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White matter hyperintensity burden and functional outcomes in acute ischemic stroke patients after mechanical thrombectomy: A systematic review and *meta*-analysis

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A R T I C L E I N F O

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A B S T R A C T

Background: The influence of white matter hyperintensity (WMH) on clinical outcomes in acute ischemic stroke (AIS) patients treated with mechanical thrombectomy (MT) remains controversial. We performed a systematic review and *meta*-analysis to examine whether WMH burden is associated with clinical outcomes in AIS patients after MT.

Methods: PubMed, Embase, and Web of Science were searched from inception to Sep 03, 2023. The registration number for PROSPERO is CRD42022340568. Studies reporting an association between the burden of WMH in AIS patients and clinical outcomes after MT were included in the *meta*-analysis. A random-effects model was used for *meta*-analysis. The quality of the included studies was assessed using the Newcastle-Ottawa Scale. Additionally, the presence of imprecise-study effects was evaluated using Egger's test and funnel plot.

Results: Fifteen studies with 3,456 patients were enrolled in this *meta*-analysis. Among AIS patients who underwent MT, moderate/severe WMH had higher odds of 90-day unfavorable functional outcomes (odds ratio [OR] 2.72, 95% confidence interval [CI] 2.14-3.44; $I^2 = 0.0\%$; 95% CI 0.0%-42.7%), 90-day mortality (OR 1.94, 95% CI 1.45-2.60; $I^2 = 19.5\%$; 95% CI 0.0%-65.2%) and futile recanalization (OR 2.99, 95% CI 1.42-6.28; $I^2 = 69.7\%$; 95% CI 0.0%-91.0%) compared with none/mild WMH. However, the two groups had no significant difference in successful recanalization, symptomatic hemorrhagic transformation, and hemorrhagic transformation. A subset analysis of patients from 3 articles showed that WMH volume was not significantly associated with these outcomes. A notable limitation is that this *meta*-analysis lacks direct adjustment for imbalances in important baseline covariates.

Conclusions: Patients with moderate/severe WMH on baseline imaging are associated with substantially increased odds of 90-day unfavorable outcomes, futile recanalization, and 90-day mortality after MT. This association suggests that moderate/severe WMH may contribute to the prediction of clinical outcomes in AIS patients after MT.

1. Introduction

Globally, stroke remains the second leading cause of death and the third leading cause of death and disability combined (Albo et al., 2021). Endovascular thrombectomy (EVT) can improve the prognosis of acute ischemic stroke (AIS) caused by large vessel occlusion (Atchaneeyasakul et al., 2017) and has gradually become a powerful tool for treating ischemic stroke with large vessel occlusion (Avci et al., 2015). However, 31%- 50% of patients who received mechanical thrombectomy (MT) suffered from futile recanalization (FR), leading to a 90-day poor

Abbreviations: WMH, white matter hyperintensity; MT, mechanical thrombectomy; mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage; FR, futile recanalization; HT, hemorrhagic transformation; mTICI, modified Thrombolysis in Cerebral Infarction; OR, odds ratio; VSS, van Swieten Scale; ARWMC, age-related white matter changes; NIHSS, National Institutes of Health Stroke Scale.

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functional outcome (modified Rankin Scale [mRS] 3–6) despite successful recanalization (Benson et al., 2021). Past studies have shown that old age, delayed reperfusion, diabetes, and site of occlusion were predictors for poor functional outcomes (Boulouis et al., 2019; Choi and Lam, 2016).

White matter hyperintensity (WMH) is a lesion of the brain parenchyma caused by small vessel disease (SVD), which can be easily detected by neuroimaging (Dávalos et al., 2017), which is common in the elderly and has a higher prevalence in stroke and transient ischemic attack compared to healthy individuals (Deng et al., 2022). Magnetic resonance imaging (MRI) demonstrates that as SVD progresses, there is a deterioration in the pathological changes in the cerebral white matter. Furthermore, white matter fibers affected by SVD may undergo degenerative alterations, leading to secondary degeneration in the remote cortex or brainstem, resulting in global cerebral effects (Derraz et al., 2021). Previous studies have reported that cerebrovascular risk factors such as age, hypertension, diabetes mellitus, hyperhomocysteinemia, high sensitivity C-reactive protein, and forced expiratory volume in 1 s are risk factors for WMH (Derraz et al., 2022; Fazekas et al., 1987; Feigin et al., 2021; Gilberti et al., 2017; Goyal et al., 2016). WMH is a critical component of the pathology of Alzheimer's disease, and a higher WMH burden is associated with worse executive function and poorer memory (Guo et al., 2019). Previous studies have found that WMH is a significant predictor of futile recanalization after MT (Hachinski et al., 1987; Henninger et al., 2014). However, controversy exists over the association between WMH burden and clinical outcomes in patients with AIS after MT.

