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Effect of leukoaraiosis on collateral circulation in acute ischemic stroke treated with endovascular therapy: a meta-analysis

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Abstract

Background and objective The recruitment of collateral circulation correlates with a balance of the microvasculature. Uncertainty remains to be made about the association of leukoaraiosis with leptomeningeal collaterals. To explore the effect of leukoaraiosis on leptomeningeal collaterals in patients treated with endovascular therapy.

Methods Observational studies exploring the correlation between leukoaraiosis and leptomeningeal collaterals in large vessel occlusion treated with endovascular therapy were searched from PubMed, EMBASE, and Cochrane Libraries databases. Two independent reviewers retrieved eligible literature, extracted purpose-related data, and utilized the Newcastle–Ottawa Scale to evaluate the risk of bias. A Mantel–Haenszel method was used to calculate the odds ratio (OR). Meta-regression and subgroup analyses were conducted to clarify heterogeneity.

Results Data from 10 studies with 1606 patients were extracted for pooled analysis. Compared to non-severe leukoaraiosis, patients with severe leukoaraiosis showed significant relevance to poor leptomeningeal collaterals (OR, 2.13; 95% confidence interval [1.27–3.57]; $P=0.004$). Meta-regression indicated that sample size (coefficient = -0.007299, $P=0.035$) and the number of female patients (coefficient = -0.0174709, $P=0.020$) were sources of heterogeneity. Furthermore, all of the countries (USA versus France versus China, $Q=3.67$, $P=0.159$), various assessment scales of leukoaraiosis (the Fazekas scale versus Non-Fazekas scales, $Q=0.77$, $P=0.379$), and different imaging methods of leukoaraiosis (computed tomography versus magnetic resonance imaging, $Q=2.12$, $P=0.146$) and leptomeningeal collaterals (computed tomography angiography versus digital subtraction angiography, $Q=1.21$, $P=0.271$) showed no contribution to the effect size.

Conclusion Severe leukoaraiosis is associated with poor leptomeningeal collaterals in patients treated with endovascular therapy. Further studies may focus on whether the finding applies to different stroke subtypes.

Keywords Cerebral small vessel disease, Leukoaraiosis, Large vessel occlusion, Collateral circulation, Endovascular therapy, Meta-analysis

Introduction

Among patients with large vessel occlusion in the anterior circulation, endovascular therapy (EVT) has been demonstrated as the first-line therapy [1]. These patients who benefit from EVT reflect a small irreversible infarction (core infarction) and extensive rescue ischemia (penumbra) of brain tissue on preoperative imaging evaluation [2]. A good leptomeningeal collateral, supplying

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abundant blood flow from a retrograde route to regions dominated by the occluded artery, correlates with extensive penumbra and small core infarction [3]. Furthermore, the status of leptomeningeal collaterals can predict the recanalization rate [4], hemorrhagic transformation [5], and outcomes after EVT [6].

Emerging evidence suggests that older age, hypertension, and metabolic syndrome affect the recruitment of leptomeningeal collaterals [7–9]; however, the mechanism remains unclear. In animal models, these risk factors may result in vasodilatory dysfunction of the leptomeningeal collaterals [10]. Given that the leptomeningeal collateral is categorized as microvasculature in anatomy and physiology, investigating the impact of cerebral small vessel disease (CSVD) on it shows a strong rationale.

Leukoaraiosis, or white matter hyperintensity, is a core neuroimaging type of CSVD, and the pathogenesis of its occurrence is relevant to chronic ischemia of white matter caused by luminal stenosis or occlusion of arterioles, a part of microvasculature [11]. In addition, both computed tomography (CT) and magnetic resonance imaging (MRI) can be used as assessment methods for leukoaraiosis [12]. However, other types of CSVD are primarily evaluated by MRI, which is restricted to emergency patients. Therefore, more studies aim to assess the association between leukoaraiosis and leptomeningeal collaterals in patients treated with EVT.

