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SYSTEMATIC REVIEW AND META-ANALYSIS

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Clinical Outcome in Acute Ischemic Stroke Patients With Microbleeds After Thrombolytic Therapy

A Meta-Analysis

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Abstract: It remains unclear whether preexisting cerebral microbleeds (CMBs) increase the risks of worse functional outcome after thrombolytic therapy. We performed a systematic review and meta-analysis to assess the risk of unfavorable outcome in patients with acute ischemic stroke and CMBs.

We searched EMBASE, PubMed, and Web of Science for relevant studies assessing functional outcome in the patients with CMBs following thrombolytic therapy. Fixed-effects and random-effects models were performed.

Five eligible studies including 1974 patients were pooled in meta-analysis. The prevalence of CMBs was 24.3%. The pooled analysis demonstrates odds ratio for preexisting CMBs and the achievement of favorable outcome to be 0.69 (95% CI 0.56–0.86; $P = 0.001$) with no evidence of statistical heterogeneity ($I^2 = 46.7\%$, $P = 0.112$).

Our meta-analysis of available published data demonstrates an increased risk of worse functional outcome after thrombolytic therapy for acute ischemic stroke in patients with pre-existing CMBs. Future studies are needed to determine whether the risk outweigh the expected benefit of reperfusion therapies.

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Abbreviations: CMB = cerebral microbleed, GRE = gradient-recalled echo, mRS = modified Rankin scale, sICH = symptomatic intracranial hemorrhage, tPA = tissue plasminogen activator.

INTRODUCTION

Cerebral microbleeds (CMBs) defined as small, rounded or circular, hypointense lesions on paramagnetic-sensitive MR sequences, such as T2∗-weighted gradient-recalled echo (GRE) or susceptibility-weighted imaging,[1] and are commonly detected in elderly individuals and patients with cerebrovascular diseases.[2,3] Histopathological analysis shows that CMBs consist of hemosiderin accumulations from red blood cells that presumably have leaked out of small vessels.[4] A recent updated pooled meta-analysis demonstrates an increased risk of symptomatic intracerebral hemorrhage (sICH) after thrombolysis for acute ischemic stroke in patients with CMBs (8.5% vs 3.9%).[5] However, whether preexisting CMBs increase the risks of worse functional outcome after thrombolytic therapy still remains uncertain.

Despite the increased postthrombolysis bleeding risk, CMB itself could also have direct effects on cognition, neurologic function, and disability.[6,7] On the other hand, the long-term benefit of thrombolytic therapy may outweigh its harms even in some patients with sICH. Most previous studies have investigated the potential association between CMBs and post-thrombolysis sICH,[8–19] whereas only a few of them reported the relationship between CMBs and functional outcome,[15–19] with conflicting results.

We thus performed a meta-analysis to assess whether the presence of CMBs on prethrombolysis MRI resulted in a decreased frequency of favorable outcome in acute ischemic stroke patients receiving thrombolytic therapy.

SUBJECTS AND METHODS

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.[20,21]

ETHICS STATEMENT

Ethical approval was not necessary for the current study. Personal data of our previous study were used for this meta-analysis.[19] The protocols of MRI-guided IVT have been approved by the human ethics committee of the second Affiliated Hospital of Zhejiang University, School of Medicine, which was decribed in detail elsewhere.[19]

Search Strategy and Eligibility Criteria

We searched appropriate articles by systematic queries of NCBI (PubMed), ISI Web of Science, and EMBASE databases on the 10th of September 2015, using the following search terms: "micro(-)bleed(s)" or "micro(-)h(a)emorrhage(s)" in association with "thromboly∗" or "fibrinoly∗" or "tissue plasminogen activator" or "rt(-)PA" or "t(-)PA" or "alteplase." Articles not published in English were translated and case reports were excluded. The references of all identified publications were reviewed for any additional studies not indexed. We contacted authors when there were questions regarding their studies. Two authors (JC and SY) identified potentially relevant studies, resolving any uncertainties with a 3rd author (CL).

