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Systematic Review

Predictors of Early Neurological Deterioration Occurring within 24 h in Acute Ischemic Stroke following Reperfusion Therapy: A Systematic Review and Meta-Analysis

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Abstract

Background: Early neurological deterioration (END), generally defined as the increment of National Institutes of Health Stroke Scale (NIHSS) score ≥4 within 24 hours, lead to poor clinical outcome in acute ischemic stroke (AIS) patients receiving reperfusion therapies including intravenous thrombolysis (IVT) and/or endovascular treatment (EVT). This systematic review and meta-analysis aimed to explore multiple predictors of END following reperfusion therapies. **Methods**: We searched PubMed, Web of Science and EBSCO for all studies on END in AIS patients receiving IVT and/or EVT published between January 2000 and December 2022. A random-effects meta-analysis was conducted and presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The quality of each included studies was assessed by calculating a total score according to the STROBE or CONSORT criteria. Publication bias and heterogeneity were also evaluated using the Eggers/Peters test, funnel plots and sensitivity analysis. **Results**: A total of 29 studies involving 65,960 AIS patients were included. The quality of evidence is moderate to high, and all studies have no publication bias. The overall incidence of END occurring after reperfusion therapy in AIS patients was 14% ((95% confidence intervals (CI), 12%–15%)). Age, systolic blood pressure (SBP), glucose levels at admission, the onset to treatment time (OTT), hypertension, diabetes mellitus, arterial fibrillation, and internal cerebral artery occlusion were significantly associated with END following reperfusion therapy. **Conclusions**: Numerous factors are associated with END occurrence in AIS patients receiving reperfusion therapy. Management of the risk factors of END may improve the functional outcome after reperfusion treatment.

Keywords: early neurological deterioration (END); intravenous thrombolysis (IVT); endovascular treatment (EVT); reperfusion therapy; predictors

1. Introduction

The past decade has witnessed substantial advances in the treatment of acute ischemic stroke (AIS). Evidence-based reperfusion therapies such as intravenous thrombolysis (IVT) and mechanical thrombectomy have been shown to improve outcomes in AIS and become the standard care for AIS patients. However, despite these major improvement, only less than half of patients achieve functional independence (mRS 0–2) at 90 days as a result of treatment, leaving the others at a high risk of disability and death [1]. Most of the poor 90-day outcomes in AIS after reperfusion therapy (i.e., IVT and/or endovascular treatment) are reported to be largely associated with early neurological deterioration (END). END generally refers to a ≥4 point increase in the National Institutes of Health Stroke Scale (NIHSS) score between baseline and 24 hours after treatment. The estimates of END incidence vary widely in AIS patients, ranging from 8% to 28% of patients after IVT [2–6], and from 35% to 42% of patients after endovascular treatment (EVT) [7–9]. However, the reasons of END occurrence were not fully understood, some of which are related to symptomatic intracranial haemorrhage (sICH), malignant edema and early recurrent ischemic stroke, while others are remaining unexplained. Since END is closely related to the increase of disability and mortality following reperfusion therapy, it is desirable to identify factors associated with END and to explore the underlying mechanism, so that possible prevention and treatment could be done to improve clinical outcomes.

