DWI confirmed lesions	3.0	Black blood sequence	0.4 × 0.5 × 2
Lim, 2015	Pontine infarction	Any stenosis (TOF MRA)	Within 24 h	N/A	N/A	N/A	Ischemic symptoms and DWI confirmed lesion	3.0	Black blood sequence	0.4 × 0.5 × 2
Natori, 2014	Acute ischemic stroke in the M1 territory	Any stenosis (TOF MRA)	Mean, 6.3 days (range, 0–14 days)	✓	N/A	N/A	Ipsilateral to the MRI confirmed lesions	1.5	3D-FSE	0.5 × 0.5 × 0.5
Chung, 2012	Lacunar infarctions	No stenosis (TOF MRA)	Median, 4 days (range, 2–15 days)	Statement: none of the patients had other etiologies related to the stroke events, such as cardiac embolism, non-atherosclerosis[a]			On the same side, and the same artery territory of the ischemic lesion	3.0	2D TSE	0.3 × 0.4 × 2
Bae, 2017	Deep subcortical infarctions	Any stenosis (TOF MRA)	Within 7 days	✓	✓	✓	Ipsilateral to the DWI confirmed lesions	3.0	N/A	0.5 × 0.2 × 1

(*continued on next page*)

Table 2 (*continued*)

Study, year	Inclusion			Exclusion			Definition of relevant plaque	vwMRI protocol		
	Patient population	Vessel stenosis degree (modality)	Interval between symptom and MRI/ stroke phase	Cardiac embolism	Stenosis at extracranial carotid/vertebral artery	Non-atherosclerosis[a]		MRI Field Strength (tesla)	High resolution MRI sequences	Resolution (mm^3)
Yoon, 2013	Acute ischemic stroke in the lenticulostriate arterial territory	No stenosis (TOF MRA)	Within 8 days	✓	✓	N/A	DWI confirmed lesions	3.0	N/A	0.4 × 0.4 × 1.5
Xu, 2014	Acute single symptomatic infarct	No stenosis (TOF MRA)	12 ± 11 days	✓	✓	N/A	Ipsilateral to the MRI confirmed lesions	3.0	2D FSE -T2WI	0.5 × 0.5 × 2
Zou, 2015	Recent small subcortical infarctions	No stenosis (TOF MRA)	Median, 12 days (range, 3–28 days)	✓	✓	✓	Same artery territory, DWI confirmed lesion	3.0	3D SPACE	Varied between 0.5 × 0.5 × 0.5 and 0.7 × 0.7 × 0.7
Zhang, 2017	Acute ischemic stroke in the M1 territory	M1 > 30% (TOF MRA)	54.5 ± 18.8 h	✓	✓	✓	Same artery territory, DWI confirmed lesion	3.0	Black blood sequence	0.4 × 0.6 × 2
Zhao, 2015	TIA or acute ischemic stroke	> 30% (TOF MRA)	Within a week	✓	✓	✓	Same artery territory	3.0	3D SPACE	0.5 × 0.7 × 0.7

✓Etiology excluded.

vwMRI: vessel wall magnetic resonance imaging; TOF MRA: time of flight magnetic resonance angiography; DWI: diffusion weighted imaging; TIA: transient ischemic attack; M1: middle cerebral artery segment 1; FSE: fast spin echo; TSE: turbo spin echo; SPACE: sampling perfection with application optimized contrasts using different flip angle evolution; VISTA: volumetric isotropic turbo spin echo acquisition.

[a] Other vasculopathies such as dissection, vasculitis or Moyamoya disease.

4. Discussion

Despite comprehensive workup of acute ischemic stroke, as many as 23–40% of strokes have no identifiable cause, and these so-called "cryptogenic strokes" are even more frequent in younger patients [42]. ICAD is increasingly recognized as an important etiology when other potential stroke causes such as cardiac etiologies and extracranial atherosclerotic stenosis were excluded [43]. However, ICAD has been likely under-appreciated due to the current reliance on conventional luminal stenosis-based imaging, which often fails to reveal such lesions. The results of our systematic review on this subject suggest that over half of ischemic stroke patients without significant stenosis or alternative stroke etiology may have a culprit intracranial arterial plaque identified on vwMRI, emphasizing the high-risk nature of intracranial plaque even in the absence of substantial stenosis.