WMH burden is usually assessed by visual assessment or semi-automatic plane segmentation volume. The severity of white matter lesions before MT is correlated with a poor 90-day outcome (i.e., mRS 3–6 at 90 days) in patients with ischemic stroke following endovascular revascularization and is an independent risk factor for a worse prognosis (Huo et al., 2021). In sharp contrast, another study has shown that WMH burden does not appear to influence clinical outcomes in patients treated with MT (Jadhav et al., 2021). One previous systematic review and *meta*-analysis showed that severe WMH was associated with a worse 90-day functional outcome and higher mortality for post-MT patients (Lam et al., 2021). This study is significant, but the number of included studies is limited. In addition, several new studies have been recently reported on this topic since then, and some conclusions remain controversial from the review (Huo et al., 2021; Liao et al., 1997; Liberati et al., 2009). Therefore, it is necessary to clarify the association between WMH and clinical outcomes of patients after MT through *meta*-analysis based on updated data to provide clinicians and researchers with up-to-date information.

2. Methods

We conducted and reported this review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Supplement Material) (Linfante et al., 2016). This review and *meta*-analysis were registered with the PROSPERO (registration number, CRD42022340568; https://www.crd.york.ac.uk/PROSPERO/).

2.1. Search strategy

Two investigators (H. Fan and L. Wei) independently searched the PubMed, Embase, and Web of Science databases for studies published from inception to Sep 03, 2023. The search was conducted using MeSH terms "White matter hyperintensity", "White matter lesions", "White matter change", "White matter disease", "leukoaraiosis", "Mechanical thrombectomy", "endovascular thrombectomy", "EVT", and "MT". The details of the search strategy used in the three databases are available in the "Supplementary Material". The reference lists of other related articles and the eligible studies were examined to identify potential studies of interest.

2.2. Selection of studies

Two investigators (H. Fan and L. Wei) independently assessed the eligibility of these articles for inclusion. The search results were initially screened by title and abstract, followed by full-text assessments of relevant articles, and objections raised by them were resolved through consultations. Eligible studies meet the following inclusion characteristics: (1) Observational or randomized studies that reported the association between WMH and clinical outcomes after MT in ischemic stroke; (2) Odds ratio (OR) or risk ratio (RR) and 95% confidence interval (CI) provided or sufficient data to calculate; (3) English language. Exclusion criteria were as follows: (1) summary of meetings; (2) animal studies; (3) case reports and reviews; (4) studies with no relevant data of interest; (5) non-independent studies. The study with the largest sample size was included if the same population data were published in multiple articles. The WMH severity followed the definitions in eligible studies, and moderate/severe WMH was defined as van Swieten Scale (VSS) 3–4 or Fazekas scale 3–6 if the WMH burden degree was not defined in the studies. Symptomatic hemorrhagic transformation (sICH) was defined as causing clinical deterioration of $\geq$ 4 points on the National Institutes of Health Stroke Scale (NIHSS) within 36 h, and FR was defined as successful recanalization without good functional outcome at 90 days.

2.3. Data extraction

Data were independently extracted into a unified Excel sheet by two investigators (H. Fan and L. Wei), and all the disputes were resolved through discussions to ensure accuracy. The following data were extracted from all included studies: first author, region, details of study design, initiation date and termination date of the studies, baseline characteristics of study participants (age, sex, type of MT device, baseline NIHSS score, and WMH assessment tool), the sample size of each group, and the effect estimates with 95% CI for the outcome of interest, including 90-day mRS score, mortality at 90 days, hemorrhagic transformation (HT), sICH, FR and successful recanalization (modified Thrombolysis in Cerebral Infarction [mTICI] 2b-3). In addition, when the effect estimate could not be obtained directly from the articles, ORs were calculated through the 2 x 2 table.

2.4. Quality assessment

Two investigators (H. Fan and L. Wei) independently conducted quality assessments of the included studies, and disagreements were resolved by discussion and further review. Newcastle-Ottawa Scale was used to assess the quality of included studies (Liu et al., 2019). Quality scores range from 0 to 9, with 9 being the highest quality. Details of the assessment included the representation of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, comparability, whether the outcome is present at the start of studies, follow-up length, and adequacy of follow-up.

2.5. Statistical analysis

We used a random effects model (Der Simonian and Laird method) to calculate the pooled ORs of all outcomes and their 95% CIs. Heterogeneities between studies were assessed by the I^2 statistic with 95% CIs (significant if $I^2 \geq 50\%$ or wide 95% CIs) (Longstreth et al., 1996), and moderate and high heterogeneities were defined by $I^2 \geq 50\%$ and $I^2 \geq 75\%$, respectively. Additionally, based on the data provided by the included articles, the association between WMH severity (moderate/severe WMH, none/mild WMH) and clinical outcome (90-day mRS score) were assessed by calculating proportional ORs and 95% CIs across the entire mRS range at 3 months (shift analysis) in ordinal logistic regression models. This model was fitted using maximum likelihood estimation and included a single random intercept. Additionally, the baseline covariates were not directly incorporated into the model since

the baseline covariates for each mRS score among studies were not directly available. Separate pooled analyses were performed for studies assessing the association between WMH volume and clinical outcome. Subsequently, we performed a subgroup analysis based on WMH assessment tools. To ensure the robustness of the results, we performed a jackknife sensitivity analysis, which investigates the influence of a single study on the overall effect estimate by omitting one study at a time and repeating the *meta*-analysis based on the remaining data (Mechtouff et al., 2019). We used Egger's test to assess the symmetry of the funnel plot for imprecise-study effects (Meguro et al., 2007). Data were analyzed using IBM SPSS, version 25.0 (IBM), and Stata Release 16 (StataCorp LLC, College Station, TX, USA).