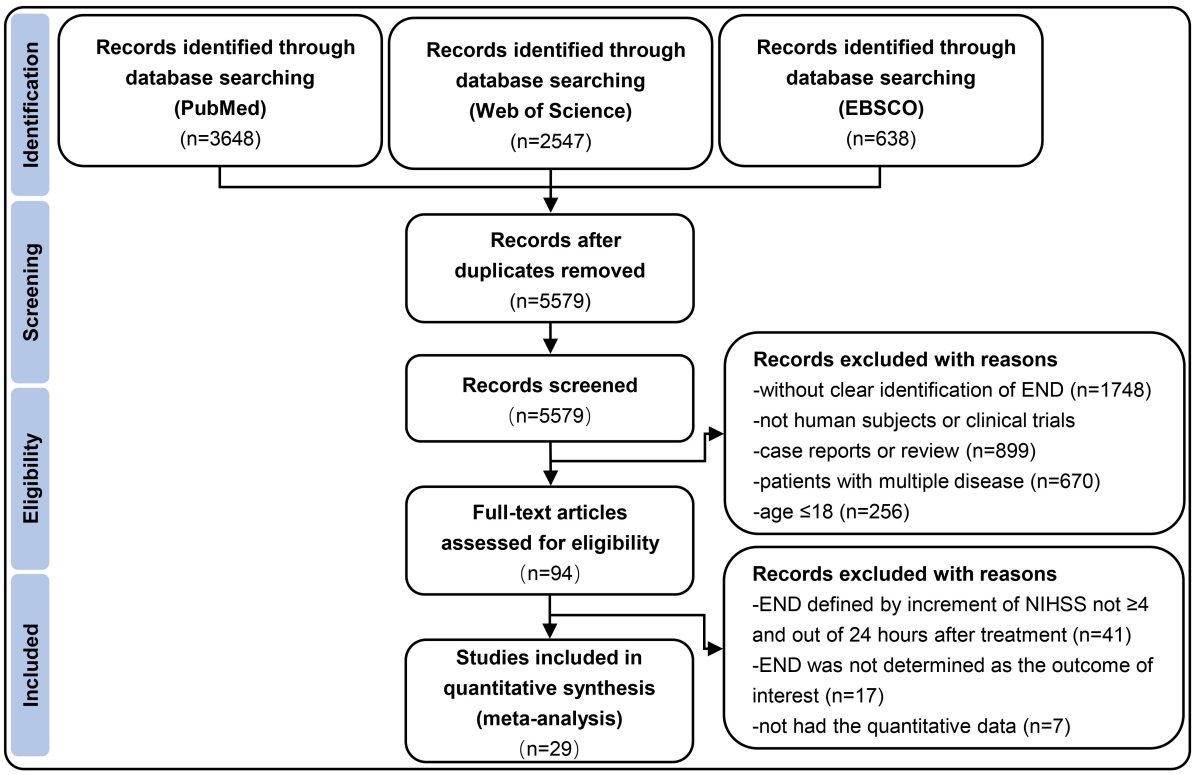

Fig. 1. Flow diagram depicting the selection of studies eligible for analysis. END indicates early neurological deterioration; NIHSS indicates National Institutes of Health Stroke Scale.

Thus far, END has only been addressed in either IVT or EVT setting. Few studies considered IVT and EVT as a whole for reperfusion therapy. Unfortunately, the latter is more like the cases in the real world. Furthermore, the exact rate and predictors of END have not been systematically investigated. Therefore, we present here a systematic review and meta-analysis of the predictors of END following reperfusion therapy (IVT and/or EVT) in AIS patients. Specifically, we categorized the predictors of END into three groups, IVT, EVT and overall reperfusion therapy, to study the treatment-specific risk factors.

2. Methods

2.1 Search Strategy

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. Studies published in English between January 2000 and December 2022 were identified by searching PubMed, Web of Science and EBSCO databases. Key search terms were 'neurological deterioration', 'neurological deficit', 'neurological decline', 'thrombolysis', 'thrombolytic treatment', 'thrombolytic therapy', 'IV rtPA', 'endovascular treatment', 'endovascular therapy', 'mechanical thrombectomy', 'acute ischemic stroke', 'acute cerebral ischaemia', 'proximal vessel occlusion', 'proximal artery occlusion', 'large vessel occlusion', 'large artery occlusion', 'vertebrobasilar artery occlusion', 'basilar artery occlusion', 'middle cerebral artery occlusion', 'internal cerebral artery occlusion'. Details of the search algorithm is shown in Appendix I and the **Supplementary Materials**. Fig. 1 presents the specific screening process.

2.2 Selection Criteria

We included all studies that investigated predictors of END for adult patients with AIS who received IVT and/or EVT if they met the following criteria: (1) age $\geq$18 years with AIS due to large vessel occlusion, including the anterior or posterior circulation; (2) arterial occlusion was confirmed by computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or digital subtraction angiography (DSA); (3) studies reported the number of patients with END; (4) having clear definition of END (END was defined as an increment of NIHSS score of $\geq$4 points within 24 hours); (5) were published in English language.