Current studies of intracranial plaque imaged using vwMRI in ischemic stroke have been mostly small of sample sizes and observational in nature, precluding wider application of results to clinical protocols. Our systematic review of literature provides comprehensive relevant information from multiple available studies to show the prevalence and clinical significance of intracranial plaque identified in the absence of significant stenosis. Comparison of the various study results has been difficult, because of the significant heterogeneity in the literature on the selection of patient criteria, definitions of relevant plaques, and MRI protocols used. Fortunately, most studies included in our systematic review excluded other common etiologies such as cardiac embolism, extracranial atherosclerotic stenosis and vasculopathies such as dissection, vasculitis or Moyamoya disease by thorough imaging and clinical evaluation. Although it is not possible to exclude all alternative stroke etiologies, the studies reported clinical evaluation equivalent to or greater than the current standards of practice to investigate stroke causation. As ICAD was left as the most likely cause of strokes in these carefully-selected study populations, the non-stenotic or low-grade stenosis intracranial arterial plaques revealed on vwMRI provided convincing evidence of the underlying causative pathogenesis.

A systematic review of these studies emphasizes that about half of the patients with acute/subacute ischemic stroke symptoms and nevertheless no significant stenosis on MRA results had intracranial active plaques revealed by high resolution vwMRI. These plaques were most relevant to the confirmed infarction territory and demonstrated to be associated with multiple clinical outcome measures. These results dispute the widespread notion that non-stenotic plaques are not clinically significant in demonstrating that these plaques may be culprit lesions in many ischemic strokes. As these studies involved careful selection of patients in specific clinical contexts, the exact frequency of culprit non-stenotic plaques in all patients with ischemic stroke is unknown. Prospective studies are required to investigate the characteristics of non-stenotic plaques and differentiate risk severity from stenotic plaques in larger populations.

This review showed almost half of patients with acute/subacute ischemic stroke symptoms had MRA studies revealing < 50% stenotic intracranial arteries. Moreover, studies have reported that the discrepancy between vwMRI and MRA was more evident in patients with mild stenosis, suggesting that vwMRI is more sensitive for detecting early ICAD, allowing more timely and targeted treatment strategies [34,43]. The prevalence of mild stenosis in stroke patients was even higher in the posterior circulation than in the anterior circulation, consistent with the previous study revealing that posterior circulation arteries had a greater capacity for positive remodeling [44]. Given the remarkable percentage of stroke patients with mild stenotic intracranial arteries, more clinical studies focused on identifying culprit non-stenotic ICAD are proposed to further benefit this patient group.

Multiple high-risk plaque features were reported by some of the included studies, including plaque enhancement, positive remodeling, and plaque surface irregularity, which agrees with the high-risk plaque characteristics in mostly severely stenotic arteries pooled in a recent

