

## Neuroradiology

# Vessel wall magnetic resonance imaging of symptomatic middle cerebral artery atherosclerosis: A systematic review and meta-analysis

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## ABSTRACT

**Objective:** A comprehensive understanding of atherosclerotic middle cerebral artery (MCA) plaques aids physicians in diagnosis and treatment of ischemic stroke. High-resolution magnetic resonance imaging (MRI) has been used to identify imaging biomarkers of symptomatic MCA plaque. We performed this systematic review and meta-analysis to evaluate which characteristics of MCA plaque are markers of culprit lesions.

**Materials and methods:** The PubMed, EMBASE, Web of Science, and Cochrane Library databases were searched for publications up to March 2022. Two independent reviewers extracted data on study design, high-resolution MRI parameters, and imaging end points. Odds ratios (ORs) for the prevalence of stroke with atherosclerotic MCA plaque features were pooled in the meta-analysis by using a random-effects model. Subgroup analysis, sensitivity analysis, and evaluation of publication bias were also conducted.

**Results:** Seventeen articles were included in this review. Symptomatic MCA plaques were significantly associated with contrast enhancement (OR, 9.4; 95 % CI, 4.3–20.4) and T1 hyperintensity (OR, 6.2; 95 % CI, 2.7–14.3). However, there was no association between symptomatic plaques and T2 hyperintensity (OR, 1.4; 95 % CI, 0.8–2.3). Plaque enhancement was significantly associated with downstream ischemic events in subgroup analyses based on different study designs and MR sequence types.

**Conclusion:** Based on current evidence, contrast enhancement and T1 hyperintensity on high-resolution MRI have high potential as imaging biomarkers of patients with MCA plaques at risk of ischemic events. Future prospective, longitudinal studies of intracranial-plaque high-resolution MRI are required to improve decision-making for the management of intracranial atherosclerotic plaques.

## 1. Introduction

Ischemic stroke is one of the leading causes of death and the leading cause of disability in the world.<sup>1</sup> Intracranial atherosclerosis (ICAS) has been recognized as the most common cause of ischemic stroke worldwide,<sup>2–4</sup> and is more prevalent in Asian than in Western populations.<sup>5,6</sup> In approximately 40–70% of Asian patients with ICAS, the affected vessel is the middle cerebral artery (MCA).<sup>7</sup> In addition, patients with symptomatic MCA stenosis in one study had an overall stroke risk of 12.5% per year, compared to that of only 2.85% in patients with asymptomatic MCA disease.<sup>8</sup>

For many years, the degree of MCA atherosclerotic stenosis was thought to be the most accurate reflection of the ischemic stroke risk.<sup>9</sup> However, accumulating evidence suggests that stenotic grade does not really differ between symptomatic and asymptomatic groups of patients with moderate to severe MCA stenosis.<sup>10,11</sup> Thus, a shift took place

toward the vessel wall imaging (VWI) for the assessment of atherosclerotic plaque features.<sup>12–14</sup> Meanwhile, high-resolution magnetic resonance imaging (hr-MRI) has emerged as a novel diagnostic tool to assess both the coronary and extracranial carotid stenosis.<sup>15,16</sup> However, VWI is not yet as commonly used for MCA stenosis owing to technical limitations in the imaging of small structures and the lack of in vivo histological results for comparison.

To successfully image the intracranial vessel wall, the black blood technique was used by suppressing the MRI signal arising from luminal blood and cerebrospinal fluid (CSF) to obtain a high contrast-to-noise ratio (CNR). Blood and CSF suppression may be attained using spin-echo imaging, pre-regional saturation pulse, or a double-inversion recovery-based sequence.<sup>17</sup> However, the most common method is the three-dimensional (3D) turbo spin-echo sequences with variable flip angle refocusing pulses.<sup>18,19</sup> Recently, numerous imaging studies on MCA plaques have been published, suggesting that, in addition to the

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degree of stenosis, radiological characteristics may be an important predictor of plaque vulnerability.<sup>20,21</sup> As many of the studies had small sample sizes and as the relationship between MCA plaque morphology and the risk of stroke is unclear, we performed this meta-analysis to quantitatively synthesize existing evidence and evaluate the strengths of association of commonly investigated imaging features of symptomatic MCA plaques.