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Randomized controlled trials or controlled observational studies (retrospective or prospective) were eligible for inclusion if they had defined and assessed functional outcome in patients with acute ischemic stroke treated with thrombolytic therapy, and quantified the odds ratio (OR) in relation to the presence of CMBs on prethrombolysis MRI.

Study Selection and Data Extraction

Two authors (JC and HH) considered all titles and abstracts for eligibility in a systematic manner and went through all articles selected as relevant and extracted data independently. We extracted information on study design, MRI parameters for CMBs detection, methodology of thrombolytic therapy, number and demographics of participants (including age and sex), clinical stroke severity (assessed by National Institutes of Health Stroke Scale), number of participants with preexisting CMBs, number of participants with different functional outcome, and the characteristics of CMBs (burden, location, and pathogenesis) by using a unified data form. Discrepancies were resolved by consensus. Authors of the included articles were contacted for data needing clarification.

Data Analysis

We used a fixed effects model (Mantel and Haenszel method) to calculate the pooled ORs and corresponding 95% CIs, with weights calculated using the inverse variance method, because of the relatively small number of included studies and outcome events. Subgroup analysis was performed to isolate patients treated only with intravenous (IV) tissue plasminogen activator (tPA). Statistical heterogeneity was assessed using I^2 statistics with inspection of the forest plot. Publication bias was evaluated with Egger test, Begg test, and the funnel plot. We repeated all analyses using random-effects models. All statistical analysis was performed with Stata 11.2 (StataCorp LP, TX).

RESULTS

We identified 87 articles of PubMed, 99 of EMBASE, and 116 of Web of Science in our initial search. Finally, 5 studies (all published) met our predetermined criteria and were pooled in a meta-analysis (Fig. 1).[15–19] The characteristics of included studies are summarized in Table 1.

CMBs were identified according to a field guide or/and a neuroimaging standard for CMBs detection.[1,22] The maximum diameter of a CMB was defined as 10 mm, except that in Gratz et al's study, was 5 mm.[16] Study demographics are summarized in Table 2. Collectively, these studies were composed of 1974 patients (study sample size range: 206–717), 480 (24.3%) of which had CMBs on pretreatment MRI scans. From inspection of each of the studies, patients with preexisting CMBs were older,[15–19] had a more severe degree of leukoaraiosis,[15,17,19] higher rate of diabetes mellitus,[17,19] and higher rate of hypertension (or higher systolic blood pressure),[16,18,19] whereas other baseline characteristics were not significantly different. The characteristics of CMBs are summarized in Table 3. About half of the patients with CMBs had exactly 1 CMB, whereas only about one fifth of them had $\geq$5 CMBs. Interestingly, about one third of the patients with CMBs had strictly lobar CMBs, most of which were considered as presumed pathogenesis of cerebral amyloid angiopathy.

A modified Rankin scale (mRS) score of $\leq$2 at 3 months was defined as favorable functional outcome in four included studies,[15,16,18,19] whereas neurologic status was quantified by mRS score at discharge in Shi et al's study.[17] Favorable

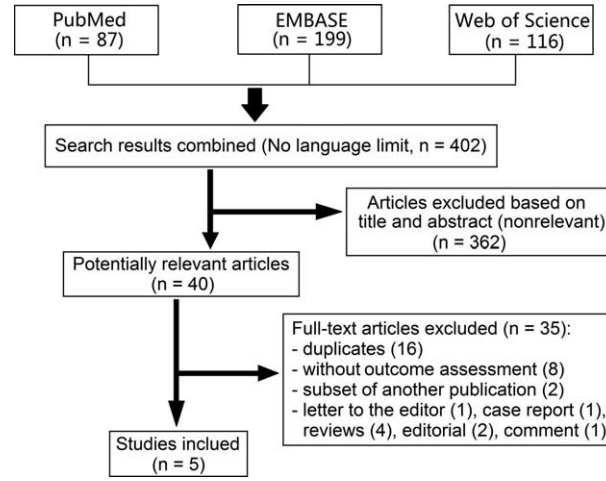

FIGURE 1. Flow diagram of literature search and study selection.