3. Results

3.1. Literature search

The literature screening flow chart is shown in Fig. 1, including the number of articles initially selected from the databases (PubMed, Embase, and Web of Science) and the number of excluded studies and reasons for exclusion. Initially, 2,866 articles were retrieved, of which five were obtained from relevant reviews (Henninger et al., 2014; Mikati et al., 2020; Miller rg., 1974; Mistry et al., 2020; Mutzenbach et al., 2020). One study (Pantoni, 2010) used the same population data as the study by Albo et al., and this study was excluded from the *meta*-analysis to avoid duplication of patient data from the same population. After deduplication and title/abstract screening, 42 articles were assessed for full text, and 15 were finally included in the systematic review (Mikati et al., 2020; Mistry et al., 2020; Mutzenbach et al., 2020; Hachinski et al., 1987; Henninger et al., 2014; Huo et al., 2021; Jadhav et al., 2021; Lam et al., 2021; Liao et al., 1997; Liberati et al., 2009; Qiu et al., 2011; Saver et al., 2012; Schmidt et al., 1992; Shi et al., 2012; Shimomura et al., 2008).

3.2. Study characteristics and quality assessment

The characteristics of the included studies are shown in Table 1. Among the 15 included studies, 2 were prospective observational studies, 1 was a randomized controlled trial (RCT), 1 had both RCT and retrospective data, and the rest were retrospective studies. Of the 3,456 patients included, 1,808 (52.3%) were male. WMH was assessed by computed tomography in 7 studies and MRI in 7 studies, using both methods in 1 study. There were 4 assessment tools for the degree of WMH, 4 studies used the VSS (Sillanpää et al., 2018), 5 studies used Fazekas score (Smith et al., 2008), 3 studies used WMH volume (Liao et al., 1997; Schmidt et al., 1992; Shi et al., 2012), and 3 studies used the age-related white matter change (ARWMC) scale (Soize et al., 2013). The timespan of eligible studies ranged from 3 to 84 months. The quality of the included studies was satisfactory, and the Newcastle-Ottawa Scale scores were between 7 and 9. Specifically, 8 studies achieved a score of 9, 6 studies received a score of 8, and 1 study obtained a score of 7. The specific details are shown in Table A. 14 studies had the baseline NIHSS score, which was used to assess stroke severity. The primary outcome was the 90-day mRS score, determined by telephone interviews, face-to-

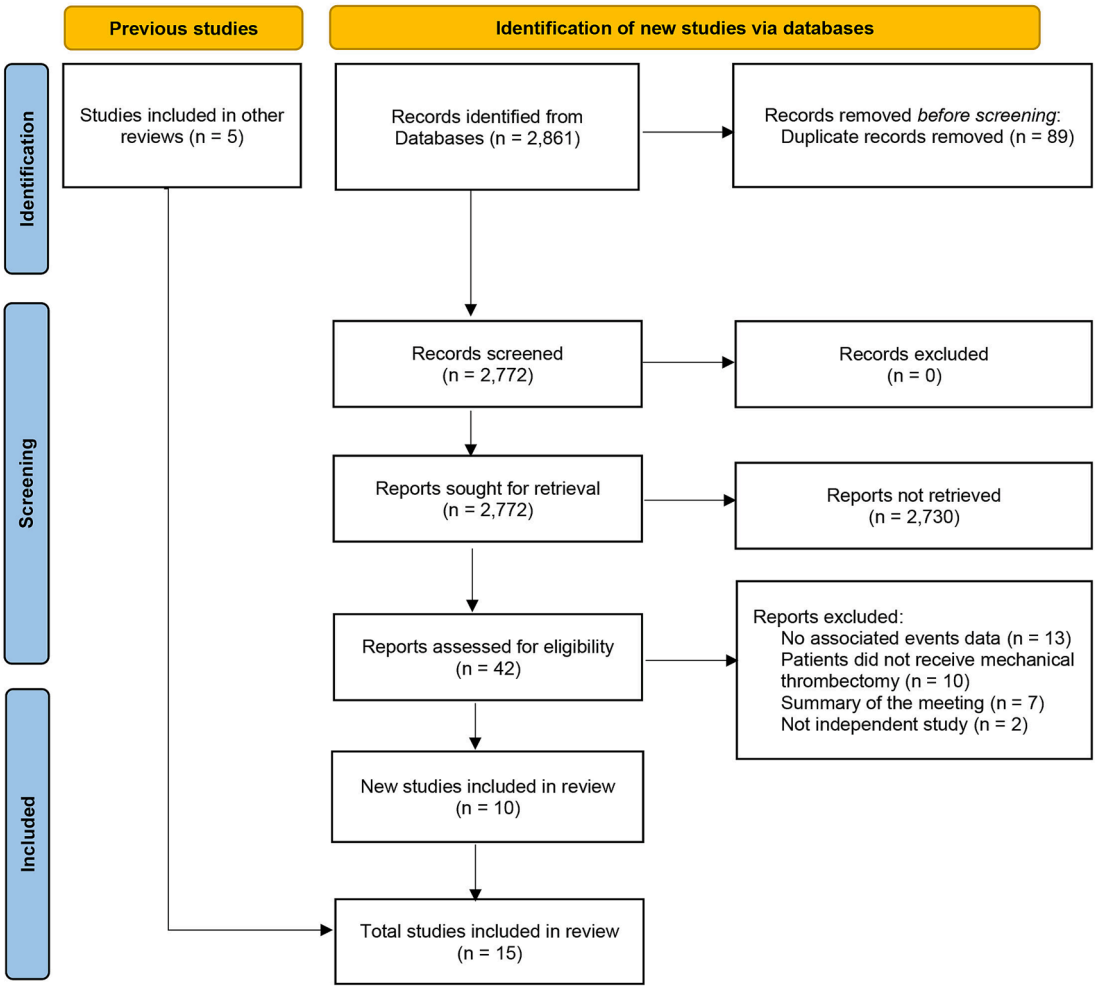

Fig. 1. Flowchart study of the selection.

