Original research

Predictors of futile recanalization after endovascular treatment in acute ischemic stroke: a meta-analysis

Gang Deng, Jun Xiao, Haihan Yu, Man Chen, Ke Shang, Chuan Qin, Dai-Shi Tian

Department of Neurology, Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei, China

Correspondence to
Dr Dai-Shi Tian, Department of Neurology, Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology, Wuhan 430030, Hubei, China; tiands@tjh.tjmu.edu.cn

ABSTRACT

Background Despite successful recanalization after endovascular treatment, many patients with acute ischemic stroke due to large vessel occlusion still show functional dependence, namely futile recanalization.

Methods PubMed and Embase were searched up to April 30, 2021. Studies that reported risk factors for futile recanalization following endovascular treatment of acute ischemic stroke were included. The mean difference (MD) or odds ratio (OR) and 95% confidence interval (95% CI) of each study were pooled for a meta-analysis.

Results Twelve studies enrolling 2138 patients were included. The pooled analysis showed that age (MD 5.81, 95% CI 4.16 to 7.46), female sex (OR 1.40, 95% CI 1.16 to 1.68), National Institutes of Health Stroke Scale (NIHSS) score (MD 4.22, 95% CI 3.38 to 5.07), Alberta Stroke Program Early CT Score (ASPECTS) (MD −0.71, 95% CI −1.23 to −0.19), hypertension (OR 1.73, 95% CI 1.43 to 2.09), diabetes (OR 1.78, 95% CI 1.41 to 2.24), atrial fibrillation (OR 1.24, 95% CI 1.01 to 1.51), admission systolic blood pressure (MD 4.98, 95% CI 1.87 to 8.09), serum glucose (MD 0.59, 95% CI 0.37 to 0.81), internal carotid artery occlusion (OR 1.85, 95% CI 1.17 to 2.95), pre-treatment intravenous thrombolysis (OR 0.67, 95% CI 0.55 to 0.83), onset-to-puncture time (MD 16.92, 95% CI 6.52 to 27.31), puncture-to-recanalization time (MD 12.37, 95% CI 7.96 to 16.79), and post-treatment symptomatic intracerebral hemorrhage (OR 6.09, 95% CI 3.18 to 11.68) were significantly associated with futile recanalization.

Conclusion This study identified female sex, comorbidities, admission systolic blood pressure, serum glucose, occlusion site, non-bridging therapy, and post-procedural complication as predictors of futile recanalization, and also confirmed previously reported factors. Further large-scale prospective studies are needed.

INTRODUCTION

Endovascular treatment (EVT) has proven to be effective in improving the outcome of patients with acute ischemic stroke (AIS) due to anterior circulation large vessel occlusion (LVO). However, nearly half of the patients who receive EVT are subject to futile recanalization (FR)—long-term functional dependence despite successful recanalization.[1] Predicting FR in patients treated with EVT may help conduct more personalized patient selection for EVT and target patients who need other timely adjuvant treatments with neuroprotectants. Several predictors of FR have hitherto been identified in a few small sample-size and retrospective studies: older age,[2] higher initial National Institutes of Health Stroke Scale (NIHSS) score,[2–4] and longer delay from onset to treatment, among others.[3] However, the importance of factors identified by several studies is controversial; these factors include the female sex and poor collateral status.[2 3 5 6] Therefore, this study aimed to conduct a meta-analysis of predictors of FR after EVT.

METHODS

We used a prospective protocol to fulfill the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. This study or its protocol was not registered at any website. The authors declare that all supporting data are available within the article and its online supplementary files.

Search strategy

To search systematically the PubMed and Embase electronic databases for the relevant literature published before April 2021, we used the following free-text keywords and query strategies: (stroke OR 'ischemic stroke' OR 'ischaemic stroke' OR 'cerebral infarct') AND ('endovascular therapy' OR EVT OR thrombectomy OR 'stent retriever' OR 'contact aspiration' OR 'intraarterial thrombolysis') AND (futile recanalization OR futile reperfusion OR futile revascularization). No language restrictions were included. Relevant reports were manually reviewed.

Eligibility criteria

The studies were included if they met the following criteria: (1) cohort or case–control studies conducted on patients with AIS due to anterior circulation LVO treated with EVT, with or without intravenous thrombolysis (IVT); (2) participants were aged ≥18 years; (3) FR was defined as a modified Rankin Scale (mRS) score of >2 at 3 months (or 90 days) despite successful recanalization, which was defined as either grade 2b–3 on the Thrombolysis in Cerebral Infarction (TICI) scale or modified TICI (mTICI) scale or 2–3 on the Thrombolysis in Myocardial Infarction (TIMI) scale; and (4) outcomes included comparisons of demographic, clinical, laboratory, radiographic, or procedural factors between FR and effective recanalization (ER). Animal research, case reports, expert opinions, reviews, editorials, and studies that did not provide sufficient clinical information were excluded.