## 2. Materials and methods

This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>22</sup> Institutional Review Board approval and written informed consent were not required because this study was retrospective. This protocol is registered on PROSPERO (registration number is CRD42022316417).

### 2.1. Literature search strategy

The PubMed, EMBASE, Web of Science, and Cochrane Library databases were searched for publications up to March 2022. The following search terms were used in relevant combinations using the Boolean operators “OR” and “AND”: “middle cerebral artery,” “plaque, atherosclerotic,” “magnetic resonance imaging,” “high resolution,” and “gadolinium contrast” (Supplemental material: Search Strategy). In addition, we screened the reference lists of the included articles for further relevant studies.

### 2.2. Eligibility criteria

Two researchers independently screened studies, and disagreements were resolved by consensus. Inclusion criteria were as follows: (1) studies in which patients with atherosclerotic stenosis of the MCA were recruited; (2) studies in which patients who underwent hr-MRI of the MCA were included; and (3) studies in which imaging features were compared between symptomatic and asymptomatic atherosclerotic plaques of the MCA. We excluded studies in which (1) there was insufficient raw data, (2) duplicate data were reported, (3) only continuous variables were assessed as imaging end points, (4) <10 participants were included, and that (5) were cohort studies, conference abstracts, or letters.

### 2.3. Quality assessment

The quality of the selected studies was independently evaluated by two investigators using the “Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies,” provided by the National Institutes of Health.<sup>23</sup>

### 2.4. Data extraction

Two reviewers independently extracted data from the eligible studies, and discrepancies were resolved by consensus. The following data were collected: study characteristics (e.g., first author’s name, publication year, patient enrollment design, country in which the study was conducted, demographic data, and prevalence of stroke risk factors), MRI protocols (e.g., MR scanner, magnetic field strength, coil type, hr-MRI sequences, and certain sequence parameters), and MRI analysis (e.g., reader characteristics, imaging end point criteria).

### 2.5. Statistical analysis

Demographic characteristics and extracted variables were described using standard descriptive statistics. Categorical variables were expressed as frequencies and percentages, and continuous variables were expressed as means with standard deviations.

In the present meta-analysis, the association between the ischemic

event and the plaque imaging feature was measured by estimating the odds ratios (ORs) and corresponding 95 % confidence intervals (CIs). Pooled ORs for dichotomous variables were estimated using a random-effects (DerSimonian-Laird) model with the assumption that individual studies did not have the same effect size. Forest plots were generated when the imaging feature of interest was present in at least three studies. These included plaque T1 hyperintensity, T2 hyperintensity, contrast enhancement, eccentricity, and positive remodeling. In order to calculate ORs for studies in which the degree of contrast enhancement was classified with a three-level grading system (0: enhancement was less than or equal to that of intracranial arterial walls without plaque, 1: less enhancement than the pituitary stalk, 2: enhancement greater than or equal to that of the pituitary stalk), we dichotomized the three-level grading system as negative (grade 0) and positive (grade 1 to 2). A continuity correction of 0.5 was applied to studies with zero cell frequencies.

Heterogeneity among studies was tested using  $I^2$  statistics,<sup>24</sup> with values higher than 50% considered to indicate substantial heterogeneity. We explored factors that may account for heterogeneity by conducting subgroup analysis according to any binary variables that may have affected the consistency of a result across the enrolled studies. We further conducted sensitivity analysis with the “leave-one-out” method to assess the robustness of the results. Publication bias was assessed with a funnel plot and Egger’s test; a  $P$ -value < 0.05 was considered to indicate publication bias.

All statistical analyses were implemented using STATA statistical software: release 16 (StataCorp LLC, College Station, TX).

## 3. Results

### 3.1. Literature search

A flow chart summarizing the literature search is presented in Fig. 1. A total of 543 studies were identified during the initial search, of which 53 were selected after title and abstract screening. After reviewing the full texts, 17 studies met the inclusion criteria for our systematic review.<sup>11,13,21,25–38</sup>

### 3.2. Quality assessment

The risk of bias of the studies is summarized in the Supplemental table. The results were satisfactory, with all the studies except one<sup>37</sup> rated “good” or “fair.” As all the included studies were cross-sectional analyses, the answer to Questions 5–7 of the assessment guidance was “no.”