Some studies demonstrated that severe leukoaraiosis was associated with poor recruitment of leptomeningeal collaterals [13–16], and others found that the status of leptomeningeal collateral was not affected by leukoaraiosis [17–22]. No randomized controlled trials have been designed to address this issue. In the present study, we conducted a meta-analysis to explore the effect of leukoaraiosis on leptomeningeal collaterals in acute ischemic stroke treated with EVT.

Methods

Search strategy

We performed the meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, 2020 edition [23]. Next, we systematically screened the PubMed, Embase, and Cochrane Library databases from inception to August 2022 by utilizing the terms: cerebral small vessel disease (CSVD), leukoaraiosis, white matter, and collateral. The detailed strategy is shown in Additional file 1.

Study selection

Followed items were eligible for inclusion criteria: (1) Observational studies; (2) patients with acute ischemic stroke in anterior circulation treated with EVT; (3) exploring the association of CSVD with collateral circulation. The animal experiments, review and meta-analysis, conference abstracts, case reports, and non-English articles were not part of our study.

Data extraction

After finding and removing the duplicates, two reviewers independently read titles and abstracts and extracted data from full texts based on selection criteria. The following variables were collected: the first author, publication year, country, recruitment time, sample size, age, sex, occlusion position, stroke pathogenesis, and methods of assessment for leukoaraiosis and leptomeningeal collaterals. Severe leukoaraiosis was defined as van Swieten scale (VSS) ≥ 2 scores [15, 17, 20], total Fazekas > 2 [13, 16, 21], as well as deep Fazekas 2 to 3 or periventricular Fazekas 3 [14, 18, 22]. Diagnostic criteria of poor leptomeningeal collaterals included American Society of Intervention and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) scores < 3 [13, 18, 20–22], contrast filling $\leq 50\%$ on the occluded territory [14–16], no collateral filling [19], and less than contralateral hemisphere [17].

Quality assessment

We utilized the Newcastle–Ottawa Scale (NOS) to evaluate the risk of bias, which scored from selection, comparability, and outcome sections and showed good quality with no fewer than 6 [24].

Statistical analysis

To explore the association of leukoaraiosis with poor leptomeningeal collaterals, we conducted pooled OR and 95% confidence interval (CI) through the inverse variance method (RevMan 5.3). Heterogeneity was testified by I^2 statistic. When $I^2 > 50\%$, we analyzed data based on a random-effect model, and when $I^2 \leq 50\%$, we used the fixed-effect model. Furthermore, publication bias was examined by the funnel plot (RevMan 5.3) and quantified through Egger's test (Stata 14.0). Aiming to elucidate heterogeneity, we incorporated covariates that affect the effect size into meta-regression for continuous variates and subgroup meta-analysis for categorial variates (Stata 14.0). Variates of sample size, mean age, and the number of female patients were delivered for meta-regression. Others were assigned for subgroup analysis, including countries (USA versus France versus China), assessment scales of severe leukoaraiosis (the Fazekas scale versus non-Fazekas scales), imaging methods of leukoaraiosis (CT versus MRI), imaging methods of leptomeningeal collaterals [digital subtraction angiography (DSA) versus CT angiography (CTA)]. The statistical significance of the P value was set at 0.05.

Results

Study selection

A total of 891 items were retrieved according to the customized strategy. Then, 168 duplicate publications were removed before reviewing the titles and abstracts, of which 50 studies required full-text reading. Last, this study included ten studies [13–22] (Fig. 1).

Study characteristics

From 2012 through 2022, 1606 patients with acute ischemic stroke in anterior circulation treated with EVT were screened at the ten sites of observational studies from China, the USA, and France. Details on age, number of female patients, occlusion position, stroke pathogenesis, and assessment methods for leukoaraiosis and leptomeningeal collaterals are shown in Table 1. Henninger et al. [17] in 2012 were included in the pooled analysis due to its criteria of patient selection suitable for EVT, evidenced as the first-line therapy for this group in 2018 [1]. All ten studies showed poor leptomeningeal collaterals as an outcome. Consequently, we extracted data from the ten studies to explore the association of leukoaraiosis with poor leptomeningeal collaterals.