Study selection, data extraction and quality assessment

Two authors (GD and HY) independently screened the articles and extracted the data. Arbitration

conducted by one of the investigators (DT) resolved disagreements through discussion and consensus. The following information was extracted from these studies: first author, publication year, country, study design, inclusion and exclusion criteria, sample size and sex composition, age of the participants, medical history, pre-morbid mRS, baseline NIHSS and Alberta Stroke Program Early CT Score (ASPECTS), use of IVT, EVT strategy, occlusion sites, and procedural times. Any other clinical, radiological or laboratory factors which were compared between FR and ER groups were also extracted. The authors of the articles were contacted by email if the data were unclear. Two reviewers (MC and KS) independently performed quality assessment using the Newcastle-Ottawa Scale (NOS) and scored the included reports for methodological quality, risk of selection, cohort comparability bias, and outcomes of the included studies. Studies were considered of high quality if they achieved seven or more stars on the NOS.

Statistical analysis

Meta-analysis was performed using STATA 12 (STATA Corporation, College Station, TX) and Review Manager (RevMan) 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark). We pooled data in the meta-analysis if there were ≥4 studies for a given predictive measure. For continuous variables, mean difference (MD) and 95% confidence interval (95% CI) were used to analyze the summary estimates. For binary variables, odds ratio (OR) and 95% CI were used. When necessary, the mean and SD were estimated from the median, range, and sample size using the method proposed by a previous study.[7] The pooled data were presented as forest plots. Heterogeneity was evaluated using the I^2 test. A random effects model was used if significant heterogeneity existed (I^2 >50%); otherwise, a fixed effects model was used (I^2 ≤50%). Subgroup analyses were performed to investigate possible sources of heterogeneity. A sensitivity analysis was performed to investigate the influence of a single study on the overall effect estimate. Publication bias was presented using a funnel plot and tested using Begg's test and Egger's test. Statistical significance was set at p<0.05.

RESULTS
Search results

Figure 1 shows a flow diagram of the study. A total of 78 records were initially identified by manual and electronic database searches. After removing the duplicates, 75 records were obtained. All abstracts were reviewed, and 39 records were excluded. The remaining 36 full-text studies were assessed, and 24 studies were further excluded due to the following reasons: 10 did not include comparisons between ER and FR, three included both anterior and posterior circulation,[8–10] one enrolled patients receiving IVT alone,[11] two did not report 90-day mRS,[12 13] and three did not define FR in the same way as our definition.[14–16] Finally, 12 articles were considered eligible for the meta-analysis.[2–6 17–23]

Study characteristics

The included 12 studies enrolled 2138 patients (1042 patients with FR and 1096 patients with ER). Overall, 48.7% (1042/2138) patients developed FR. Seven studies were retrospective, observational studies[4–6 17 19 20 22]; three were prospective cohort or registry studies[2 18 23]; one was a post-hoc analysis of a randomized controlled trial (RCT)[3]; and one included patients both prospectively and retrospectively.[21] Six studies were conducted in Europe,[4–6 18 20 21] four in Asia,[2 17 22 23] and
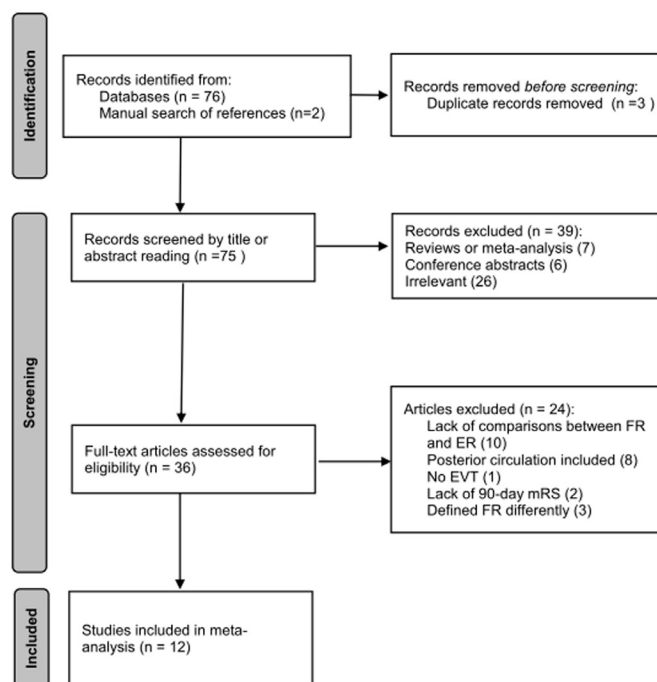

Figure 1 Flow chart of the study. ER, effective recanalization; EVT, endovascular treatment; FR, futile recanalization; mRS, modified Rankin score.

two in the USA.[3 19] The publication year ranged from 2013 to 2021. EVT was conducted within 3–16 hours of stroke onset, and pre-treatment IVT was allowed in all studies except one.[22] Patients with occlusion of the internal carotid artery (ICA) and M1 segment of the middle cerebral artery (MCA) were included, and the M2 segment was also included in all studies except for three.[18 20 21] Pre-stroke mRS was ≤1 in five studies,[2 17 21–23] ≤2 in three,[3 5 20] and unmentioned in four.[4 6 18 19] Quality assessment by the NOS showed that all of the included studies were of high quality. Other details of the study characteristics are presented in table 1.