functional outcome occurred in 52.9% (range: 35.0%–58.5%) of the entire population. Notably, data on functional outcome were not available for 6 patients in Dannenberg et al's study,[15] and for 52 patients in Gratz et al's study,[16] and 62 patients with pre-stroke mRS score of >2 in Turc et al's study were also excluded from this meta-analysis.[18] Among patients with preexisting CMBs, 191 of 443 (43.1%) achieved favorable outcome after thrombolytic therapy compared with 702 of 1411 patients (49.8%) without CMBs. Pooled analysis demonstrated OR for the presence of preexisting CMBs and the achievement of favorable outcome to be 0.69 (95% CI 0.56–0.86; $P = 0.001$) with no evidence of statistical heterogeneity ($I^2 = 46.7\%$, $P = 0.112$) (Fig. 2). There was no evidence of a publication bias either from the result of Egger test ($P = 0.812$) or Begg test ($P = 1.000$), and the shape of the funnel plot seemed symmetrical (Fig. 3).

Four studies, including 1199 patients (n = 312 with CMBs), provided data on patients treated with IV tPA only.[15,16,18,19] Pooled analysis of these studies demonstrated OR for the presence of preexisting CMBs and the achievement of favorable outcome to be 0.83 (95% CI 0.74–0.95; $P = 0.004$) with no evidence of statistical heterogeneity ($I^2 = 35.1\%$, $P = 0.202$) (Fig. 4). All analyses were consistent using a random-effects model.

DISCUSSION

Our meta-analysis in nearly 2000 patients with acute ischemic stroke shows that the presence of preexisting CMBs is associated with a statistically significant decreased rate of favorable functional outcome following thrombolytic therapy. This remains consistent in a subgroup pooled analysis including patients treated with IV tPA only.

The prevalence of CMBs was reported from 4.7% to 15.3% in normal individuals[23–26] and might be much higher among patients with ischemic or hemorrhagic strokes because old age and hypertension are risk factors for both conditions. A total of 12.2% to 39.9% of acute ischemic stroke patients receiving thrombolytic therapy were noted to have CMBs on prethrombolysis MRI.[8–19] The MRI parameters used varied among previous studies, which was likely to affect the prevalence of

TABLE 1. Characteristics of Included Studies

Study Reference	Design	Inclusion Criteria	MRI Parameters				Treatment	Outcome Measures
			Sequence	Field Strength	Echo Time	Slice Thickness		
Dannenberg et al, 2014[15]; Western cohort	Prospective, single center	(1) Acute ischemic stroke (2) Received IVT (3) Pretreatment MRI (4) Posttreatment MRI or CT within 36 hours after IVT	T2*-GRE	3.0 T	20 ms	5.0 mm	IV rtPA within 4.5 hours	(1) sICH (2) PH (3) mRS ≤2 at 3 months
Gratz et al, 2014[16]; Western cohort	Prospective, single center	(1) Acute ischemic stroke (2) Received IVT, EVT, or IVT followed by EVT (3) Pretreatment MRI (4) Posttreatment MRI or CT within 72 hours after therapy	SWI	1.5/3.0 T	40/20 ms	1.8/2.0 mm	IV alteplase only; IA urokinase with or without mechanical intervention; mechanical intervention only; or bridging therapy	(1) sICH (2) Asymptomatic ICH (3) ICH outside infarct (4) mRS ≤2 at 3 months (5) 3-month survival
Shi et al 2015[17]; Western cohort	Prospective, single center	(1) Acute ischemic stroke with large vessel occlusion (2) Received mechanical thrombectomy (3) Pretreatment MRI	T2*-GRE	1.5/3.0 T	15/20 ms	5.0/5.0 mm	IV or/and IA tPA followed by mechanical thrombectomy; or mechanical thrombectomy only	(1) TICI score (2) Any ICH, PH and SAH (3) Procedure-related adverse events