Quality assessment

Six studies were demonstrated for good quality with NOS ≥ 6 (Table 1), and specific items were found in Additional file 2.

Meta-analysis outcomes

The meta-analysis, utilizing a random-effect model with I^2 of 74%, showed a significant correlation between severe leukoaraiosis and poor leptomeningeal collaterals (pooled OR 2.13, 95% CI 1.27–3.57, $P=0.004$) (Fig. 2). Meta-regression indicated that sample size (coefficient = -0.007299, $P=0.035$) and the number of female patients (coefficient = -0.0174709, $P=0.020$) rather than mean age ($P=0.991$) were potential sources of heterogeneity. As Fig. 3 shown, the effect size decreased with increasing sample size (Fig. 3a) and the number of female patients (Fig. 3b). Mechtouff et al. [21] did not report the number of females out of 109 patients as an outcome analysis; therefore, the covariate of this study was eliminated from meta-regression (Fig. 3b). Among categorical variates of countries (Q = 3.67, $P=0.159$), assessment scales of leukoaraiosis (Q = 0.77, $P=0.379$), images of leukoaraiosis (Q = 2.12, $P=0.146$), images of leptomeningeal

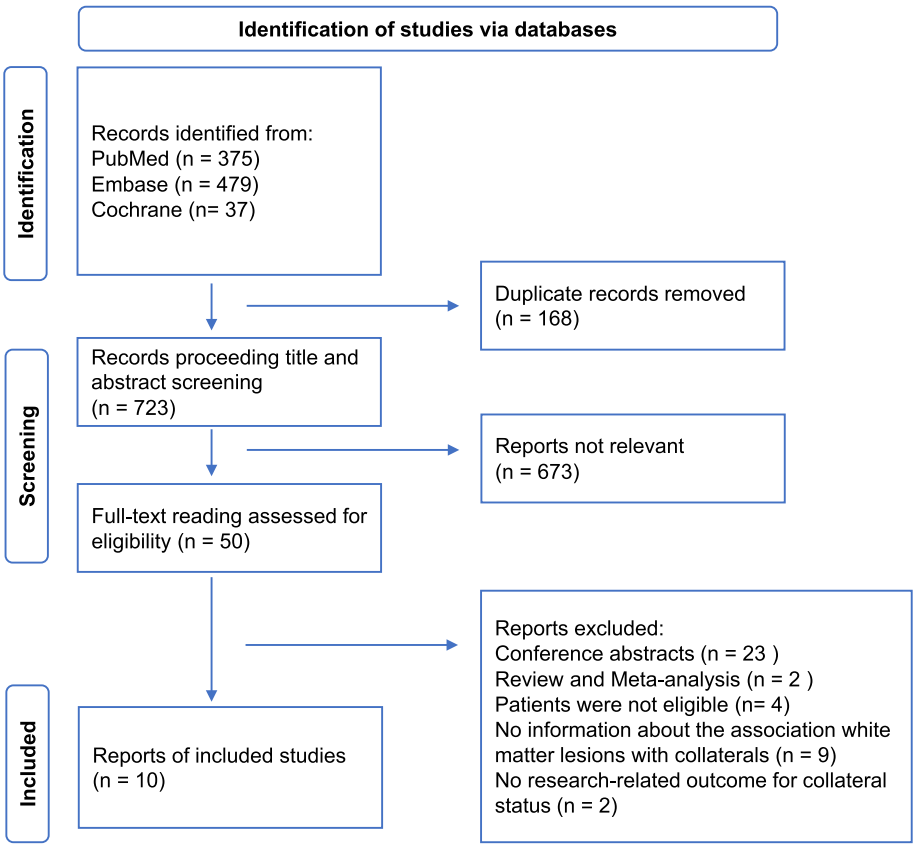

Fig. 1 PRISMA screening flowchart

Table 1 Summary of the included studies

Author (Year)	Country	Recruitment year	Sample, n	Severe leukoaraiosis/poor collateral, n	Severe leukoaraiosis/good collateral, n	Age [Mean ± SD or Median (IQR)]	Female, n (%)	Occlusion position	Stroke etiology, n (%)	Leukoaraiosis			Leptomeningeal collaterals			NOS
										Image	Scale	Definition of severe leukoaraiosis	Image	Scale	Definition of poor leptomeningeal collaterals	
Henninger (2012) [17]	USA	2007–2010	87	19/68	2/19	67.0 ± 16.0	39 (45.0)	intracranial ICA, M1, M2	LAA 20 (23) CE 38 (44) Others 29 (33)	CT	VSS	≥ 3	CTA	proposed by Lima et al	absent or less than the contralateral hemisphere	4