We excluded studies (1) in animals and studies that did not provide sufficient information needed in the meta-analysis; (2) patients with baseline pre-stroke mRS score $\geq$3; (3) artery occlusion of non-atherosclerotic etiology such as dissection, moyamoya disease, vasospasm, or vasculitis; (4) reviews, letters, case reports, protocols or conference abstracts; (5) studies involved other definitions of END.

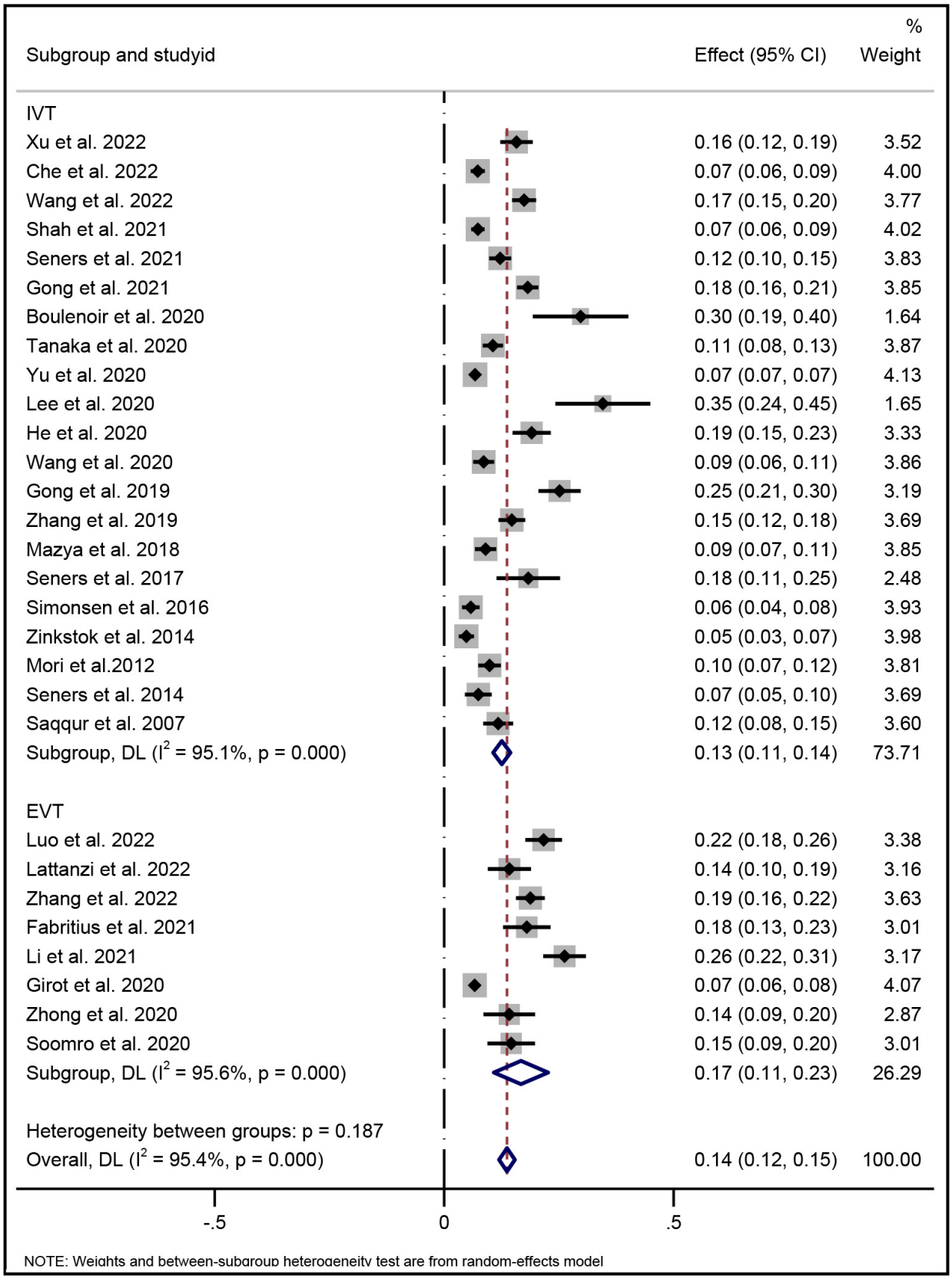

Fig. 2. Forest plot of pooled incidence of END with random-effect method in AIS patients underwent reperfusion therapy (IVT and/or EVT). END indicates early neurological deterioration; IVT indicates intravenous thrombolysis; and EVT indicates endovascular therapy.