Table 1
Study characteristics of all the studies included in the *meta*-analysis.

Study (Author, year)	Regions/ Country	Study Design	WMH sample	Control group sample	Age (years)	Age (years)		Male (%)	Male (%)		Initiation date	Termination date	WMH imaging method	WMH assessment tool	Baseline NIHSS	Primary outcome	Quality score
						moderate/ severe WMH	none/mild WMH		moderate/ severe WMH	none/ mild WMH							
Albo 2020	USA	retrospective	33 (VSS 3–4)	148 (VSS 0–2)	68 (57–81)	82 (74–85)	66 (54–76)	54.1	51.5	54.7	01–2012	11–2016	CT	VSS	18 (14–22)	90-day mRS	9
Atchaneeyasakul 2017	USA	retrospective	28 (WMH Q3-4)	28 (WMH Q1-2)	67.3 ± 14.2	–	–	53.6	–	–	06–2012	12–2015	MRI	semiautomated volumetric analysis	16 (13.75–20)	90-day mRS	8
Benson 2020	USA	retrospective	94 (Fazekas 3–6)	80 (Fazekas 0–2)	68.0 ± 9.1	76.8 ± 8.8	60.5 ± 14.5	48.8	40.0	61.3	12–2018	09–2019	CT	Fazekas scale	-	90-day mRS	9
Boulouis 2019	French	RCT + retrospective	434 (WMH Q1-4)	62 (None)	68.1 ± 15.0	–	–	49.6	–	–	01–2015	01–2018	MRI	semiautomated planimetric segmentation	16.43 ± 5.98	90-day mRS	9
Derraz 2022	French	retrospective	366 (WMH Q1-4)	-	69 ± 19	73 ± 19	62 ± 18	48.6	44.9	53.5	01–2015	12–2017	MRI	semiautomated volumetric analysis	16 (11–21)	90-day mRS	9
Gilberti 2017	Brescia	retrospective	23 (VSS 2–4)	45 (VSS 0–1)	74 (66–79)	77 (70–81)	73 (64–78)	50.0	43.5	53.4	08–2012	04–2016	CT	VSS	17 (14–21)	90-day mRS	8
Guo 2018	China	retrospective	38 (VSS 3–4)	213 (VSS 0–2)	64.4 ± 11.8	74.6 ± 9.2	62.6 ± 11.3	62.2	42.1	65.7	01–2014	09–2017	CT	VSS	16 (12–20)	90-day mRS	9
Liu 2019	China	retrospective	54 (Fazekas 3–6)	43 (Fazekas 0–2)	70.0 ± 12.4	74.9 ± 8.3	63.9 ± 14.0	61.9	64.8	58.1	10–2015	12–2017	MRI	Fazekas scale	13 (9–17)	90-day mRS	8
Mechtouff 2019	French	retrospective	202 (Fazekas 1–6)	91 (Fazekas 0)	67.12 ± 16.23	–	–	54.6	–	–	07–2013	06–2019	MRI	Fazekas scale	15.5 (10–19)	90-day mRS	8
Mistry 2020	USA	prospective	74 (VSS 3–4)	315 (VSS 0–2)	67.9 ± 15.0	76 ± 12	66 ± 15	50.0	43.0	52.0	11–2017	09–2018	CT	VSS	16 (11–20)	90-day mRS	8
Mutzenbach 2020	Austria	retrospective	35 (ARWMC 3)	174 (ARWMC 0–2)	75 (63–81)	82.0 (77.0–86.0)	73.0 (61.2–79.8)	46.9	28.6	50.6	01–2012	01–2019	MRI/CT	ARWMC scale	17 (12–21)	90-day mRS	9
Shi 2012	USA	retrospective	26 (Fazekas 2–3)	79 (Fazekas 0–1)	65.9 ± 18.9	79.0 ± 10.1	61.6 ± 19.1	41.0	–	–	08–2002	08–2008	MRI	Fazekas scores	18.1 ± 6.1	Hemorrhagic transformation	8
Sillanpää 2018	Finland	prospective	31 (ARWMC 1–3)	36 (ARWMC 0)	70.6 ± 8.8	–	–	53.0	–	–	01–2013	12–2014	CT	ARWMC scale	15 (5)	90-day mRS	7
Soize 2013	French	retrospective	13 (Fazekas 2–3)	42 (Fazekas 0–1)	63 ± 16	–	–	45.8	–	–	05–2010	04–2012	MRI	Fazekas scores	17.7 ± 6.2	90-day mRS	8
Yi 2023	China	RCT	217 (ARWMC 1–3)	432 (ARWMC 0)	69.5 (-)	–	–	56.1	–	–	02-2018	07–2019	CT	ARWMC scale	16.8 (-)	90-day mRS	9

Data are mean ± SD or median (IQR). SD, standard deviation; IQR = interquartile range.
USA, the United States of America; IVT, Intravenous thrombolysis; MT, Mechanical thrombectomy; WMH, White matter hyperintensity; VSS, van Swieten Scale; ARWMC, age-related white matter changes; MRI, magnetic resonance imaging;
CT, computed tomography; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; "-" indicates that the data is not available.

face visits with professional physicians, or the mRS questionnaire.