Eker (2019) [18]	France	2013–2018	240	19/104	33/136	68.7 ± 16.1	118 (49.2)	intracranial ICA, M1, M2	NA	MRI	Fazekas	Deep Fazekas 2–3; Periventricular Fazekas 3	DSA	ASITN/SIR	0–2 score on the occluded territory	6
Lin (2020) [14]	USA	2012–2017	100	24/46	6/54	64.6 ± 16.1	55 (55)	ICA, M1, M2	ICAS 33 (33) TL 32 (32)	MRI	Fazekas	Deep Fazekas 2–3; Periventricular Fazekas 3	CTA	Tan score	contrast filling < 50% on the occluded territory	6
Mark (2020) [13]	USA	NA	178	33/49	48/129	67.6 ± 14.8	91 (51.1)	Anterior circulation	NA	CT	Fazekas	Total Fazekas > 2	CTA/DSA	ASITN/SIR	0–1 score on the occluded territory	6
Mechtouff (2020) [21]	France	2013–2019	293	NA/33[a]	NA/76[a]	67.1 ± 16.2	133 (45.6)	intracranial ICA, M1	NA	MRI	Fazekas	Total Fazekas > 2	DSA	ASITN/SIR	0–2 score on the occluded territory	4
Mutzenbach (2020) [19]	USA	2012–2019	209	9/50	26/159	75(63–81)	111 (53.1)	M1	LAA 23 (11) CE 115(55)	MRI/CT	ARWMC	Top 25 percentiles	CTA	Tan score	contrast filling = 0 on the occluded territory	4
Mikat (2020) [20]	USA	2012–2016	144	7/38	15/106	68(57–81)	71 (49.3)	Anterior circulation	LAA 30 (21) CE 74 (51) ESUS 27(19)	CT	VSS	≥ 3	DSA	ASITN/SIR	0–2 score on the occluded territory	4
Forestier (2022) [22]	France	2015–2020	312	59/207	27/105	67.8 ± 14.9	146 (46.8)	intracranial ICA or M1	NA	MRI	Fazekas	Deep Fazekas 2–3; Periventricular Fazekas 3	DSA	ASITN/SIR	0–2 score on the occluded territory	6
Hashimoto (2022) [16]	USA	2015–2019	108	36/41	33/67	76.5 (63.3–86.0)	49 (45.3)	terminus ICA, M1, M2	CE 82 (76) TL 12 (11) ESUS 10 (9)	MRI	Fazekas	Total Fazekas > 2	CTA	Tan score	contrast filling ≤ 50% on the occluded territory	6
Zhou (2022) [15]	China	2018–2021	119	16/40	15/79	74(61–84)	51 (42.9)	M1, M2	ICAS 93 (78.2)	MRI	VSS	≥ 2	CTA	Tan score	contrast filling < 50% on the occluded territory	6