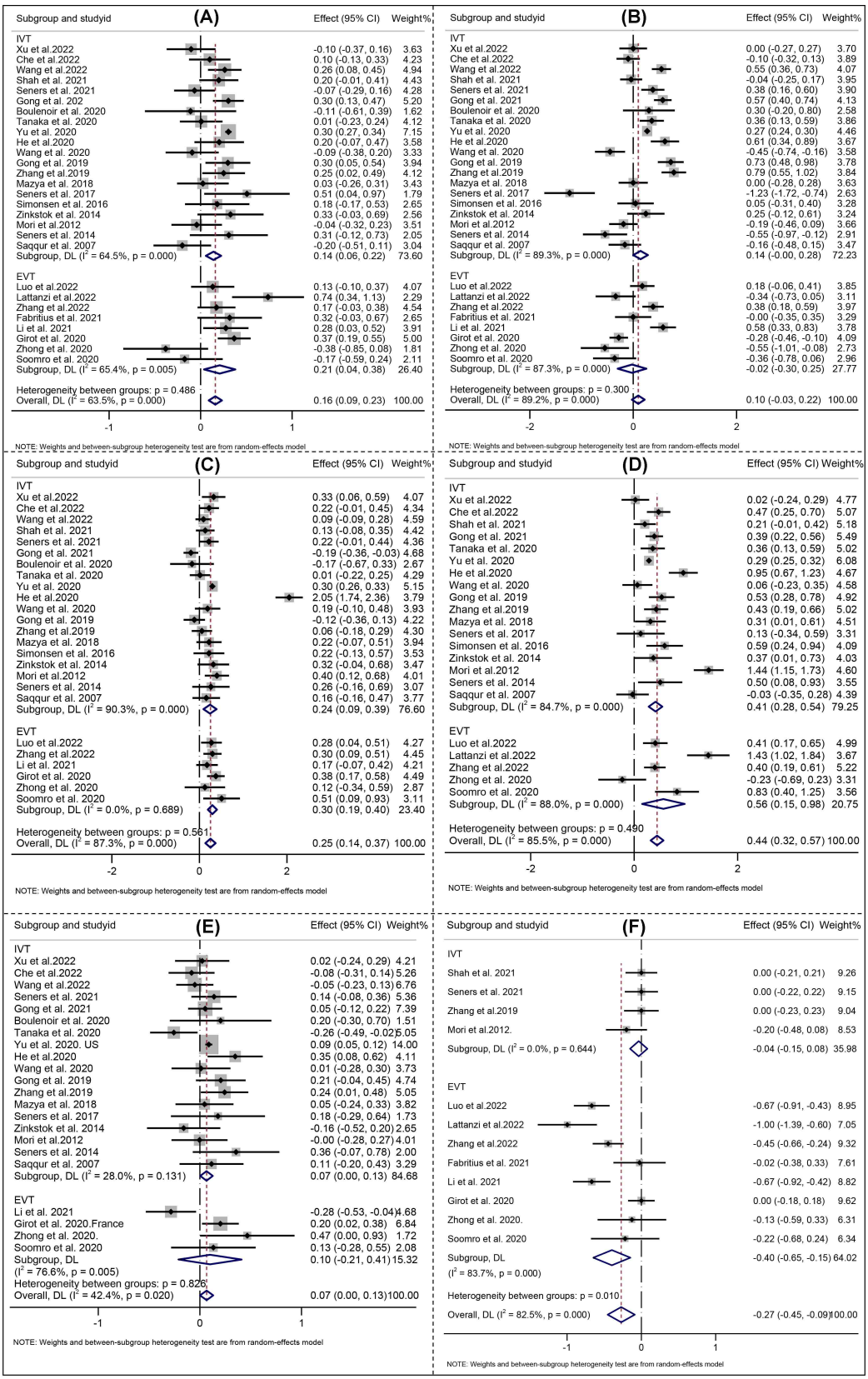

Fig. 3. Forest Plots of (A) Age; (B) Initial NIHSS; (C) Systolic blood pressure; (D) Serum glucose; (E) Onset to treatment time; (F) ASPECT score. NIHSS indicates National Institutes of Health Stroke Scale; ASPECT indicates Alberta Stroke Early CT score. IVT indicates intravenous thrombolysis, and EVT indicates endovascular therapy. The solid squares denote the standardized mean differences (Effects), the horizontal lines represent the 95% confidence intervals (CIs), and the diamonds denote the pooled effect size.