### 3.3. Characteristics of included studies

The basic demographic data and the prevalence of risk factors of the 17 studies are summarized in Table 1. In total, 1192 MCA atherosclerotic plaques of 1165 patients were eligible for the meta-analysis. The 17 included studies were all based on the Asian population: 16 were from China<sup>11,13,21,25–37</sup> and one from South Korea.<sup>38</sup> Eight<sup>11,21,25–27,30,37,38</sup> and nine<sup>13,28,29,31–36</sup> studies were prospective and retrospective cross-sectional studies, respectively.

In all the included studies, VWI was performed on 3.0 Tesla scanner using different types of coils. Hr-MR protocols used two-dimensional (2D),<sup>11,13,25–32,38</sup> 3D,<sup>33,35–37</sup> or both 2D and 3D sequences.<sup>21,34</sup> All but two studies<sup>35,36</sup> involved more than one reader evaluating plaque images for MCA stenosis (Table 2).

### 3.4. Data synthesis and statistical analysis

We included 533 plaques in eight studies<sup>13,27,28,30,33–35,37</sup> and 540 MCA atherosclerotic plaques in six studies<sup>13,28,29,31,34,35</sup> in the meta-analyzed for plaque contrast enhancement and T1 hyperintensity,

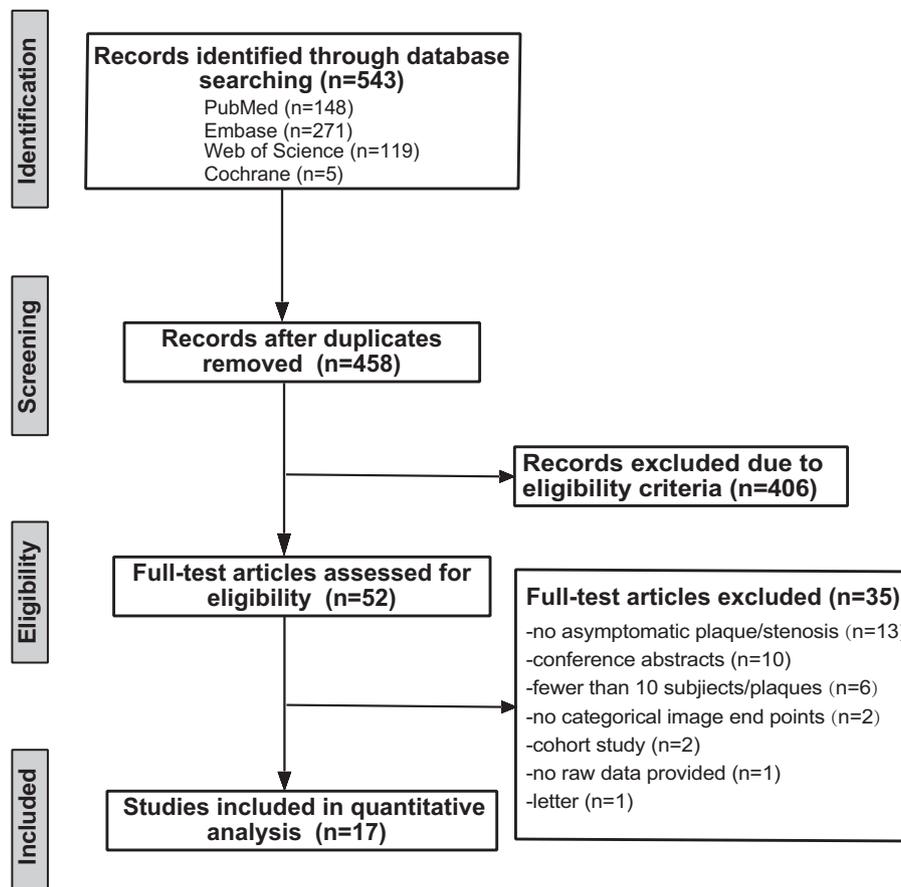


Fig. 1. Literature search flow diagram.