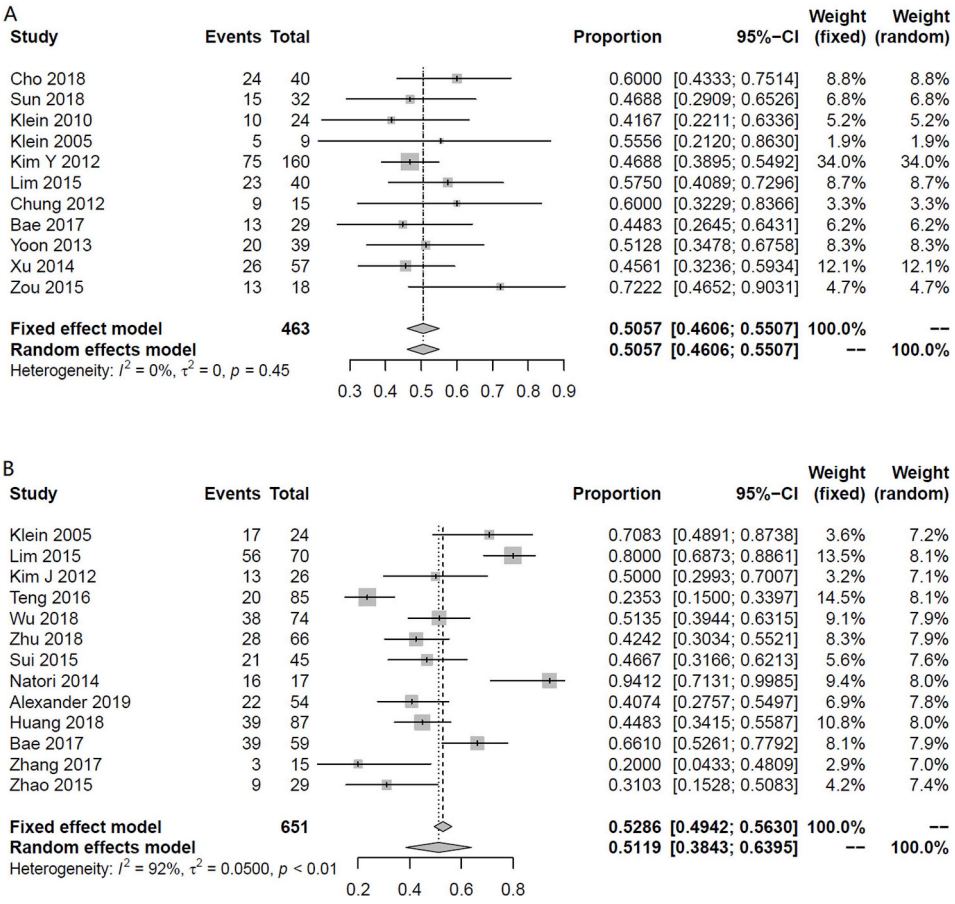

Fig. 2. Forrest plots.
(A) Forrest plot of the patient percentage with intracranial plaque detected by vwMRI, among symptomatic patients without stenosis on MRA. (B) Forrest plot of the patient percentage with < 50% stenosis on MRA, among all ischemic stroke patients with clinical diagnosis of ICAD.

meta-analysis [12]. Notably, there is evidence to suggest that the prevalence IPH does not differ significantly between low- and high-grade stenotic plaque [7]. The results of this systematic review further support the clinical relevance of non-to-mildly stenotic plaques, as these high-risk plaque features can occur regardless of the degree of stenosis.

Our analysis supports the increasing recognition that stroke mechanism cannot be accurately assessed without visualization of the intracranial arterial walls and characterization of plaque properties such as location, composition and vulnerability [9,45]. Identifying stroke etiologies in individual patients may eventually help improve treatment and prevention strategies, especially given that large-vessel disease is associated with the highest risk of early stroke recurrence among other subtypes proposed by the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria [22,43]. Studies have explored the utility of vwMRI in mildly stenotic intracranial arteries in identifying and differentiating between stroke mechanisms of branch occlusive disease and small vessel lipohyalinosis with vwMRI being able to visualize branch atheromatous plaques near the orifice of perforator arteries even when the parent artery was not stenotic [29–31,36]. Furthermore, vwMRI was explored to discriminate A-to-A embolic infarction and non-A-to-A infarction by identification of vulnerable plaque characteristics in arteries with various stenotic degrees, as embolic infarction could be caused by shedding of vulnerable plaque debris or plaque surface thrombus [27,28]. The differentiating of stroke subtypes might prompt distinct management strategies (e.g., A-to-A embolization from plaque rupture may require more aggressive antiplatelet therapy to mitigate clot progression whereas stenotic disease might benefit more from angioplasty [20]), although further work is needed to ascertain the clinical relevance of different treatment approaches. Nonetheless, the expanded use of vwMRI would undoubtedly result in the reclassification of many strokes from cryptogenic to being related to non-stenotic ICAD and thereby enhance clinical decision-making and prognostication.