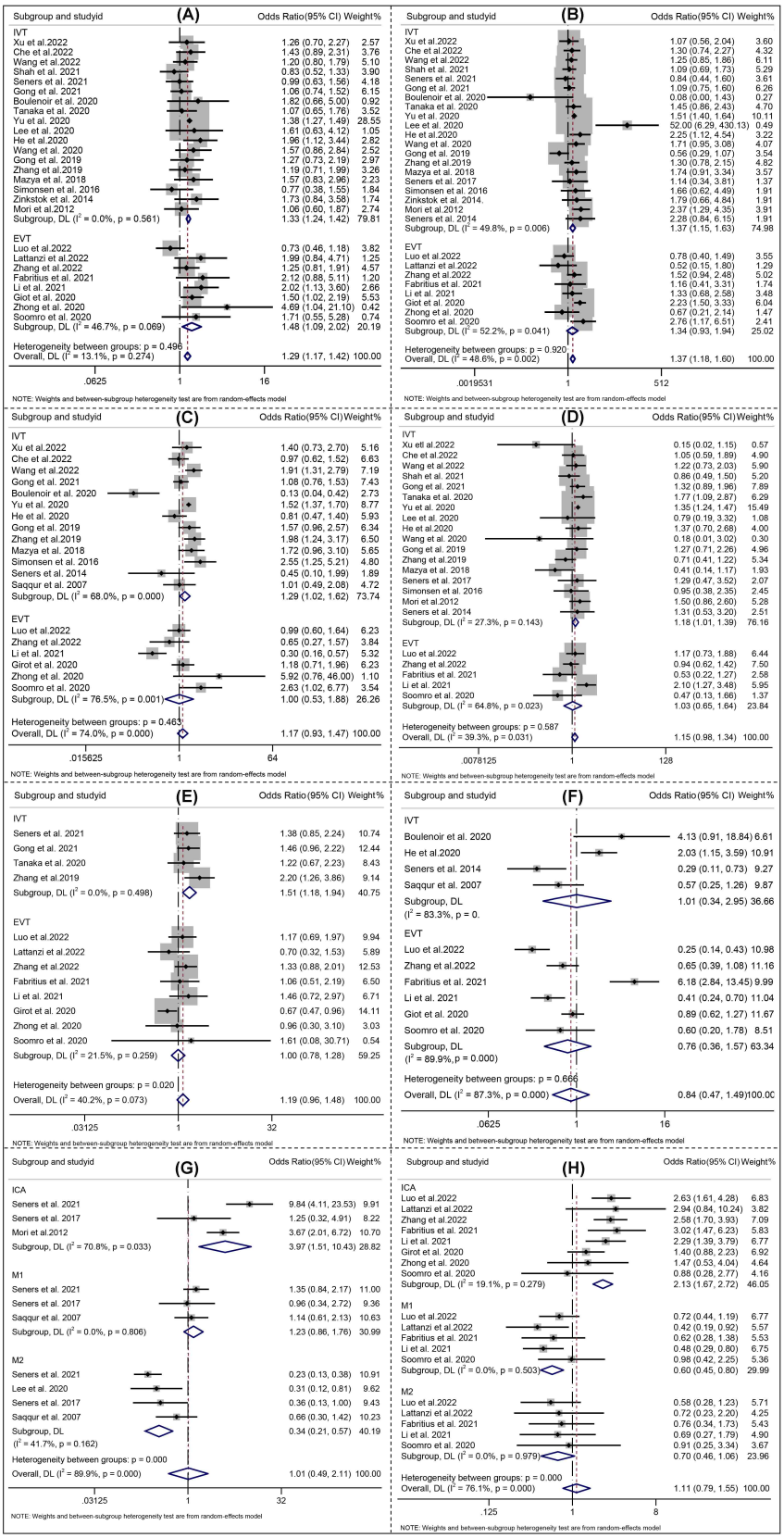

Fig. 4. Forest plots of (A) Hypertension; (B) Diabetes mellitus; (C) Etiology atherosclerosis; (D) Atrial fibrillation; (E) Lesion location; (F) Successful recanalization; (G) Lesion location_IVT; (H) Lesion location_EVT. IVT indicates intravenous thrombolysis, and EVT indicates endovascular therapy. The solid squares denote the risk ratios (RRs), the horizontal lines represent the 95% confidence intervals (CIs), and the diamonds denote the pooled RRs.

2.3 Data Extraction and Quality Assessment

Two authors (L.J. and S.H.X.) independently searched the literature, screened eligible studies, and extracted data on the first author's name, year of publication, study design, sample size, number of patients in END and non-END groups, baseline characteristics, vascular comorbid conditions (history of hypertension, diabetes, atrial fibrillation), NIHSS on admission, Alberta Stroke Program Early CT Scores (ASPECT), lesion location (Internal Carotid Artery (ICA), Middle Cerebral Artery (MCA)), treatment strategy, and the onset to treatment time (OTT). Any disagreement was discussed and resolved by consensus among three other authors (L.C., Z.Y.Q., and L.X.). Three independent authors (L.A.F., L.Y.E, and W.S.) assessed the quality of each included study by using the CONSORT checklist for randomized controlled trials or the STROBE checklist for observational studies [11,12]. Studies with quality scores of 8–10 were recognized as high quality whereas those who scored 7 or less were considered as low quality. Details of quality assessment scoring are shown in Appendix II and **Supplementary Fig. 1**.