Meta-analysis

Meta-analyses were performed for the following factors which were evaluated in ≥4 studies: age, sex, baseline NIHSS and ASPECTS, hypertension, diabetes mellitus, atrial fibrillation, dyslipidemia, admission systolic blood pressure (SBP), diastolic blood pressure and serum glucose, occlusion sites, IVT, collateral status, etiology classification according to TOAST (Trial of ORG 10172 in Acute Stroke Treatment), onset-to-puncture time (OTP), onset-to-recanalization time (OTR), puncture-to-recanalization time (PTR), and post-procedural symptomatic intracranial hemorrhage (sICH). The pooled analysis showed that age (MD 5.81, 95% CI 4.16 to 7.46; p<0.00001), female sex (OR 1.40, 95% CI 1.16 to 1.68; p=0.0004), hypertension (OR 1.73, 95% CI 1.43 to 2.09; p<0.00001), diabetes mellitus (OR 1.78, 95% CI 1.41 to 2.24; p<0.00001), atrial fibrillation (OR 1.24, 95% CI 1.01 to 1.51; p=0.04), admission SBP (MD 4.98, 95% CI 1.87 to 8.09; p=0.002), admission serum glucose (MD 0.59, 95% CI 0.37 to 0.81; p<0.00001), NIHSS (MD 4.22, 95% CI 3.38 to 5.07; p<0.00001), ASPECTS (MD −0.71, 95% CI −1.23 to −0.19; p=0.007), ICA occlusion (OR 1.85, 95% CI 1.17 to 2.95; p=0.009), IVT (OR 0.67, 95% CI 0.55 to 0.83; p=0.0001), OTP (MD 16.92, 95% CI 6.52 to 27.31; p=0.001), PTR (MD 12.37, 95% CI 7.96 to 16.79;

Table 1 Main characteristics of the included studies in the meta-analysis

Study	Design	No. of patients	Definition of SR	IVT, % (FR/ER)	EVT	Occlusion sites	Pre-stroke mRS	NOS
Singer et al[21]	Prospective /retrospective	103	TICI 2b–3/TIMI 2 or 3	NM	SRe or other	M1, carotid T occlusion	≤1	7
Lee et al[17]	Retrospective	440	TICI 2b–3	68.1/72	NM	M1, M2, ICA	≤1	8
Mechtouff et al[18]	Prospective	164	TICI 2b–3	41.3/62.1	NM	ICA, M1	NM	7
Zang et al[23]	Prospective	61	mTICI 2b–3	41.2/40.7	SRe	tICA, M1, proximal M2	≤1	7
Pedraza et al[20]	Retrospective	295	mTICI 2b–3	33.8/43.7	NM	Intracranial ICA, M1	≤2	8
Rueda et al[6]	Retrospective	150	TICI 2b–3	45.3/43.8	SRe, TA, CAP, or stenting	Intracranial ICA, MCA, tandem	NM	7
Wang et al[22]	Retrospective	56	mTICI 2b–3	0	SRe	Intracranial ICA, proximal M1, M2	≤1	8
Gilberti et al[4]	Retrospective	68	TICI 2b–3	27.3/58.7	SRe or TA	Intracranial tICA, M1, proximal M2	NM	8
Xu et al[2]	Prospective	403	mTICI 2b–3	30/39.9	SRe, BA, IAT or stenting	ICA, M1, M2	≤1	7
Hussein et al[3]	Post hoc analysis of a RCT	130	TICI 2b–3	100	SRe or IAT	ICA, M1, M2	≤2	NA
van Horn et al[5]	Retrospective	123	TICI 3	59	SRe or CA	ICA, MCA	≤2	8
Mohammaden et al[19]	Retrospective	56	mTICI 2b–3	NM	SRe or CA	ICA, MCA	NM	8