Study Reference	Design	Inclusion Criteria	MRI Parameters				Treatment	Outcome Measures
			Sequence	Field Strength	Echo Time	Slice Thickness		
								(4) mRS ≤3 at discharge (5) In-hospital mortality
Yan et al 2015[19]; Asian cohort	Prospective, single center	(1) Acute ischemic stroke (2) Received IVT (3) Pretreatment MRI (4) Posttreatment MRI or CT 24 hours after IVT	SWI	3.0 T	11 echoes: first 4.5 ms, interecho 4.5 ms	2.0 mm	IV rtPA from 4.5 to 6 hours	(1) PH (2) sICH (3) mRS ≤2 at 3 months
Turc et al 2015[18]; Western cohort	Prospective, 2 centers	(1) Acute ischemic stroke (2) Received IVT (3) Pretreatment MRI	T2∗-GRE	1.5/1.5 T	13/32 ms	6.0/5.0 mm	IV alteplase within 4.5 hours	(1) mRS score at 3 months (2) sICH of 4 definitions

EVT = endovascular therapy, GRE = gradient-recalled echo, IA = intraarterial, IVT = intravenous thrombolysis, mRS = modified Rankin scale, PH = parenchymal hemorrhage, rtPA = recombinant tissue plasminogen activator, SAH = subarachnoid hemorrhage, sICH = symptomatic intracranial hemorrhage, SWI = susceptibility-weighted imaging, TICI = thrombolysis in cerebral infarction.

TABLE 2. Study Demographics and Outcomes

Study	Dannenberg et al	Gratz et al	Shi et al	Yan et al	Turc et al	Total
Population size	326	392	206	333	717	1974
Age, year	76 (Median)	68.1 (Mean)	66.8 (Mean)	67 (Median)	74 (Median)	–
Male	159 (48.8%)	223 (56.9%)	87 (42.2%)	223 (67.0%)	351 (48.9%)	1043 (52.8)
Microbleed prevalence	81 (24.8%)	79 (20.2%)	37 (18.0%)	133 (39.9%)	150 (20.9%)	480 (24.3%)
Baseline NIHSS	8 (Median)	9 (Median)	17.7 (Mean)	10 (Median)	11 (Median)	–
Any ICH	N/A	96 (24.5%)	91 (44.2%)	102 (30.6%)	N/A	31.0%
sICH	10 (3.1%)	21 (5.4%)	N/A	8 (2.4%)	64 (8.9%)*	5.8%
PH	23 (7.1%)	N/A	39 (18.9%)	28 (8.4%)	N/A	10.4%
Favorable outcome (mRS ≤2)	162 (50.6%)†	199 (58.5%)‡	72 (35.0%)§	193 (58.0%)	388 (54.1%)	52.9%

mRS = modified Rankin scale, NIHSS = National Institute of Health Stroke Scale, PH = parenchymal hemorrhage, sICH = symptomatic intracranial hemorrhage.
* ECASS II definition; N/A, information not provided.
† Data available for 320 patients.
‡ Data available for 340 patients.
§ mRS ≤3 at discharge.

CMBs. It has been demonstrated that longer echo time, higher spatial resolution (3D Fourier transform technique), and increased field strength can increase the sensitivity of CMBs detection.[1] CMBs might be missed due to a large slice thickness or/and a large interslice gap of MRI scans.[27] Moreover, Asian cohort might have a higher proportion of patients with at least one CMB (39.9%) and an important CMB burden (742 CMBs in 133 patients),[19] which needs further investigation.