There are several limitations to this review. First, the sample sizes of the included studies are relatively small. Second, there is a lack of a control group of subjects without strokes. Few included studies enrolled asymptomatic subjects, and the lack of data made it hardly possible to compare between stroke patients and asymptomatic controls. Third, heterogeneity exists regarding the inclusion criteria, MRI protocol, and methodological quality. In the second calculation of pooled prevalence, significant heterogeneity was found with an I^2 value of 92%, and that is

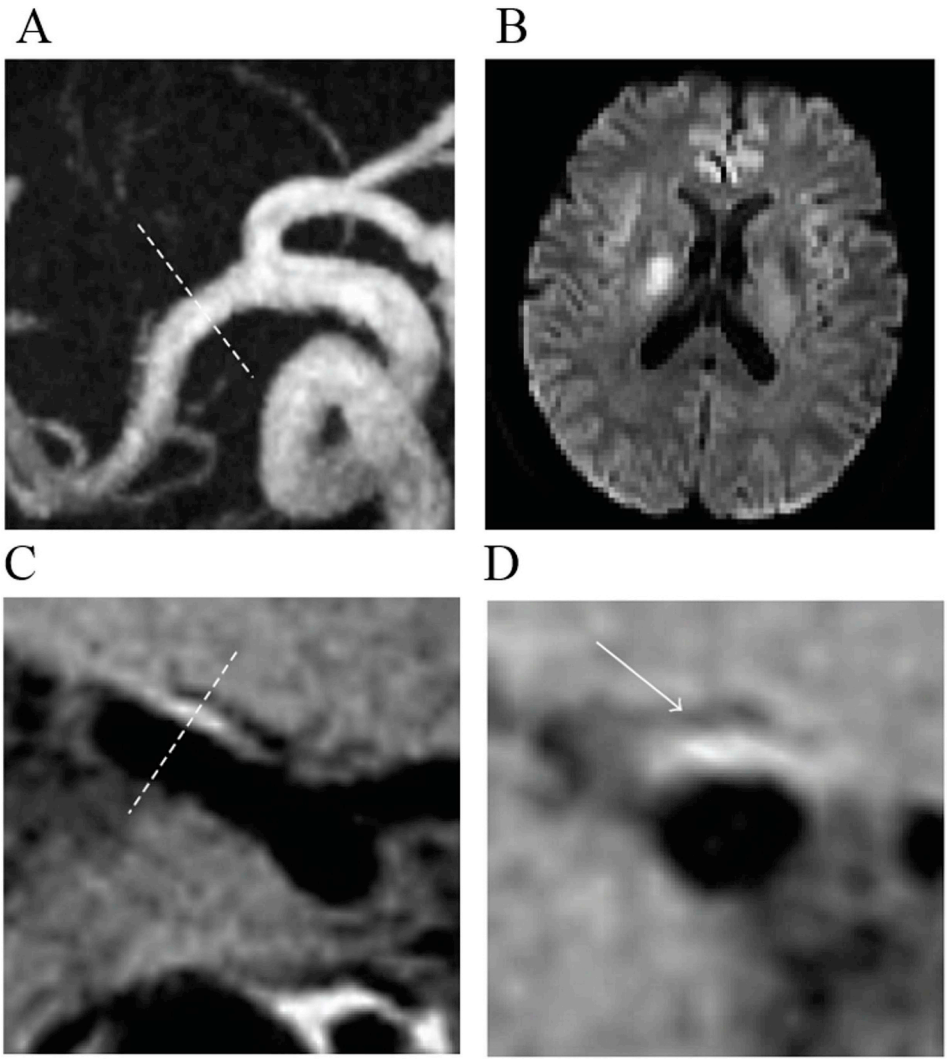

Fig. 3. Patient with left-side weakness.
(A) MRA shows no stenosis on the right middle cerebral artery (MCA); (B) the diffusion-weighted image shows a hypertensive lesion in the right lenticular nucleus, which extends to the coronal radiate; post-contrast high resolution T1-weighted images show wall thickening ipsilateral to the infarct on both the long axis (C) and short axis ((D), arrow) of the MCA (Reprinted from Zou et al. [37], open access from BioMed Research International, with permission from Science Publishing, Copyright 2015, Hindawi).

why this is presented as a systematic review despite of the original attempt of a meta-analysis. Fourth, nearly all studies focused on the primary sections of the arteries, partly because it is very challenging for current MRI techniques to visualize the plaques of distal small branches or deep penetrating branches. The recent development of 3D high resolution MRI at high filed strength might improve the reliability and accuracy for plaque feature identification and quantification [46]. Fifth, it was noticed in the searching process that several studies had the data of mild stenotic intracranial arteries unable to be separated from severely stenotic arteries. We have tried our best to reach all these corresponding authors, but their partial response might lead to some bias of study inclusion.