BA, balloon angioplasty; CA, contact aspiration; CAP, carotid angioplasty; ER, effective recanalization; EVT, endovascular treatment; FR, futile recanalization; IAT, intra-arterial thrombolysis; ICA, internal carotid artery; IVT, intravenous thrombolysis; M1, first segment of middle cerebral artery; M2, second segment of middle cerebral artery; MCA, middle cerebral artery; mRS, modified Rankin scale; mTICI, modified Thrombolysis in Cerebral Infarction; NA, not applicable; NM, not mentioned; NOS, Newcastle-Ottawa Scale; RCT, randomized controlled trial; SR, successful recanalization; SRe, stent-retriever; TA, thromboaspiration; tICA, terminal ICA; TIMI, Thrombolysis in Myocardial Infarction.

p<0.00001), and post-procedural sICH (OR 6.09, 95% CI 3.18 to 11.68; p<0.00001) were significantly associated with FR (figures 2 and 3 and online supplemental figure 1). The rest of the factors were not correlated with FR (online supplemental figures 1 and 2). Detailed information about OR/MD, 95% CIs, number of involved studies, and p values are shown in online supplemental table 1.

High risk of heterogeneity (I² >50%) was seen in the outcomes of seven factors (age, NIHSS, ASPECTS, ICA and tandem occlusion, collateral status, and OTR). Subgroup analysis was conducted for age, NIHSS, ASPECTS and OTR according to study design (prospective or retrospective studies, RCT considered as a prospective study) or recanalization scales (TICI 2b–3, mTICI 2b–3 or TICI 3) (online supplemental figures 3–6), but the source of heterogeneity was not found. Sensitivity analysis showed that the statistical significance of the pooled estimates did not change for all factors except for atrial fibrillation and OTP (online supplemental figure 7).

Overall, six predictors (age, sex, NIHSS, hypertension, diabetes, and atrial fibrillation) were analyzed in ≥10 studies.
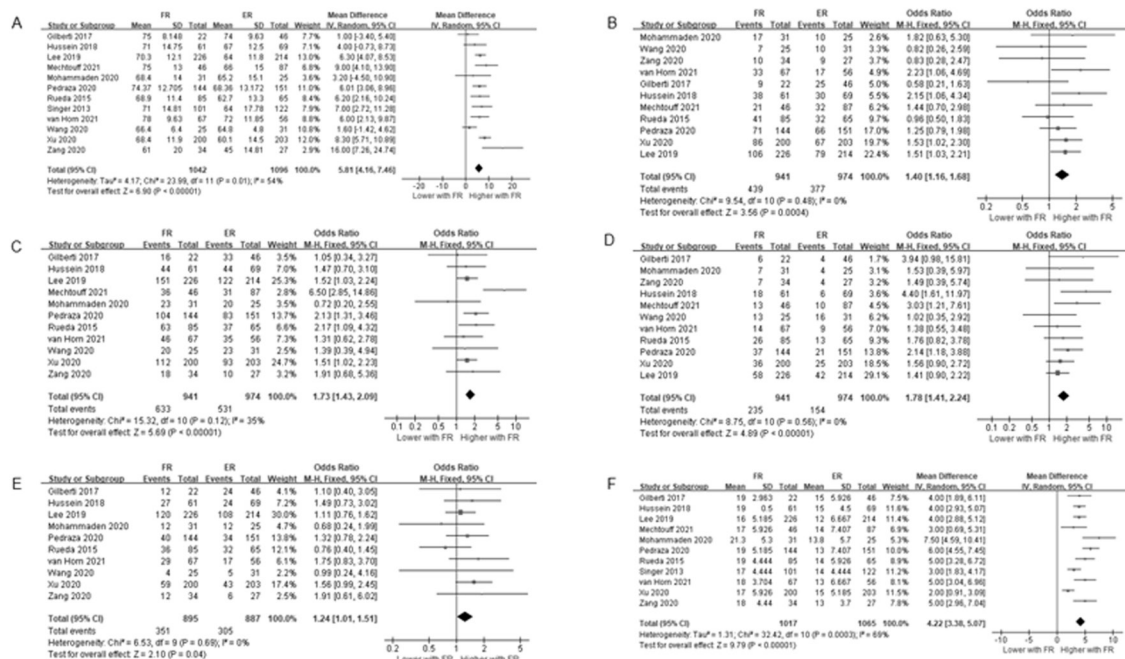