LAA Large-artery atherosclerosis, *CE* Cardiogenic embolism, *TL* Tandem lesions, *ICAS* Intracranial atherosclerosis, *ESUS* Embolic stroke of undetermined source, *ICA* Internal carotid artery, *M1* The first segment of the middle cerebral artery, *NOS* Newcastle–Ottawa Scale, *VSS* Van Swieten scale, *ASITN/SIR* American Society of Intervention and Therapeutic Neuroradiology/Society of Interventional Radiology, *DSA* Digital subtraction angiography, *CTA* Computed tomography angiography, *SD* Standard deviation, *IQR* interquartile range, *NA* Not available

[a] Mechtouff et al. reported odds ratio (OR) about the association of severe leukoaraiosis with poor leptomeningeal collateral based on 109 patients who acquired the scores of leptomeningeal collaterals

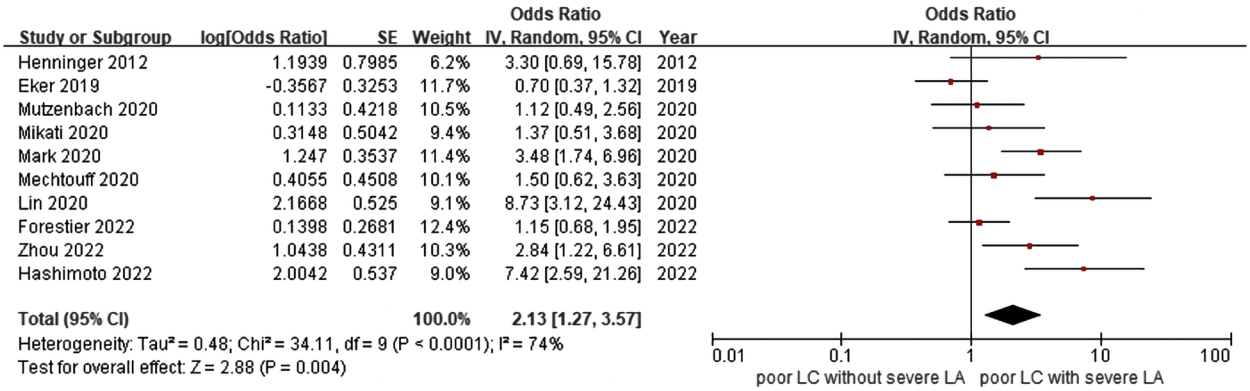

Fig. 2 Forest map of the association between leukoaraiosis and poor leptomeningeal collaterals

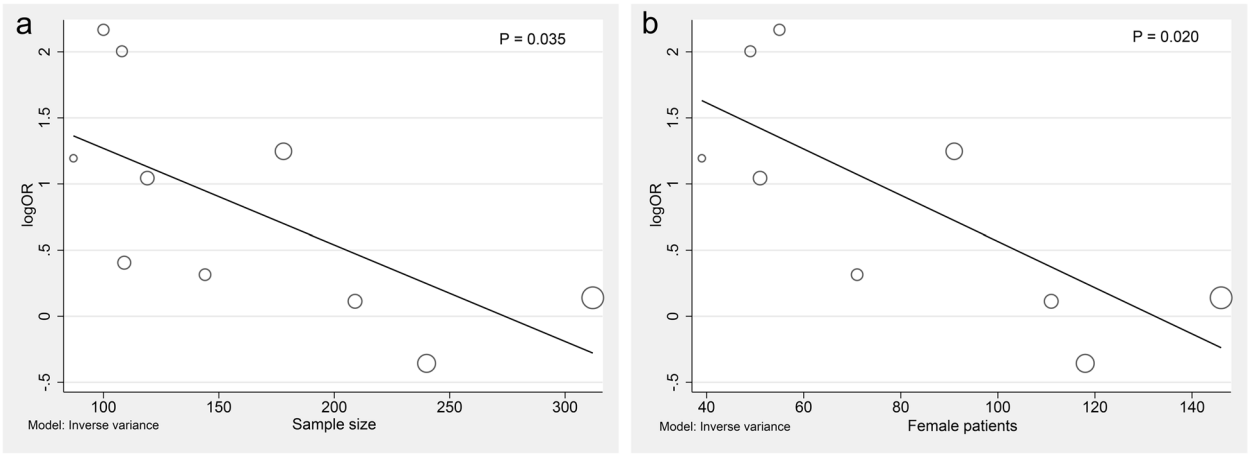

Fig. 3 Bubble plot of the association of sample size and female patients with effect size. **a** the association between sample size and effect size; (**b**) the association between number of female patients and effect size

collaterals (Q = 1.21, $P = 0.271$), all the subgroup analysis demonstrated no significant difference between groups (Fig. 4).