**Table 1**  
Demographics and risk factors of enrolled studies.

Study	Study design	Country	No. of subjects (plaques)	Age (years)	Male (%)	HTN (%)	DM (%)	Dyslipidemia (%)	Smoking (%)
Xu et al <sup>29</sup>	Retro	China	104 (109)	56.7 ± 12.8	81.3	67.3	30.8	44.9	61.7
Chung et al <sup>38</sup>	Pro	South Korea	30 (30)	65.8 ± 9.7	63.3	56.7	46.7	70.0	43.3
Xu et al <sup>11</sup>	Pro	China	61 (54)	62.4 ± 11.6	63.9	68.9	29.5	31.1	36.1
Yang et al <sup>28</sup>	Retro	China	73 (65)	63.0 ± 11.3	63.0	N/A	N/A	N/A	N/A
Xu et al <sup>30</sup>	Pro	China	32 (32)	65.8 ± 13.1	46.9	78.1	28.1	59.4	34.4
Zhao et al <sup>21</sup>	Pro	China	51 (51)	67.4 ± 8.8	58.8	64.7	35.3	NR	31.4
Teng et al <sup>13</sup>	Retro	China	139 (165)	57.1 ± 10.4	64.7	71.2	34.5	NR	29.5
Zhang et al. <sup>26</sup>	Pro	China	33 (33)	68.1 ± 11.8	81.8	81.8	51.5	NR	57.6
Lin et al <sup>36</sup>	Retro	China	53 (53)	53.6 ± 9.7	77.4	64.2	20.8	54.7	26.4
Lu et al <sup>33</sup>	Retro	China	46 (53)	60.7 ± 12.6	69.6	76.1	39.1	34.8	32.6
Meng et al <sup>32</sup>	Retro	China	192 (196)	57.0 ± 12.9	69.4	66.8	30.1	44.9	34.7
Shi et al <sup>31</sup>	Retro	China	88 (88)	N/A	N/A	N/A	N/A	N/A	N/A
Zhang et al <sup>27</sup>	Pro	China	65 (65)	68.1 ± 13.1	76.9	73.8	66.2	N/A	56.9
Zhang et al <sup>25</sup>	Pro	China	38 (38)	66.7 ± 12.3	78.9	65.8	57.9	N/A	52.6
Liang et al <sup>37</sup>	Pro	China	47 (47)	58.6 ± 8.8	44.7	66	63.8	38.3	29.8
Liu et al <sup>35</sup>	Retro	China	67 (67)	58.0 ± 12.4	61.2	61.2	22.4	38.8	38.8
Lu et al <sup>34</sup>	Retro	China	46 (46)	56.1 ± 15.1	67.4	76.1	28.3	47.8	28.3

SD, standard deviation; HTN, hypertension; DM, diabetes mellitus; N/A, data not available.

respectively. Symptomatic plaques were significantly associated with contrast enhancement (OR, 9.4; 95 % CI, 4.3–20.4;  $I^2 = 49.3\%$ ;  $P < 0.001$ ) and T1 hyperintensity (OR, 6.2; 95 % CI, 2.7–14.3;  $I^2 = 10.7\%$ ;  $P < 0.001$ ) (Fig. 2A, B).

In terms of plaque T2 hyperintensity, 411 plaques in six studies<sup>11,13,21,28,33,38</sup> provided data that were eligible for the meta-analysis. Symptomatic plaques were not significantly associated with T2 hyperintensity (OR, 1.4; 95 % CI, 0.8–2.3;  $I^2 = 0\%$ ;  $P = 0.19$ ) (Fig. 2C).

Eight<sup>11,21,25–27,35,36,38</sup> and seven<sup>11,28,30,32,34,35,38</sup> studies were meta-

analyzed for eccentricity and positive remodeling, respectively. However, the results were not pooled because we observed significant heterogeneity in the analysis.

### 3.5. Subgroup analyses and sensitivity analysis

Because plaque contrast enhancement was the most frequently studied imaging feature (n = 8 studies) and the pooled results had a moderate heterogeneity ( $I^2 = 49.3\%$ ), subgroup analysis was performed based on the (1) patient enrollment design (retrospective vs.