Figure 2 Forest plots illustrating association of age (A), female sex (B), hypertension (C), diabetes mellitus (D), atrial fibrillation (E) and NIHSS (F) with futile recanalization after endovascular therapy for acute ischemic stroke. ER, effective recanalization; FR, futile recanalization; NIHSS, National Institutes of Health Stroke Scale score.
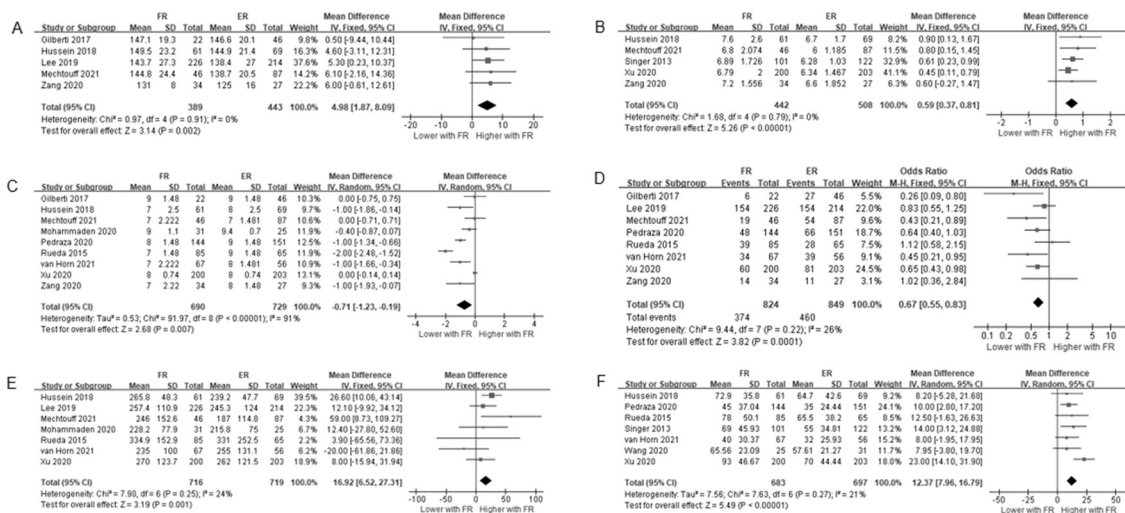
Figure 3 Forest plots illustrating association of admission systolic blood pressure (A), serum glucose (B), ASPECTS (C), intravenous thrombolysis (D), onset-to-puncture time (E) and puncture-to-recanalization time (F) with futile recanalization after endovascular therapy for acute ischemic stroke. ASPECTS, Alberta Stroke Program Early CT score; ER, effective recanalization; FR, futile recanalization.

Although funnel plots (online supplemental figure 8) regarding these six factors are not symmetric, Begg's test and Egger's test found that the risk of publication bias was low (online supplemental table 1).

DISCUSSION

This meta-analysis investigated the predictors of FR after EVT in patients with AIS due to anterior circulation LVO. The proportion of FR ranged from 32.4% to 56.7%. The novelty of this study lies in the fact that we identified female sex, comorbidities (hypertension, diabetes, and atrial fibrillation), admission SBP and serum glucose, ICA occlusion, non-bridging therapy, and post-procedural sICH as predictors of FR. Meanwhile, those conventional indicators for FR such as age, higher NIHSS, lower ASPECTS, and longer treatment delay were also confirmed in accordance with previous reports. The included studies were generally of high quality, as confirmed by the NOS score, and the risk of publication bias was low.

EVT, with or without intravenous thrombolysis, is the standard treatment for AIS due to anterior circulation LVO. However, the rate of FR, which indicates functional dependency at 90 days despite successful recanalization, can be as high as 54%.[1] To date, the mechanisms of FR remain incompletely understood. Proposed mechanisms include poor collateral circulation, per-procedural distal embolization, early re-occlusion, large hypoperfused volumes, microvascular compromise (ie, no-reflow), and impaired cerebral autoregulation.[24]

In line with previous studies,[2 9 21 25] we found that older age was a strong predictor of FR. Advanced age is constantly associated with undesirable neurological outcomes after stroke, which may be due to more comorbidities, higher occurrence of complications, higher rate of cardioembolic strokes, and less rehabilitation potential.[21 26] Nevertheless, setting a strict upper limit of age for EVT seems unreasonable. The observed association between sex and FR may either be a coincidence or the product of physiological differences in coagulation, hormone exposure, and immunity.[27]

Among the vascular risk factors, we found that hypertension, diabetes, admission SBP, and admission serum glucose were associated with FR. Hypertension and hyperglycemia may increase blood–brain barrier permeability,[28 29] impair cerebrovascular

reactivity in the microvasculature,[30 31] and aggravate reperfusion injury,[32 33] thus exacerbating the effects of stroke. The impact of atrial fibrillation on FR were not conclusive, as the sensitivity analysis indicated the results to be unstable. However, atrial fibrillation may be related to FR compared with atherosclerotic pathology as different types and morphology of the thrombus appear to influence the efficacy of EVT.[34]

A higher baseline NIHSS score, indicating a more severe stroke, is a consistently strong predictor of FR.[35 36] However, the clinical benefit of successful reperfusion after EVT still outweighs its risks.[17] Therefore, excluding patients with an initial high NIHSS score from the EVT is unnecessary. A lower baseline ASPECTS score, indicating a more severe early ischemic lesion, has been associated with poor clinical outcomes and reperfusion after EVT.[37 38] It is noteworthy that ASPECTS informed by a CT angiography source image or multi-model CT was more reliable in predicting FR than ASPECTS sourced from non-contrast CT.[6] Relative to MCA occlusion, ICA occlusion generally leads to more severe stroke and contributes to higher rates of FR.