Publication bias

The funnel plot showed that three studies were away from the interval range of effect value (Fig. 5). Egger's test ($p = 0.085$) showed no significant publication bias for included studies.

Discussion

In this study, we found that severe leukoaraiosis was associated with poor recruitment of leptomeningeal collaterals in patients treated with EVT. Compared with non-severe leukoaraiosis, severe leukoaraiosis increased 2.13 times risk for emerging poor leptomeningeal collaterals.

Included studies showed no publication bias; nevertheless, our results demonstrated that the sample size and the number of female patients correlated with significant heterogeneity based on the meta-regression and subgroup analysis. Heterogeneity in sample size may be due to the fact that larger sample size is usually associated with greater statistical power, a smaller source of error, and higher study quality. Heterogeneity caused by sex may be related to Estrogen, a sex steroid, which showed protection for the neurovascular unit, including the leptomeningeal collaterals and brain parenchyma [25, 26]. Female patients in our study were in the stage of menopause; therefore, low-concentration Estrogen may show poor neuroprotection.

According to our report, the study countries among China, USA, and France showed no heterogeneity in concluding the association of severe leukoaraiosis with poor leptomeningeal collaterals. However, a recent meta-analysis demonstrated that patients from the USA contributed to the heterogeneity [27]. This discrepancy may result from two categories (USA vs. Non-USA) for the