The presence of CMBs on prethrombolysis MRI is not an exclusion criterion for thrombolytic therapy in current guidelines. Most previous studies have been focused on whether the presence, location, or burden, of preexisting CMBs predicts the risk of postthrombolysis sICH,[8–19] whereas only a few of them investigated the relationship between CMBs and functional outcome.[15–19] Among which, 2 studies found that the presence of CMBs was not associated with 3-month outcome or in-hospital mortality,[16,17] while 2 studies observed a significant association between CMB burden and unfavorable outcome in univariate analysis, which lost significance after adjustment for confounding factors.[15,18] The rest 1 observed a significant association between extensive (≥3) CMBs and poor outcome in multivariable analysis.[19] In above-mentioned studies, patients with preexisting CMBs were older,[15–19] had a more severe degree of leukoaraiosis,[15,17,19] higher rate of diabetes mellitus,[17,19] and higher rate of hypertension (or higher systolic blood pressure).[16,18,19] Since leukoaraiosis is highly correlated with CMBs,[28] it is unclear if the presence of CMBs is the independent predictor or rather severity of small vessel disease overall. Only a few studies adjusted the severity of leukoaraiosis in multivariate regression analyses.[15,17,19] The severity of concomitant leukoaraiosis should be took into consideration in future investigations.

This meta-analysis showed that the presence of pre-existing CMBs was associated with worse functional outcome following thrombolytic therapy. On one hand, patients with CMBs on prethrombolysis MRI developed more sICH than those without (8.5% vs 3.9%),[5] meanwhile the presence of sICH independently increased the risk of worse outcome. On the other hand, histopathologic analysis of CMBs generally found these lesions were associated with some degree of surrounding tissue

TABLE 3. Characteristics of CMBs

Study	Dannenberg et al	Gratz et al	Shi et al	Yan et al	Turc et al
Number of patients with CMBs	81	79	37	133	150
CMB burden					
1 CMB	52 (64.2%)	45 (57.0%)	23 (62.2%)	59 (44.4%)*	92 (61.3%)
>1 CMB	29 (35.8%)	34 (43.0%)	14 (37.8%)	74 (55.6%)*	58 (38.7%)
≥5 CMBs	10 (12.3%)	9 (11.4%)†	1 (2.7%)	34 (25.6%)*	25 (16.7%)
Lobar CMBs only	N/A	27 (34.2%)	12 (32.4%)	45 (33.8%)	45 (30.0%)
Presumed pathogenesis of CAA	42 (51.9%)	21 (26.6%)	N/A	32 (24.1%)*	60 (40.0%)
Favorable outcome (mRS ≤2)	31 (38.8%)‡	27 (43.5%)§	12 (32.4%)‖	67 (50.4%)	54 (41.2%)¶

CMB = cerebral microbleed, mRS = modified Rankin scale, N/A = information not provided.
* From personal data.
† Data of ≥6 CMBs.
‡ Data available for 80 patients.
§ Data available for 62 patients.
‖ mRS ≤3 at discharge.
¶ Data available for 131 patients.