**Table 2**  
HR-MR images protocol and review.

Study	MR scanner	Field strength (T)	Coil type (channel)	Image protocol	Sequence to detect plaque	Field of view (cm)	Matrix	Image criterion of plaque	No. of MR readers
Xu et al <sup>29</sup>	GE Signa, VH/i	3.0	8	2D FSE T1W/T2W	N/A	Protocol 1: 13 × 13 Protocol 2: 16 × 16	Proto1: 256 × 256 Proto2: 384 × 224	N/A	2
Chung et al <sup>38</sup>	Siemens, Verio	3.0	8	2D BB T1W/T2W/PDW	N/A	10 × 12.5	256 × 204	N/A	2
Xu et al <sup>11</sup>	GE Signa, VH/i	3.0	8	2D FSE-T2W; DIR-T1W	T2W	13 × 13	256 × 256	Eccentric or focal wall thickening	2
Yang et al <sup>28</sup>	GE Signa, Excite HD	3.0	8	2D BB pre/post T1W; 2D FSE T2W	T2W	13 × 13	256 × 256	Eccentric or focal wall thickening	2
Xu et al <sup>30</sup>	GE, Piscataway	3.0	16	2D PDW; pre/post T1W	N/A	12 × 12	256 × 256	N/A	2
Zhao et al <sup>21</sup>	Siemens, Magnetom Verio	3.0	8	2D BB T1W/T2W/PDW; 3D SPACE T1W	N/A	2D:14 × 14 3D:20 × 17.5	2D: 256 × 256 2D: 225 × 256	N/A	2
Teng et al <sup>13</sup>	GE, HDx	3.0	8	2D BB FSE T2W, pre/post T1W;	T2W	10 × 10	320 × 256	PB >40%	3
Zhang et al <sup>26</sup>	Philips, Ingenia	3.0	8	2D BB T1W/T2W/PDW	PDW	0.8 × 0.8	180 × 144	N/A	2
Lin et al <sup>36</sup>	Siemens, Magnetom Skyra	3.0	20	3D SPACE pre/post T1W	T1W	20 × 17.8	N/A	N/A	1
Lu et al <sup>33</sup>	Siemens, Skyra	3.0	20	3D BB SPACE pre/post T1W	T1W	24 × 21.6	N/A	Focal wall thickening	2
Meng et al <sup>32</sup>	GE Signa, VH/I; Discovery MR750	3.0	8	2D FSE T2W	T2W	13 × 13	225 × 256	Eccentric or concentric wall thickening	2
Shi et al <sup>31</sup>	GE, Signa; Siemens, Skyra	3.0	8/20	2D FSE T2W, pre/post T1W	T2W	10 × 10	320 × 256	Eccentric or focal wall thickening with PB > 40%	2
Zhang et al <sup>27</sup>	Philips, Ingenia	3.0	8	2D BB PDW, pre/post T1W	PDW	0.8 × 0.8	180 × 144	N/A	2
Zhang et al <sup>25</sup>	Philips, Ingenia	3.0	8	2D BB PDW, pre/post T1W	PDW	0.8 × 0.8	180 × 144	N/A	2
Liang et al <sup>37</sup>	GE, MR750	3.0	8	3D FSE pre/post T1W	T1W	23 × 18.4	480 × 320	N/A	N/A
Liu et al <sup>35</sup>	Siemens, MAGNETOM	3	64	3D IR-SPACE PDW, pre/post T1W	N/A	N/A	N/A	PB > 40%	3
Lu et al <sup>34</sup>	Siemens, Verio/Skyra	3.0	32/16	3D BB SPACE PDW, pre/post T1W; 2D BB TSE T2W/T1W	T1W	3D PDW: 16 × 13 3D T1W: 24 × 21.6 2D: 13 × 13	2D: 320 × 320	N/A	2

HR-MR, high-resolution magnetic resonance; T1W, T1-weighted; T2W, T2-weighted; PD, proton density; 2D, two dimensional; 3D, three dimensional; BB, black blood; FSE, fast spin echo; SPACE, sampling perfection with application optimized contrasts using different flip angle evolution; PB; plaque burden; DIR, double inversion recovery; IR, inversion recovery; DSC, dynamic susceptibility contrast; PWI, perfusion-weighted imaging; N/A, data not available.

prospective), (2) MRI sequence type (2D vs. 3D), and (3) grading scheme of the degree of contrast enhancement (two vs. three levels).