3.3. WMH burden and 90-day functional outcome

Data on unfavorable functional outcomes (90-day mRS 3–6) were obtained from 14 included studies, and our *meta*-analysis identified that moderate/severe WMH increased the chance of worse functional outcomes at 90 days after MT (OR 2.72, 95% CI 2.14-3.44; $I^2 = 0.0\%$; 95% CI 0.0%-42.7%) (Fig. 2). Subgroup analysis revealed a significant association between the severity of WMH and unfavorable outcomes in three different groups: the VSS group (OR 3.45, 95% CI 2.17–5.48; $I^2 = 0.0\%$; 95% CI 0.0%-25.5%), the Fazekas group (OR 2.45, 95% CI 1.65–3.64; $I^2 = 3.9\%$; 95% CI 0.0%-69.2%), and the ARWMC group (OR 2.74, 95% CI 1.57–4.78; $I^2 = 34.8\%$; 95% CI 0.0%-82.4%) (Fig. 3). Based on the results, there are differences in the actual effect sizes of the three assessment tools, possibly stemming from inconsistencies in their application for clinic. Nonetheless, the effect estimates still indicate a statistically significant association between WMH burden and unfavorable outcomes. In addition, there was no significant trend in the association between increased WMH volume and poor functional outcome (OR 1.032, 95% CI 0.998–1.066; $I^2 = 77.5\%$; 95% CI 0.0%-95.5%) in the analysis based on a subset of patients (Fig. 2). Moreover, we performed a shift analysis based on 6 studies that reported the patient distributions of mRS scores (0–6) (Henninger et al., 2014; Huo et al., 2021; Liao et al., 1997; Mikati et al., 2020; Mistry et al., 2020; Shimomura et al., 2008), showing that moderate/severe WMH was associated with an increased risk for poor 3-month functional outcome after MT (OR 2.44, 95% CI 2.03–2.92; $p < 0.001$) (Fig. 4). The increased risk of poor 90-day functional outcomes remained consistent in the jackknife sensitivity analysis, with ORs and corresponding 95% CIs greater than 2 each time the *meta*-analysis was repeated with one study omitted (Fig. A).

3.4. WMH burden and other clinical outcomes

Moderate/severe WMH was associated with statistically significant higher odds of 90-day mortality (OR 1.94, 95% CI 1.45–2.60; $I^2 = 19.5\%$; 95% CI 0.0%-65.2%) and FR (OR 2.99, 95% CI 1.42–6.28; $I^2 = 69.7\%$; 95 %CI 0.0%-91.0%) when compared with none/mild WMH. There was no statistically significant difference in successful recanalization (OR 0.91, 95% CI 0.72–1.14; $I^2 = 0.0\%$; 95% CI 0.0%-55.9%), sICH (OR 1.180, 95% CI 0.830–1.662; $I^2 = 0.0\%$; 95% CI 0.0%-11.4%) and HT (OR 1.53, 95% CI 0.35–6.56; $I^2 = 83.9\%$; 95% CI 0.0%-96.8%) between groups. Likewise, the association between increased WMH volume and 90-day mortality (OR 1.012, 95% CI 0.994–1.031; $I^2 = 23.6\%$; 95% CI 0.0%-79.8%), successful recanalization (OR 1.295, 95% CI 0.704–2.383), and sICH (OR 0.999, 95% CI 0.978–1.021; $I^2 = 0.0\%$; 95% CI 0.0%-0.0%) were not statistically different. These findings are shown in Fig. 2.

3.5. Study heterogeneity and imprecise-study effects

In the *meta*-analysis of WMH severity and clinical outcomes, a high risk of heterogeneity ($I^2 \geq 50\%$ or wide 95% CIs) was only found in the outcomes of FR and HT, and no significant heterogeneity was found for other outcomes. However, in the *meta*-analysis of the association between WMH volume and clinical outcomes, the 95% CIs for I^2 was wide due to the small number of included studies. Since only 90-day unfavorable functional outcomes included more than 10 studies, we only performed a funnel plot assessment for this. The funnel plot showed that the studies are distributed symmetrically. In addition, there is no clear evidence to suggest imprecise-study effects, as indicated by the results of Egger's regression on funnel plot asymmetry ($p = 0.420$) (Fig. 5).

4. Discussion

The results of our systematic review and *meta*-analysis indicated that acute stroke individuals with moderate/severe WMH experience an elevated risk of 90-day unfavorable functional outcomes, FR, and 90-day mortality after MT.