2.4 Statistical Analysis

The risk ratio (RR) of the binary variable or the standardized mean difference (SMD) of the continuous variable with the 95% confidence intervals (CI) were calculated as summary statistics in this meta-analysis. The overall RR and SMD for all pooled data were calculated using the random effect method. Mean and standard deviation (SD) were calculated using the method described by Luo *et al*. [13] if the studies reported median and inter-quartile range (IQR). We assessed the publication bias using Egger's test for continuous variables and Peters test for binary variables in addition to visual analysis of the funnel plots. The I^2 statistic was used to evaluate the heterogeneity across included studies and considered as a low, moderate and high heterogeneity using thresholds of 25%, 50% and 75%, respectively [14]. The sensitivity analysis was conducted to explain the heterogeneity. We performed subgroup analyses for END by treatment administered to patients. All statistical analyses were performed using STATA 16.0 (StataCorp, College Station, TX, USA).

3. Results

The search yielded 6833 relevant records from PubMed, Web of Science, and EBSCO. Finally, a total of 29 studies involving 65,960 AIS patients suffering from END within 24 hours following IVT and/or EVT were included [1,15–43]. The specific study selection process was reported in a PRISMA flowchart (Fig. 1). The basic characteristics of all included articles were shown in Table 1 (Ref. [15–43]).