A strong body of evidence has demonstrated that collateral status plays a crucial role in the prognosis of AIS. Good collaterals are associated with smaller infarcts and better neurological outcomes after thrombolytic therapy.[39 40] Recently, collaterals have been shown to predict responses to EVT. A meta-analysis enrolling studies of EVT for AIS showed that good collaterals were associated with favorable functional outcomes.[41] However, our meta-analysis failed to detect a difference between the FR and ER groups. It is presently impossible to draw a definite conclusion concerning the relationship between collateral status and FR because of the limited number of studies (only four) eligible for the pooled analysis, variation in scales assessing collateral status, and presence of heterogeneity.

In the perioperative period, our meta-analysis showed that OTP and PTR were associated with FR. Longer treatment delay was shown to be a consistent predictor of FR in previous studies.[2 9 21 22 25] Notably, post-procedural complications, including sICH, are also strong predictors of FR after EVT. This finding highlights the importance of shortening treatment time, improving operational skills, and choosing proper patient subgroups with a low risk of FR. The observation

that pre-procedural IVT therapy is associated with a lower incidence of FR may be explained by the synergistic action of IVT and EVT in targeting small vessel recanalization and improving distal microvascular perfusion. But this hypothesis needs further investigation because evidence suggests that IVT did not influence the occurrence of EVT-induced peripheral emboli detected on high-resolution diffusion-weighted imaging.[42] Meanwhile, the observed association may be confounded by the time from last seen well, since IVT is always given in an early time window.

Several other potential radiological, laboratory and procedural predictors of FR are emerging but have only been assessed occasionally. First, large deep white-matter lesions on diffusion-weighted MRI,[12] moderate-severe leukoaraiosis and brain atrophy,[4 20] ASPECTS from multimodal CT,[6 11] and MRI as the initial imaging modality (vs CT)[16] were shown to be independent predictors of FR. These findings highlight the crucial role of advanced imaging in predicting FR. Second, plasma biomarkers such as interleukin 6,[43] high sensitivity C-reactive protein,[23] ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13),[8 23] matrix metalloproteinase-9,[23] tenascin-C,[23] and thioredoxin[23] were independent predictors of FR. These findings implicate inflammation, oxidative stress, blood–brain barrier breakdown, and microcirculatory disturbances in the pathogenesis of FR. As plasma biomarkers benefit from being simple and economical to measure, future research into the possibility of incorporating them with clinical and imaging parameters to construct a risk scoring system may improve the early screening of FR. Third, EVT procedural-related factors may be associated with FR. Compared with first-pass effect, multiple-pass effect is associated with worse outcomes even if achieving successful or complete recanalization independently contributes to FR.[44] Five or more retrieval passes were an independent predictor of FR, and the functional outcomes did not differ between patients with ≥5 passes and those without recanalization.[45] These highlight the importance of sophisticated EVT devices and techniques.

This study has several limitations. First, substantial heterogeneity between the studies was observed. This can be attributed to variations in inclusion and exclusion criteria, study design, scales for assessing recanalization, rate of IVT, EVT strategy, occlusion sites, and premorbid mRS. Second, the retrospective nature of most included studies may introduce selection bias. The included studies were mostly of small sample size, and the number of studies for some predictors was limited; hence, some clinically important differences (such as in poor collaterals) may not have been detected. Third, many identified predictors might be covariates, but not independent predictors. Large-scale prospective studies adjusted for multiple confounders are needed to confirm our results. Finally, further search terms could have modified our results, for instance, studies that did not include the term 'futile' may have been omitted.

In conclusion, this meta-analysis demonstrated that female sex, a history of hypertension, diabetes, higher admission systolic pressure and serum glucose level, ICA occlusion, non-bridging therapy, and post-procedural sICH are also predictors of FR following EVT in AIS due to anterior circulation LVO, in addition to older age, higher NIHSS score and longer OTP, which were repeatedly proved to be predictors in previous studies. Further large-scale prospective studies with more comprehensive indices (including neuroimaging and plasma biomarkers) are needed to confirm these observations. It is important to note that identification of factors associated with futile thrombectomy should not be pursued to exclude patients from treatment (based on randomized evidence), but should rather focus on the identification of modifiable factors, or identification of further treatment targets (ie, adjuvant treatment with neuroprotectants, etc). A prediction model for FR based on our findings may help to improve the selection of patients suitable for EVT. Meanwhile, modifiable factors (such as blood pressure, glucose level, thrombolysis, and length of time to treatment) should be well controlled through the application of new devices and improvement of techniques to facilitate ER.