It is undeniable that WMH does have a high prevalence in the elderly; previous studies have demonstrated that the prevalence of WMH is as high as 85.6% in people aged 55–72 years (Swieten et al., 1990), and the

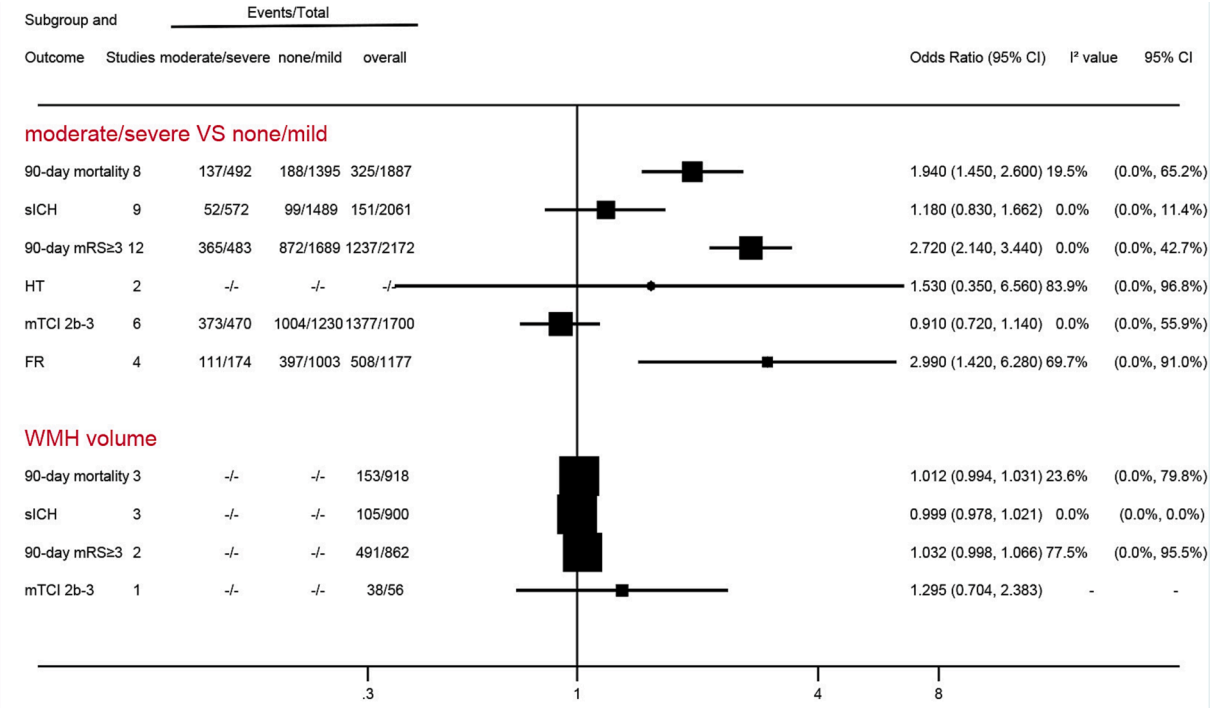

Fig. 2. Forest plot of pooled odds ratios for all outcomes from random effects models. *WMH, white matter hyperintensity; mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage; mTICI, modified Thrombolysis in Cerebral Infarction.*