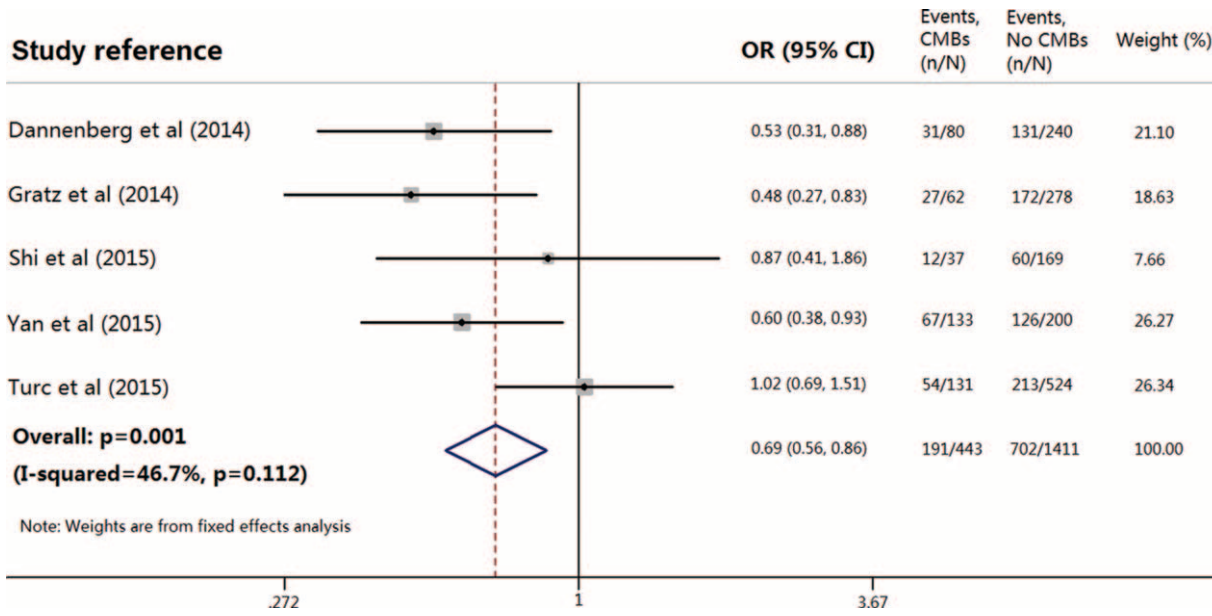

FIGURE 2. Meta-analysis of the association between favorable functional outcome in patients with acute ischemic stroke treated with thrombolytic therapy, in relation to the presence of preexisting cerebral microbleeds.

damage,[1] and the number of CMBs was found to be independently associated with increased mRS.[7] Therefore, pre-existing CMBs might have an additional effect on functional outcome, besides the increased sICH risk.[19]

Based on current evidence, patients with CMBs on pretreatment MRI do have higher frequencies of sICH and poor functional outcome after thrombolytic therapy. However, the presence of preexisting CMBs should not yet be considered as a contraindication to thrombolysis in otherwise eligible patients. On one hand, these results might be confused by several potential confounders, for example, age and severity of leukoaraiosis, and should thus be treated with caution. On the other hand, since no control groups without thrombolytic therapy were designed in previous studies, it was still questionable whether CMBs-related sICH was likely to exceed the benefits of thrombolysis. Nevertheless, it might be reasonable to take CMBs into account as 1 factor to help guide risk-benefit assessment in difficult decisions. Clinicians should target interventions to reduce sICH in patients with CMBs, such as lowering pretreatment blood pressure targets, in future randomized

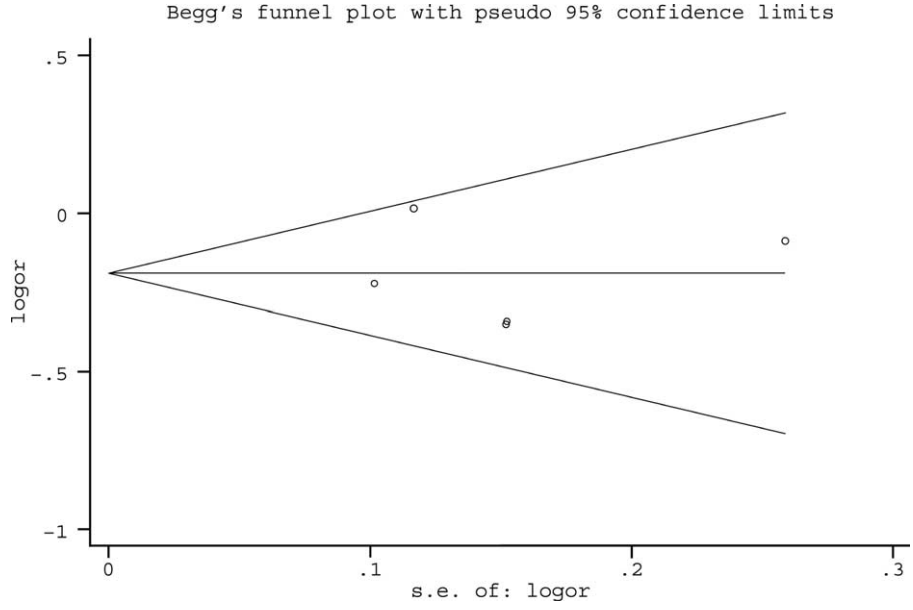

FIGURE 3. Publication bias from studies about the association between favorable functional outcome and the presence of preexisting cerebral microbleeds.