Plaque enhancement had a significantly higher ( $P < 0.001$ ) association with downstream ischemic events in retrospective studies (OR, 12.4; 95 % CI, 3.2–47.7) than in prospective studies (OR, 8.5; 95 % CI, 3.7–19.9). The association was also significantly higher ( $P < 0.001$ ) when a two-level grading system was employed to evaluate enhancement (OR, 15.6; 95 % CI, 2.6–93.6) than when a three-level grading system was used (OR, 7.6; 95 % CI, 3.1–18.6). The strength of the association did not differ based on MRI sequence type for plaque enhancement ( $P = 0.56$ ) (Table 3).

Sensitivity analysis revealed that our results were robust (Fig. 3).

### 3.6. Publication bias

The funnel plot for plaque enhancement and an Egger's test ( $P = 0.09$ ) suggested no obvious publication bias (Fig. 4).

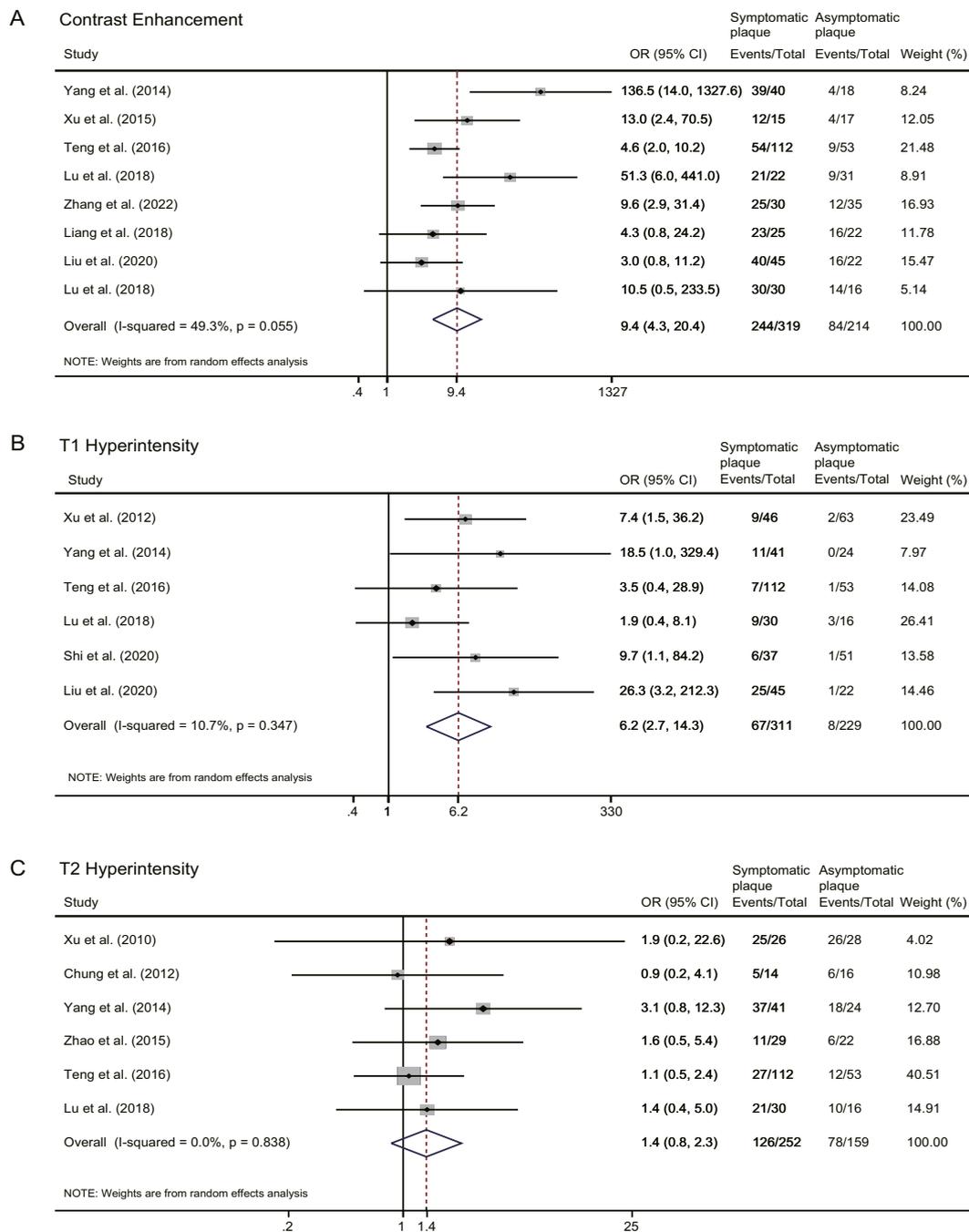
## 4. Discussion

It is important to improve the diagnostic confidence that an MCA

atherosclerotic plaque is the cause of a patient's ischemic stroke because it can help guide effective stroke prevention and treatment strategies. Our results indicate that MCA plaques with contrast enhancement and T1 hyperintensity are related to downstream ischemia. Unlike two previously published meta-analyses,<sup>39,40</sup> we only included studies in which VWI was used to evaluate atherosclerotic plaques of the MCA, rather than those of all intracranial arteries.

Based on previous postmortem MCA, carotid artery, and coronary artery pathological control studies,<sup>41,42</sup> T1 hyperintensity of hr-MRI may be due to both recent and fresh intraplaque hemorrhages (IPH). IPH is mostly attributed to fragile and leaky neovascularity with endothelial disruption and large local deformation.<sup>43</sup> It is closely linked to plaque progression, thin or ruptured fibrous caps, and clinical symptoms.<sup>44–47</sup> A meta-analysis revealed that T1 hyperintensity is a reliable predictor of subsequent stroke or transient ischemic attack for patients with extracranial carotid plaques.<sup>48</sup>