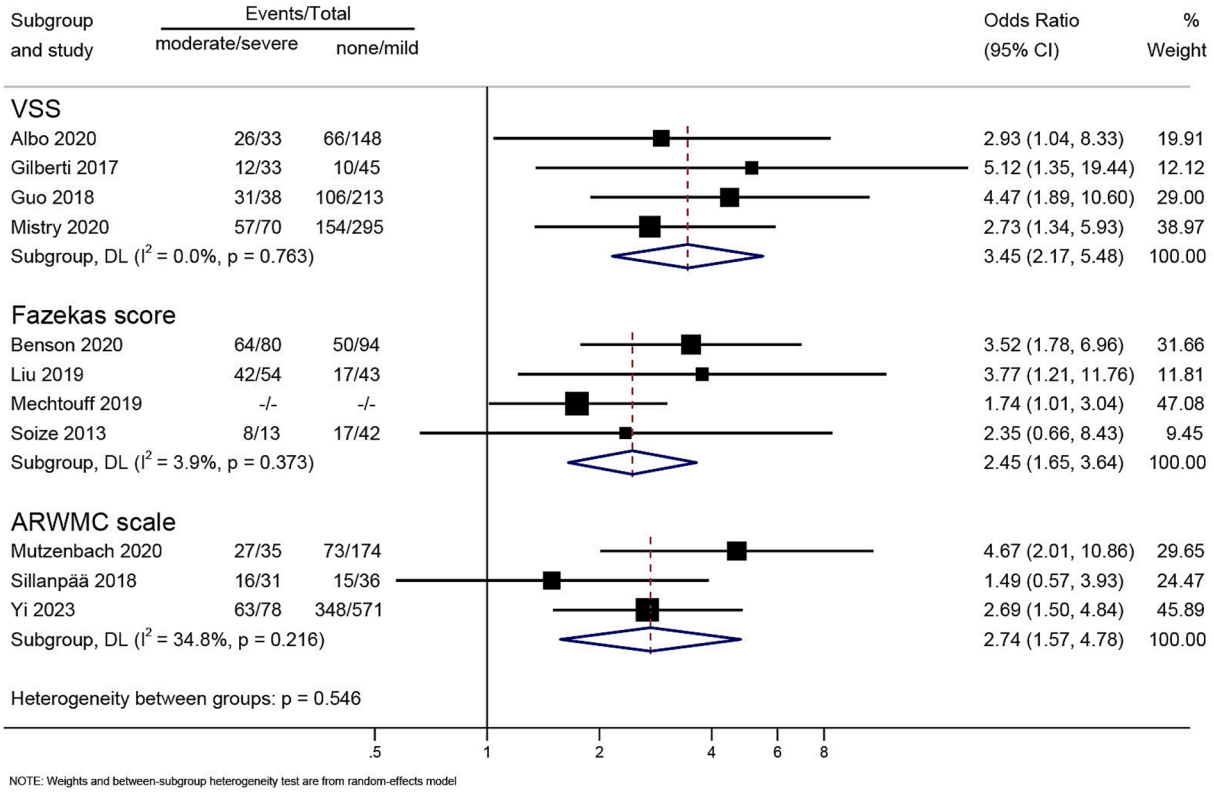

Fig. 3. Forest plot of pooled odds ratios for 90-day unfavorable outcomes (mRS 3–6) in different WMH assessment tools. *WMH, white matter hyperintensity; mRS, modified Rankin Scale; VSS, van Swieten Scale; ARWMC, age-related white matter changes.*

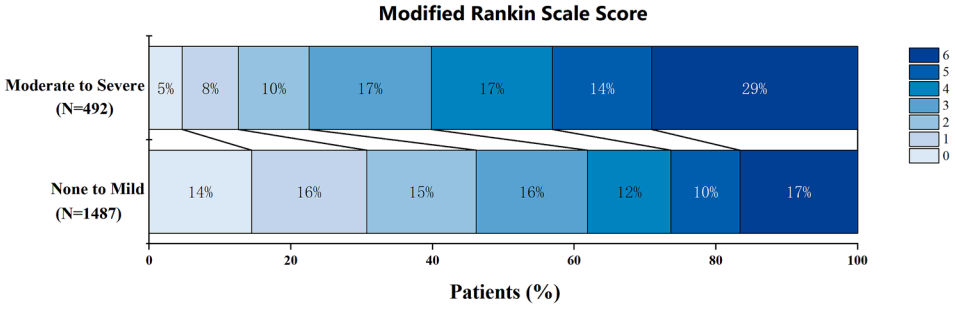

Fig. 4. Patients with moderate to severe white matter hyperintensity (WMH) had significantly worse 90-day functional outcomes than patients with none to mild WMH as assessed by the modified Rankin Scale (mRS).

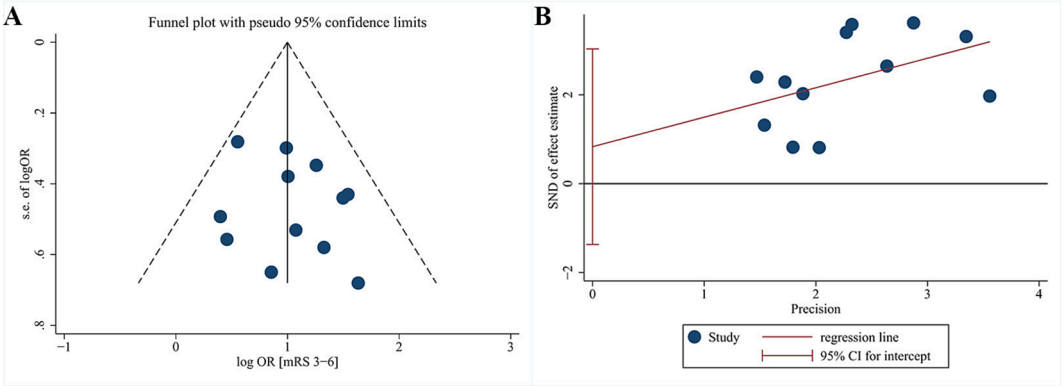

Fig. 5. Funnel plots (A) and graphical representations of Egger test (B) for the OR for 90-day poor outcomes (mRS 3–6) of moderate/severe WMH after MT. *Funnel plot represents a visual approach to check for the existence of imprecise-study effects by assessing the symmetry of study distribution, whereas Egger's test is a regression assay that permits to statistically quantify the extent of Funnel plot asymmetry. SND, standard normal deviation; mRS, modified Rankin Scale.*

prevalence increases with age (Derraz et al., 2022). This *meta*-analysis revealed that patients with moderate/severe WMH had worse outcomes after MT compared to those with none/mild WMH. This conclusion holds true when using various commonly employed assessment tools. Due to insufficient data from the included studies, a separate subgroup analysis of patients with successful recanalization (mTICI 2b-3) was not conducted. However, according to our *meta*-analysis based on four studies, we found that WMH burden is associated with an increased risk of FR. This indicates that even with successful recanalization, patients with moderate/severe WMH may still face a higher risk of FR than those with none/mild WMH. The progression of WMH severity has been linked to poor collateral grade in ischemic stroke patients with anterior circulation large vessel occlusion (Uh et al., 2010). Adequate collateral circulation can help maintain tissue viability until recanalization occurs and has been demonstrated to impact post-recanalization recovery (Vermeer et al., 2003). Qiu et al. also found a close correlation between clinical motor function and cerebral white matter integrity in patients 3 to 9 months after stroke (von Hippel, 2015). This underscores the need for comprehensive evaluation and personalized treatment strategies for stroke patients. Additionally, further research is warranted to elucidate the specific pathways through which WMH contributes to brain tissue damage and functional impairment, ultimately affecting the efficacy of recanalization procedures. In contrast, WMH severity did not appear to affect the rate of successful recanalization, sICH, and HT. Furthermore, there was no statistically significant association between WMH volume and the above-mentioned outcome. Given that we included few studies investigating the association between WMH volume and outcomes, and because different MRI sequence parameters and acquisition protocols can cause differences in the assessment of WMH volume, more studies are needed to further validate the conclusions.