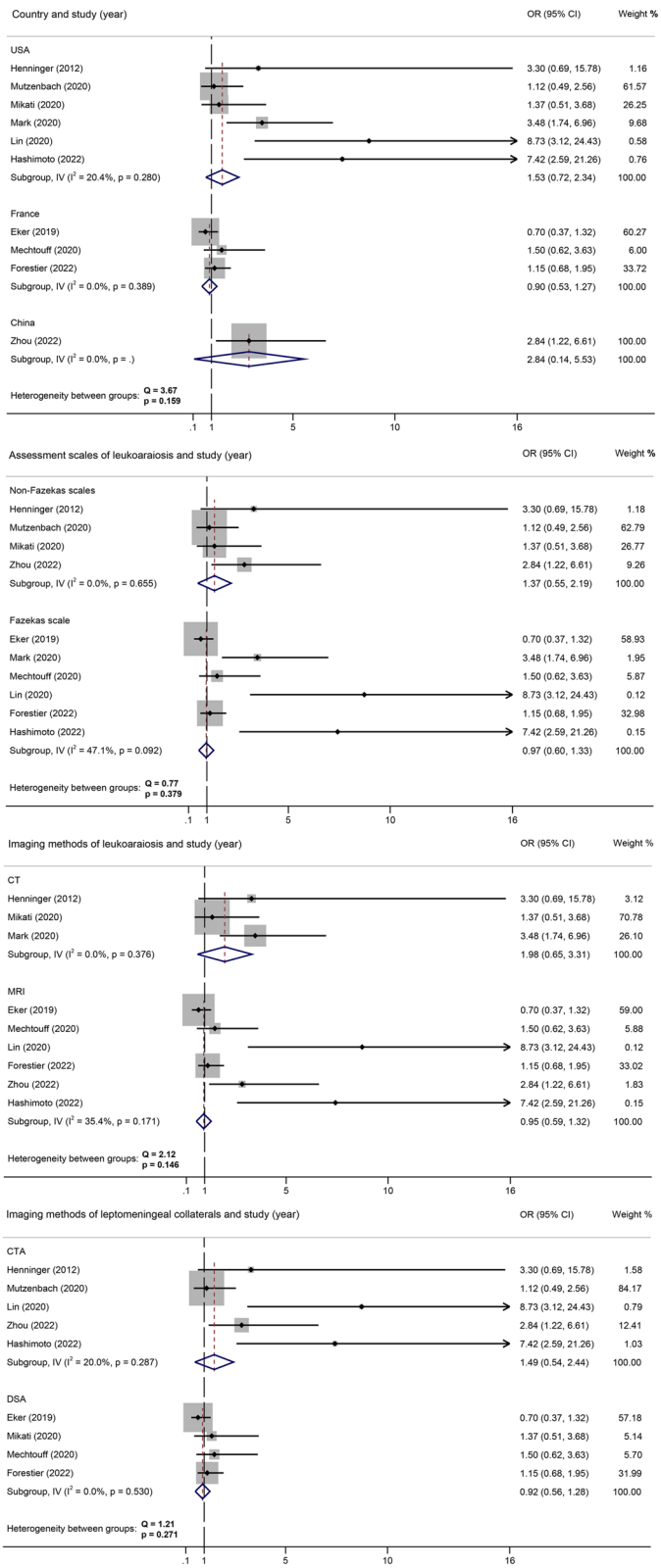

Fig. 4 Subgroups meta-analysis of the association between leukoaraiosis and poor leptomeningeal collaterals. Legend: MRI, magnetic resonance image; CT, computed tomography; DSA, digital subtraction angiography; OR, odds ratio. Mutzenbach et al. reported both CT and MRI as images of leukoaraiosis; therefore, this study was excluded from analysis in this subgroup. Mark et al. reported both DSA and CTA as images of leptomeningeal collateral; therefore, this study was excluded from analysis in this subgroup

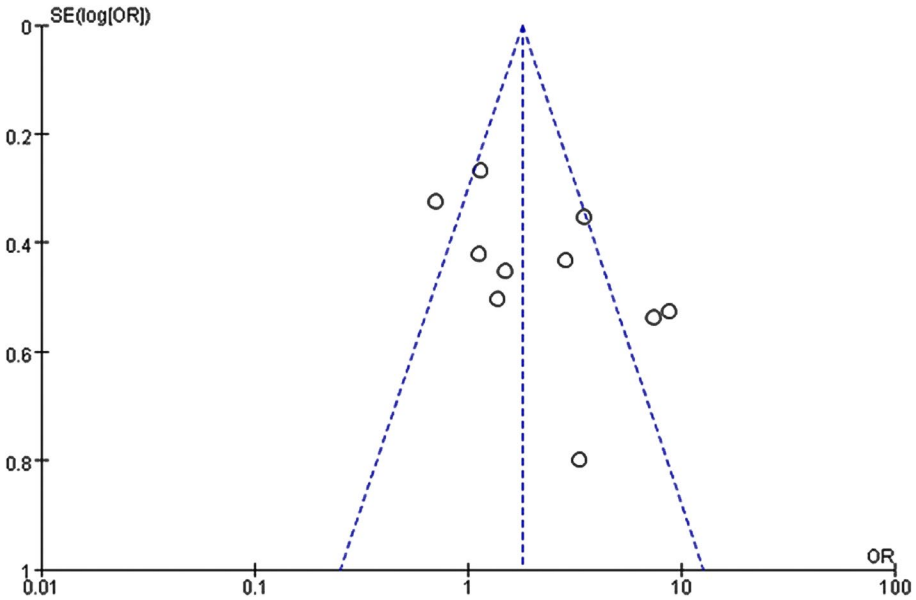

Fig. 5 Funnel plot of the association between leukoaraiosis and poor leptomeningeal collaterals

previous meta-analysis and three for ours. In addition, all patients in our study were suitable for EVT due to large vessel occlusion, while part of the formers was included with large vessel stenosis. Types of stroke etiology vary among different countries; for example, intracranial atherosclerosis (ICAS) is a common mechanism in China [28], and cardiogenic embolism (CE) in Western counties [29]. Patients with atherosclerosis-related stroke, including intracranial or extracranial segment, constructed better collateral flow to resist chronic ischemia compared with CE-related sudden occlusion [30, 31]. However, from the perspective of study design for stroke etiology, only Hashimoto et al. demonstrated that severe leukoaraiosis decreased the recruitment of leptomeningeal collaterals in CE-related occlusion [16]. In our study, we could not conduct subgroup analysis based on the stroke subtype due to the absence of stratification in original studies. Further research is required to address this issue.