In our meta-analysis, T1 hyperintensity was more common in patients with symptomatic atherosclerotic stenosis than in those with asymptomatic plaques, which suggests that MCA atherosclerosis may share a common potential pathophysiology with carotid atherosclerosis. A major limitation to the use of T1 hyperintensity in intracranial plaques



**Fig. 2.** Forest plots of imaging features of symptomatic plaque. Forest plots of pooled data are graphically shown for 3 imaging features. Squares represent point estimates of a study's effect size and their sizes are proportional to the sample sizes. Horizontal lines show the corresponding 95 % confidence intervals (CIs). The vertical line represents an odds ratio of 1 (no effect). Diamonds represent pooled estimates with the diamond width representing 95 % CIs.

is that it has a low prevalence at the site of the stenosis due to the small size and deep location of the target vessel.<sup>29</sup> However, Lu et al<sup>34</sup> and Liu et al<sup>35</sup> improved the T1 hyperintensity rates in symptomatic MCA stenoses to 30% and 55.6%, respectively, using 3D sequences.

Plaque contrast enhancement, being a very attractive imaging marker of plaque vulnerability in both extracranial and intracranial arteries, is thought to be related to active inflammation, neovascularity, and increased endothelial permeability.<sup>38</sup> A postmortem study found that neovascularity in MCA atherosclerotic plaque was associated with ipsilateral infarction.<sup>41</sup> In our study, plaque enhancement was statistically significantly associated with symptomatic MCA plaques, and some of the included studies revealed that such enhancement may be

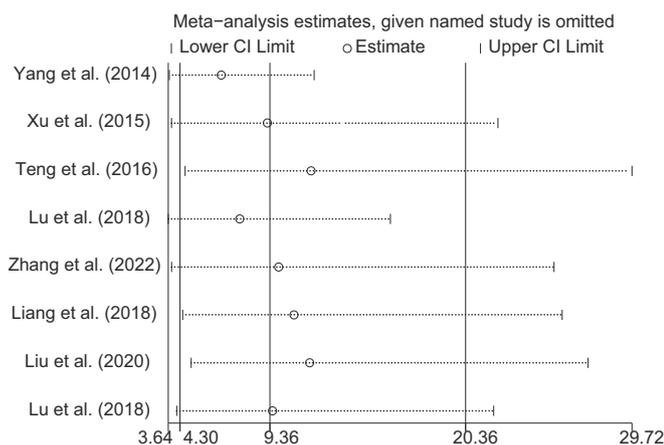
independent of the degree of stenosis. Infarction was approximately 10 times more likely to occur in patients with an enhancing MCA stenosis than in those with a non-enhancing MCA stenosis.