3.1 Incidence of END

Fig. 2 shows the pooled overall incidence of END following reperfusion therapy in AIS patients was 14% (95% CI, 12%–15%). In the subgroup analysis, the incidence of END occurring after IVT was 13% (95% CI, 11%–14%), and was 17% after EVT (95% CI, 11%–23%).

3.2 Predictors of END

The following risk factors of END in AIS patients after reperfusion therapies were evaluated: age, initial NIHSS, systolic blood pressure (SBP), glucose level at admission, OTT, ASPECT, history of hypertension, diabetes mellitus (DM), arterial fibrillation (AF), stroke subtype by TOAST criteria (large artery atherosclerosis, cardioembolism, others or unknown), occlusion site, and successful recanalization (SR).

For all included studies, the meta-analysis showed that higher age (Effect, overall: 0.16, 95% CI: 0.09–0.23), SBP (Effect, overall: 0.25, 95% CI: 0.14–0.37), glucose level at admission (Effect, overall: 0.44, 95% CI: 0.32–0.57), OTT (RR, overall: 0.07, 95% CI: 0.00–0.13), history of hypertension (RR, overall: 1.29; 95% CI: 1.17–1.42), DM (RR, overall: 1.37; 95% CI: 1.18–1.60) were significantly associated with END after reperfusion therapies (Figs. 3,4).

Analysis of the pooled data from studies on END following IVT demonstrated that higher age (Effect: 0.14, 95% CI: 0.06–0.22), SBP (Effect 0.24, 95% CI: 0.09–0.39), glucose level at admission (Effect 0.41, 95% CI: 0.28–0.54), OTT (Effect 0.07, 95% CI: 0.00–0.13), history of hypertension (Effect 1.33; 95% CI: 1.24–1.42), DM (Effect 1.37; 95% CI: 1.15–1.63), AF (Effect 1.20; 95% CI: 1.10–1.31), large artery atherosclerosis (Effect 1.18; 95% CI: 1.01–1.39), internal carotid artery occlusion (Effect 3.97; 95% CI: 1.51–10.43), middle cerebral artery M2 occlusion (Effect 0.34; 95% CI: 0.21–0.57) and bridging therapy (Effect 1.51; 95% CI: 1.18–1.94) were significantly associated with END after IVT (Figs. 3,4).

For studies focusing on END after EVT, four risk factors including SBP (Effect 0.30, 95% CI: 0.19–0.40), history of hypertension (RR 1.48; 95% CI: 1.09–2.02), internal carotid artery occlusion (RR 2.13; 95% CI: 1.67–1.72), and middle cerebral artery M1 occlusion (Effect 0.60; 95% CI: 0.45–0.80) were found to be significantly associated with END (Figs. 3,4).

3.3 END and Outcome

We noted that the risk of dependency or death (modified Rankin Score $\geq$3) at 3 months was considerably higher in patients with END after reperfusion therapies (Effect 0.13; 95% CI: 0.07–0.26). Similar results were observed in the IVT group (Effect 0.16; 95% CI: 0.07–0.39) or in the EVT group (Effect 0.07; 95% CI: 0.04–0.12) (Data not shown).

Table 1. Participants' characteristics of each study.