ORCID iD
Dai-Shi Tian http://orcid.org/0000-0003-4753-1485

REFERENCES

1. Goyal M, Menon BK, van Zwam WH, Zwam W, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723–31.
2. Xu H, Jia B, Huo X, et al. Predictors of futile recanalization after endovascular treatment in patients with acute ischemic stroke in a multicenter registry study. *J Stroke Cerebrovasc Dis* 2020;29:105067.
3. Hussein HM, Saleem MA, Qureshi AI. Rates and predictors of futile recanalization in patients undergoing endovascular treatment in a multicenter clinical trial. *Neuroradiology* 2018;60:557–63.
4. Gilberti N, Gamba M, Premi E, et al. Leukoaraiosis is a predictor of futile recanalization in acute ischemic stroke. *J Neurol* 2017;264:448–52.
5. van Horn N, Kniep H, Leischner H, et al. Predictors of poor clinical outcome despite complete reperfusion in acute ischemic stroke patients. *J Neurointerv Surg* 2021;13:14–18.
6. Espinosa de Rueda M, Parrilla G, Manzano-Fernández S, et al. Combined multimodal computed tomography score correlates with futile recanalization after thrombectomy in patients with acute stroke. *Stroke* 2015;46:2517-22.
7. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005;5:13.
8. Bustamante A, Ning M, García-Berrocoso T, et al. Usefulness of ADAMTS13 to predict response to recanalization therapies in acute ischemic stroke. *Neurology* 2018;90:e995–1004.
9. Shi Z-S, Liebeskind DS, Xiang B, et al. Predictors of functional dependence despite successful revascularization in large-vessel occlusion strokes. *Stroke* 2014;45:1977–84.
10. Wirtz MM, Hendrix P, Goren O, et al. Predictor of 90-day functional outcome after mechanical thrombectomy for large vessel occlusion stroke: NIHSS score of 10 or less at 24 hours. *J Neurosurg* 2019;134:115–21.
11. Kawiorski MM, Martínez-Sánchez P, García-Pastor A, et al. Alberta stroke program early CT score applied to CT angiography source images is a strong predictor of futile recanalization in acute ischemic stroke. *Neuroradiology* 2016;58:487–93.

12 Tateishi Y, Wisco D, Aoki J, *et al*. Large deep white matter lesions may predict futile recanalization in endovascular therapy for acute ischemic stroke. *Interv Neurol* 2014;3:48–55.

13 Tsogkas I, Knauth M, Schregel K, *et al*. Added value of CT perfusion compared to CT angiography in predicting clinical outcomes of stroke patients treated with mechanical thrombectomy. *Eur Radiol* 2016;26:4213–9.

14 Nawabi J, Flottmann F, Hanning U, *et al*. Futile recanalization with poor clinical outcome is associated with increased edema volume after ischemic stroke. *Invest Radiol* 2019;54:282–7.

15 Nawabi J, Flottmann F, Kemmling A, *et al*. Elevated early lesion water uptake in acute stroke predicts poor outcome despite successful recanalization - When "tissue clock" and "time clock" are desynchronized. *Int J Stroke* 2019;1747493019884522:174749 3019884522.

16 Meinel TR, Kaesmacher J, Mosimann PJ, *et al*. Association of initial imaging modality and futile recanalization after thrombectomy. *Neurology* 2020;95:e2331–42.

17 Lee S-H, Kim BJ, Han M-K, *et al*. Futile reperfusion and predicted therapeutic benefits after successful endovascular treatment according to initial stroke severity. *BMC Neurol* 2019;19:11.

18 Mechtouff L, Bochaton T, Paccalet A, *et al*. Association of interleukin-6 levels and futile reperfusion after mechanical thrombectomy. *Neurology* 2021;96:e752–7.

19 Mohammaden MH, Stapleton CJ, Brunozzi D, *et al*. Predictors of poor outcome despite successful mechanical thrombectomy of anterior circulation large vessel occlusions within 6 H of symptom onset. *Front Neurol* 2020;11:907.

20 Pedraza MI, de Lera M, Bos D, *et al*. Brain atrophy and the risk of futile endovascular reperfusion in acute ischemic stroke. *Stroke* 2020;51:1514–21.

21 Singer OC, Haring H-P, Trenkler J, *et al*. Age dependency of successful recanalization in anterior circulation stroke: the ENDOSTROKE study. *Cerebrovasc Dis* 2013;36:437–45.

22 Wang D, Shu H, Meng Y, *et al*. Factors promoting futile recanalization after stent retriever thrombectomy for stroke affecting the anterior circulation: a retrospective analysis. *World Neurosurg* 2020;133:e576–82.