Accurate evaluation of leukoaraiosis was essential to predict the status of leptomeningeal collaterals. Our results found no heterogeneity among visual assessment scales and imaging methods. To date, the Fazekas devised in 1987 [32], VSS in 1990 [33], and age-related white matter change (ARWMC) in 2001 [12] were still the most common scales to assess leukoaraiosis and any of the scales showed good efficiency between inter- and intra-raters. MRI showed more sensitivity than CT to detect white matter changes, especially for small lesions, whereas severe lesions were evaluated equally with CT and MRI [12, 34]. Although volumetric quantification of leukoaraiosis was superior to rating scales [35], it may be poorly applicable to clinical practice. The selection of patients treated before EVT demands assessment methods compatible with brevity and effectiveness to shorten recanalization time. Hence, to predict the status of leptomeningeal collaterals, we may choose CT as a priority to evaluate whether the patients treated with EVT emerge with severe leukoaraiosis. Similarly, our results found no heterogeneity between the imaging techniques used to assess leptomeningeal collaterals (CTA and DSA). However, the dichotomous leptomeningeal collaterals for ordinal classification in the original literature were not always consistent, so the classification systems for leptomeningeal collaterals may be a potential source of heterogeneity.

Arteriolosclerosis is a common pathogenic classification of leukoaraiosis and belongs to age-related and vascular risk-factor-related small vessel disease [36]. Age and heredity are non-interventional factors; however, decreasing the variability of blood pressure may alleviate the process of leukoaraiosis [37]. Furthermore, proper management of diabetes and ceasing smoking show neuroprotection for white matter [38, 39]. Recently, Dl-3-butyl phthalide, a neuroprotective drug approved in clinical practice for the Chinese in 2005, established its value in improving cerebral hypoperfusion by increasing the flow of collateral circulation in patients with carotid artery atherosclerotic stenosis [40]. However, the protective effect of Dl-3-butyl phthalide on the white matter was just demonstrated in mice models [41]. This drug might be a promising therapy for leukoaraiosis in clinical practice.

The strengths of our study include one study population (patients treated with EVT) and a detailed

exploration of heterogeneity by meta-regression and subgroup analysis. Cautiously, our results are appropriate for patients treated with EVT. We excluded non-English studies, which may result in a selection bias due to published language. The relatively small number of original studies weakens the ability to draw meaningful conclusions about subgroups. More research is needed to validate our findings.

Conclusion

In summary, severe leukoaraiosis was associated with poor leptomeningeal collaterals in patients treated with EVT. Further studies may focus on whether the finding applies to different stroke subtypes.

Abbreviations

EVT	Endovascular therapy
CSVD	Cerebral small vessel disease
CT	Computed tomography
MRI	Magnetic resonance imaging
CI	Confidence interval
ICAS	Intracranial atherosclerosis
CE	Cardiogenic embolism

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-023-03266-8.

Additional file 1: Table 1. A search strategy in the PubMed database.

Additional file 2: Table 2. Quality assessment of the included studies using the Newcastle-Ottawa scale.

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None

Authors' contributions
W.H. conceiving and planning the presented meta-analysis. W.C. and Y.Q. searching the literature, extracting data and writing the first draft. S.Y. analyzing the data. L.Y. and Y.H. helping with editing the paper. All authors contributed to the development of the manuscript and had agreed to submit the final version.

Availability of data and materials
The datasets supporting the conclusions of this article are included within the paper and its additional files.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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