WMH is the neuroimaging manifestation of lesions originating from cerebral small vessels, which usually present with decreased density on CT and are hyperintense on T2-weighted sequences on MRI; due to different sequence parameters and severity of pathological changes in WMH, it may appear as isointense or hypointense on T1-weighted sequences (von Kummer et al., 1995; Wahlund et al., 2001). We found no significant differences in successful recanalization after MT between patients with moderate/severe WMH (81.0%) and those with none/mild WMH (67.9%). However, patients with moderate/severe WMH had a worse prognosis. According to Mutzenbach et al. (Liberati et al., 2009), only 22.9% of patients with severe WMH achieved good outcomes after 3 months despite successful recanalization. Recently, several studies have speculated why WMH burden may be associated with a worse prognosis after MT. It has previously been observed that WMH impairs the integrity of the blood–brain barrier (BBB) and that cerebral blood flow and cerebrovascular reactivity are reduced in WMH regions (Wardlaw et al., 2019). Disruption of the BBB often increases the risk of blood extravasation; however, we did not find a significant association between WMH burden and HT after MT, possibly due to fewer included studies reporting HT (Jadhav et al., 2021; Mutzenbach et al., 2020); more high-quality research on this topic is necessary. WMH is considered an independent risk factor for cerebral infarction (Wardlaw et al., 2013), and the severity of WMH may be associated with the progression and increase in infarct volume (Wells et al., 2022). In addition, WMH is associated with the risk of progression from normal to mild cognitive impairment and is an independent predictor of dementia, with clinically significant WMH burden indicating increased cerebrovascular risk (Yi et al., 2023; Zamboni et al., 2019).

MT reduced the disability and improved health-related quality of life in patients with ischemic stroke in the anterior circulation of large vessels, benefiting all age ranges, with a satisfactory successful recanalization rate (Zhuang et al., 2018). The results of our *meta*-analysis suggest that although the substantial reperfusion (mTICI 2b-3) rate of MT did not decrease in moderate/severe WMH, it remained a strong independent predictor of FR and unfavorable 90-day functional outcomes. However, clinicians should not withhold MT from otherwise eligible patients solely due to moderate/severe WMH. Based on our results, it is recommended that clinicians pay more attention to the neurological recovery of moderate/severe WMH after MT and implement stricter monitoring and active management of potential medical complications to improve the overall prognosis of patients with moderate/severe WMH.

There are several advantages to this study. Our *meta*-analysis was based on protocols pre-registered on the PROSPERO website and in strict compliance with the PRISMA guidelines. Compared with the previous review (Lam et al., 2021), we included eight more studies in a pooled analysis, performed a subgroup analysis of the WMH assessment tool, and examined the effect of WMH volume on unfavorable outcomes.

At the same time, our *meta*-analysis had certain limitations that need to be acknowledged. First, most included studies were retrospective, and only 3 studies investigated the association between WMH volume and outcome. Second, the assessment tools and definitions of WMH severity varied among studies, but a consistent conclusion was reached. Third, the sample size of the included studies varied greatly, and our *meta*-analysis pooled results combining crude and adjusted ORs, where the crude OR was calculated by the researchers using 2×2 table data extracted from the studies. However, we compared the results for crude and adjusted ORs, and the combined estimates were similar and robust. Fourth, we did not search for grey literature, which could lead to publication bias. Another notable limitation is that the analysis lacks direct adjustment for imbalances in important baseline covariates, such as variations in thrombectomy techniques, adjunct devices, and onset to treatment times, during the analyses.

5. Conclusion

In summary, this *meta*-analysis demonstrated that, in AIS patients after MT, moderate/severe WMH was associated with increased odds of unfavorable 90-day functional outcomes (mRS 3–6), FR, and mortality, but did not have a statistical connection with the rate of successful recanalization, sICH, and HT. Furthermore, analysis based on a subset of patients who have shown increased WMH volume did not appear to be associated with the outcomes mentioned above. These findings suggest that moderate/severe WMH may contribute to predicting patients' prognosis after MT. The implications of these findings suggest the need for further research to investigate the potential benefits of mechanical thrombolysis compared to traditional thrombolysis in patients with moderate/severe WMH. This line of inquiry will play a vital role in determining the most suitable individualized treatment and care regimen for stroke patients presenting with this particular imaging characteristic. To summarize, understanding the impact of moderate/severe WMH on the outcomes of AIS patients undergoing MT is vital for optimizing treatment strategies and enhancing patient prognostication. Future research endeavors should uncover mechanisms underlying the association between WMH and stroke outcomes, paving the way for personalized approaches in stroke management.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Informed consents

No informed consent was required for this review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2023.103549.

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