23 Zang N, Lin Z, Huang K, *et al*. Biomarkers of unfavorable outcome in acute ischemic stroke patients with successful recanalization by endovascular thrombectomy. *Cerebrovasc Dis* 2020;49:583–92.

24 Nie X, Pu Y, Zhang Z, *et al*. Futile recanalization after endovascular therapy in acute ischemic stroke. *Biomed Res Int* 2018;2018:1–5.

25 Hussein HM, Georgiadis AL, Vazquez G, *et al*. Occurrence and predictors of futile recanalization following endovascular treatment among patients with acute ischemic stroke: a multicenter study. *AJNR Am J Neuroradiol* 2010;31:454–8.

26 Marini C, Baldassarre M, Russo T, *et al*. Burden of first-ever ischemic stroke in the oldest old: evidence from a population-based study. *Neurology* 2004;62:77–81.

27 Howe MD, McCullough LD. Prevention and management of stroke in women. *Expert Rev Cardiovasc Ther* 2015;13:403–15.

28 Ennis SR, Keep RF. Effect of sustained-mild and transient-severe hyperglycemia on ischemia-induced blood-brain barrier opening. *J Cereb Blood Flow Metab* 2007;27:1573–82.

29 Santisteban MM, Ahn SJ, Lane D, *et al*. Endothelium-macrophage crosstalk mediates blood-brain barrier dysfunction in hypertension. *Hypertension* 2020;76:795–807.

30 Kawai N, Keep RF, Betz AL, Betz F. Hyperglycemia and the vascular effects of cerebral ischemia. *Stroke* 1997;28:149–54.

31 Maeda H, Matsumoto M, Handa N, *et al*. Reactivity of cerebral blood flow to carbon dioxide in hypertensive patients: evaluation by the transcranial Doppler method. *J Hypertens* 1994;12:191–7.

32 Leonardi-Bee J, Bath PMW, Phillips SJ, *et al*. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke* 2002;33:1315–20.

33 Martini SR, Kent TA, Kent R, Thomas A. Hyperglycemia in acute ischemic stroke: a vascular perspective. *J Cereb Blood Flow Metab* 2007;27:435–51.

34 Madjidyar J, Pineda Vidal L, Larsen N, *et al*. Influence of thrombus composition on thrombectomy: Adapt vs. balloon guide catheter and stent retriever in a flow model. *Fortschr Röntgenstr* 2020;192:257–63.

35 Adams HP, Davis PH, Leira EC, *et al*. Baseline NIH stroke scale score strongly predicts outcome after stroke: a report of the trial of ORG 10172 in acute stroke treatment (TOAST). *Neurology* 1999;53:126–31.

36 Cooray C, Fekete K, Mikulik R, *et al*. Threshold for NIH stroke scale in predicting vessel occlusion and functional outcome after stroke thrombolysis. *Int J Stroke* 2015;10:822–9.

37 Broocks G, Hanning U, Flottmann F, *et al*. Clinical benefit of thrombectomy in stroke patients with low aspects is mediated by oedema reduction. *Brain* 2019;142:1399–407.

38 Yoo AJ, Zaidat OO, Chaudhry ZA, *et al*. Impact of pretreatment noncontrast CT Alberta stroke program early CT score on clinical outcome after intra-arterial stroke therapy. *Stroke* 2014;45:746–51.

39 van den Wijngaard IR, Boiten J, Holswilder G, *et al*. Impact of collateral status evaluated by dynamic computed tomographic angiography on clinical outcome in patients with ischemic stroke. *Stroke* 2015;46:3398–404.

40 Yeo LLL, Kong WY, Paliwal P, Leonard LL, Yeo W, Yee K, *et al*. Intravenous thrombolysis for acute ischemic stroke due to cervical internal carotid artery occlusion. *J Stroke Cerebrovasc Dis* 2016;25:2423–9.

41 Leng X, Fang H, Leung TWH, *et al*. Impact of collaterals on the efficacy and safety of endovascular treatment in acute ischaemic stroke: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2016;87:537–44.

42 Broocks G, Meyer L, Kabiri R, *et al*. Impact of intravenous alteplase on sub-angiographic emboli in high-resolution diffusion-weighted imaging following successful thrombectomy. *Eur Radiol* 2021;17.

43 Mechtouff L, Nighoghossian N, Amaz C, *et al*. White matter burden does not influence the outcome of mechanical thrombectomy. *J Neurol* 2020;267:618–24.

44 Bai X, Zhang X, Yang W, *et al*. Influence of first-pass effect on recanalization outcomes in the era of mechanical thrombectomy: a systemic review and meta-analysis. *Neuroradiology* 2021;63:795–807.

45 Baek J-H, Kim BM, Heo JH, *et al*. Number of stent retriever passes associated with futile recanalization in acute stroke. *Stroke* 2018;49:2088–95.