In the subgroup analysis for the patient enrollment design, the association between contrast enhancement and symptomatic plaques was higher for retrospective studies than for prospective studies, which may be because of selection bias. The association was also higher in studies in which a two-level grading system was used rather than a three-level grading system, probably because of increased measurement variability. Finally, although the strength of the association did not differ between studies in which 2D-sequences were used and those in which 3D-sequences were used, there was an increased association between

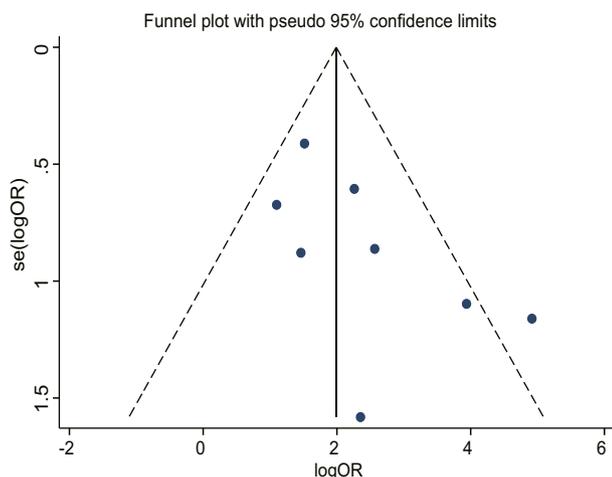
**Table 3**  
Results of subgroup analyses of contrast enhancement of symptomatic plaque.

Category	Subgroup	Studies no.	Odds ratio (95 % CI)	I <sup>2</sup> (%)	P value
Subject enrollment design	Retrospective enrollment	5	12.4 (3.2, 47.7)	68.9	<0.001
	Prospective enrollment	3	8.5 (3.7, 19.9)	0	
MR sequence type	2D sequence	4	12.0 (3.9, 37.2)	63.7	0.56
	3D sequence	4	7.4 (2.0, 27.0)	44.5	
Degree of contrast enhancement	Two grading	3	15.6 (2.6, 93.6)	75.5	<0.001
	Three grading	5	7.6 (3.1–18.6)	29.2	

MR, magnetic resonance; no., number; CI, confidence interval.



**Fig. 3.** Sensitivity analysis using a leave-one-out method.



**Fig. 4.** Funnel plot of studies evaluating plaque enhancement.

plaque enhancement and symptomatic plaques in studies in which 2D-sequences were used. A possible explanation is that a relatively low spatial resolution may be sufficient to detect enhancement of a lesion as a result of an increase in CNR caused by the contrast uptake.<sup>49</sup> In addition, Balu et al revealed that 3D-sequences improve small plaque component visualization of the carotid artery, while providing poor image quality caused by motion artifacts.<sup>50</sup>

Plaque hyperintensity on T2-weighted images has been documented to reflect plaque components, such as fibrous caps, IPH, or thrombi.<sup>51,52</sup>

In our study, T2 hyperintensity was not seen to be significantly associated with symptomatic plaques, which suggests that the T2 hyperintensity alone may not be a high-risk imaging biomarker.

#### 4.1. Limitations

There are several limitations to this study. First, most of the included studies had small sample sizes, with limited power for subgroup analyses. Second, all included studies were from Asian populations, which may cause publication bias. This is because ICAS accounts for 30–50% and 10% of ischemic cerebrovascular events in Asian and Western populations, respectively.<sup>6,53</sup> Especially in Chinese populations, it accounts for approximately 33–50% of stroke and 45% of TIA, which is far more than in other Asian countries.<sup>54,55</sup> Third, the wide CIs suggest low statistical power, leading to imprecise effect estimates. Finally, different methodologies were used in the included studies. Although the statistical analysis of heterogeneity in effect sizes showed homogeneity among studies, the methodological diversity may have led to misinterpretation of the pooled estimates.

#### 5. Conclusion

In this study, by pooling the available evidence, we identified two imaging markers for symptomatic MCA plaques: contrast enhancement and plaque T1 hyperintensity. These imaging features may help clinicians to improve patient diagnosis and treatment decisions. Future prospective, longitudinal studies of patients with ischemia are required to validate the utility of these imaging features as predictive markers.

#### Declaration of competing interest

None.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinimag.2022.08.001>.

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