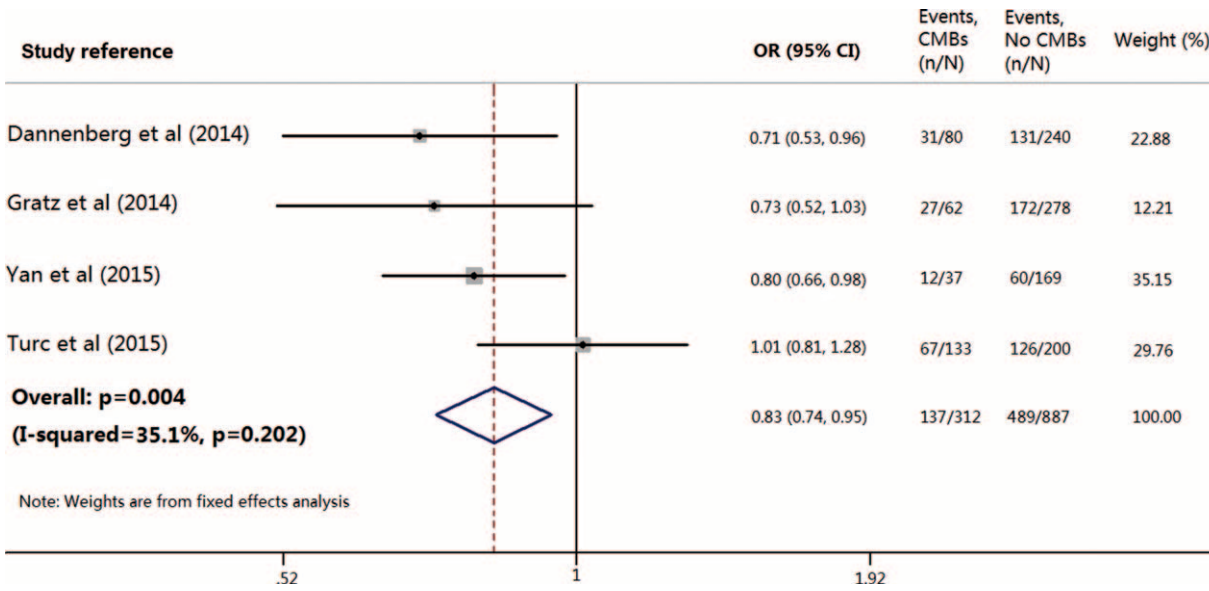

FIGURE 4. Meta-analysis of the association between favorable functional outcome in patients with acute ischemic stroke treated only with intravenous thrombolysis, in relation to the presence of preexisting cerebral microbleeds.

controlled studies. Our study also provides additional support for more widespread use of MRI in hyperacute stroke treatment.

Our study had several limitations. First, our analysis had inherent biases associated with the use of observational studies. All studies are subject to selection bias since not all acute ischemic stroke patients undergo MRI, and such patients were excluded. However, there was no randomized controlled trial evaluating the risks and benefits of thrombolytic therapy in the patients with preexisting CMBs so far. Second, the use of unadjusted data rendered our analysis vulnerable to confounding variables. Some studies did not provide full information of baseline characteristics likely to be associated with CMBs. Age and the severity of leukoaraiosis are most important. Third, the MRI parameters used varied among included studies. Echo time, field strength, slice thickness, and interslice gap can affect the sensitivity of CMBs detection.

In conclusion, our analysis showed that the presence of preexisting CMBs significantly decreased the rate of favorable functional outcome following thrombolytic therapy. Future large multicenter studies and individual patient data meta-analysis are needed to determine whether the risk outweigh the expected benefit of reperfusion therapies. In addition, current data are limited on whether CMBs are related to the risk of unfavorable functional outcome following endovascular treatment in acute ischemic stroke, which needs further investigations.

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