In conclusion, this systematic review demonstrates intracranial high-risk plaque with zero or mild degree of stenosis is more prevalent than previously acknowledged, and is associated with ischemic stroke and unfavorable outcomes. Vessel wall MRI can identify the high-risk plaque features which may act as a promising tool to better risk stratify these patients.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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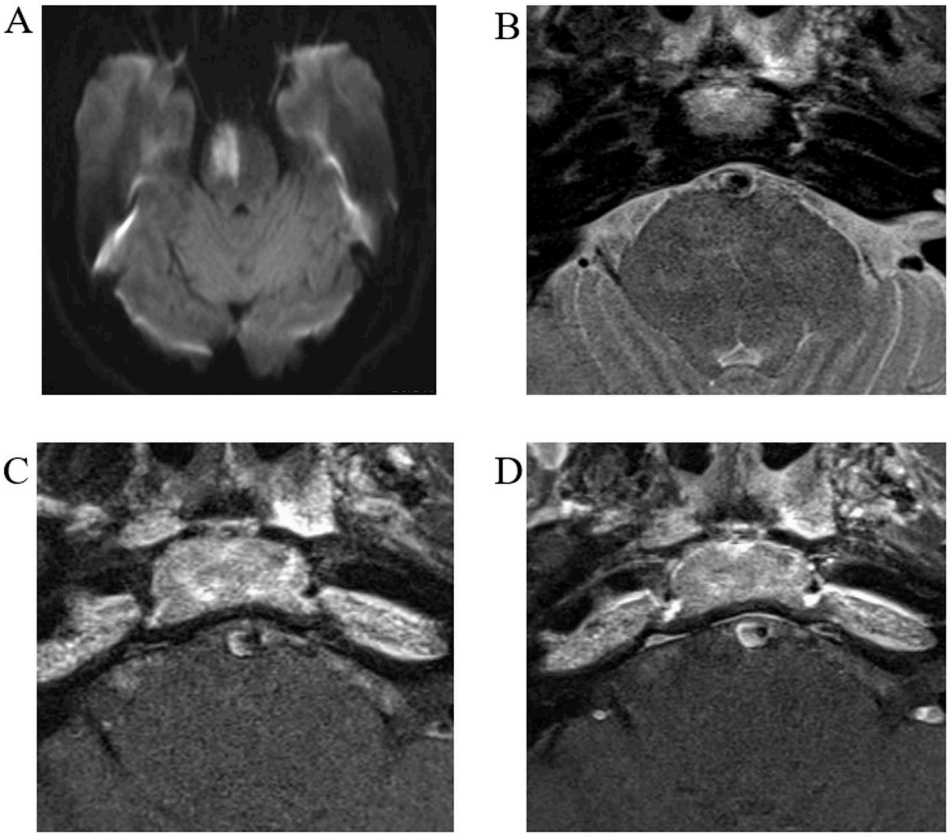

Fig. 4. Patient with mild stenosis (30%) and acute stroke.
(A) The diffusion-weighted image shows a hypertensive lesion in the right side of the pons. (B) Pre-contrast T1-weighted MRI showing eccentric thickening of the left wall of basilar artery. (C) Pre-contrast T2-weighted MRI showing hyperintensity of the plaque. (D) Post-contrast T1-weighted MRI showing contrast enhancement of the plaque.

Author contributions

Chengcheng Zhu designed the main ideas and methodology of the review. Yuting Wang and Xinke Liu did data collection, extraction, calculation, summary and wrote the manuscript. Xiao Wu helped with data analysis and preparation of figures. Andrew J Degnan and Ajay Malhotra gave critical suggestions on the design of this review. All authors revised the manuscript and approved the final submission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.06.907.

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