No.	Source (Author/Year/Country)	Sample size (Total, END, non-END)	Age, year	Study design	Interventions	Location lesion	Time of stroke onset	Quality score
1	Luo *et al*. 2022. China [15]	T = 406 END = 88 Non-END = 318	END 70 (60–78) Non-END 71 (64–77)	A retrospective analysis of a prospectively maintained data	EVT	M1, M2, ICA, ACA, BA	Within 4.5 h	9
2	Lattanzi *et al*. 2022. Italy [16]	T = 211 END = 30 Non-END = 181	END 72 ± 10 Non-END 79 ± 5	A retrospective analysis based a longitudinal study	EVT	M1, M2, internal carotid artery, internal carotid artery terminus, middle cerebral artery	Within 4.5 h	9
3	Xu *et al*. 2022. China [17]	T = 406 END = 64 Non-END = 342	END 63.0 (56.0–69.5) Non-END 64.5 (55.0–73.0)	A retrospective cohort analysis based on prospectively collected data	IVT	ICA, M1, basilar artery	Within 4.5 h	9
4	Zhang *et al*. 2022. China [18]	T = 591 END = 111 Non-END = 480	END 70 (63–78) Non-END 69 (60–76)	A multicenter, prospective, randomized, open-label trial	EVT	MCA, Intracranial ICA	Within 4.5 h	10
5	Che *et al*. 2022. China [19]	T = 1107 END = 81 Non-END = 1026	END 64.47 ± 9.34 Non-END 63.34 ± 11.48	A multicenter prospective stroke registry	rtPA	N/A	Within 4.5 h	10
6	Wang *et al*. 2022. China [20]	T = 798 END = 139 Non-END = 659	END 69 ± 12.5 Non-END 66 ± 11.1	A retrospective analysis of a prospectively maintained data	IVT	N/A	Within 4.5 h	9

Table 1. Continued.

No.	Source (Author/Year/Country)	Sample size (Total, END, non-END)	Age, year	Study design	Interventions	Location lesion	Time of stroke onset	Quality score
7	Shah *et al*. 2021. USA [21]	T = 1238 END = 91 Non-END = 1147	END 72 ± 16 Non-END 69 ± 15	A retrospective analysis of a prospectively maintained data	IV tPA	ICA, M1, P1, and basilar artery, Vertebrobasilar	Within 4.5 h	10
8	Fabritius *et al*. 2021. Germany [22]	T = 211 END = 38 Non-END = 173	END 78 (72-80) Non-END 74 (63–81)	A prospective consecutive cohort study	EVT or bridging therapy (IVT plus EVT)	Anterior circulation of LVO ICA, MCA	Within 4.5 h	9
9	Li *et al*. 2021. China [23]	T = 343 END = 90 Non-END = 214	AD 70.7 ± 10.7 Non-ND 67.7 ± 10.9	Retrospective analysis of prospectively collected observational study	EVT	Anterior circulation of LVO ICA, MCA	ND, 257 (210–300)	9
10	Seners *et al*. 2021. France [24]	T = 721 END = 88 Non-END = 633	END 69 ± 15 Non-END 70 ± 15	A retrospective analysis based a longitudinal study	IVT	BA, ICA, M1 or M2	Within 4.5 h	10
11	Gong *et al*. 2021. China [25]	T = 1060 END = 193 Non-END = 469 ENI = 398	END 73.2 ± 11.5 Non-END 69.6 ± 12.0 ENI 68.1 ± 12.1	A prospective longitudinal study	IVT	Anterior circulation Posterior circulation	Within 4.5 h	10
12	Boulenoir *et al*. 2020. France [26]	T = 74 END = 22 Non-END = 52	END 62 (54–71) Non-END 64 (54–74)	A multicenter retrospective analysis based on prospective study	IVT	iICAo, ICA, MCA, basilar artery	Within 4.5 h	8

Table 1. Continued.

No.	Source (Author/Year/Country)	Sample size (Total, END, non-END)	Age, year	Study design	Interventions	Location lesion	Time of stroke onset	Quality score
13	Girot *et al.* 2020. France [27]	T = 1925 END = 128 Non-END = 1797	END 75.1 ± 11.8 Non-END 69.8 ± 14.6	Multicenter prospective observational registry	EVT alone or bridging therapy (IVT plus EVT)	ICA. M1/ M2	Within 4.5 h	10
14	Tanaka *et al.* 2020. Japan [28]	T = 744 END = 79 Non-END = 665	END H: 78 (67–87.5); I: 75 (64–81) Non-END 75 (66–82)	a retrospective design on Multicenter retrospective observational study	IVT (IVT bridging EVT)	ICA, MCA, BA	Within 4.5 h	10
15	Yu *et al.* 2020. United Kingdom [29]	T = 50726 END = 3415 Non-END = 47311	END 76 (69–83) Non-END 72 (63–81)	a retrospective analysis on a multinational open registry project	IVT	Left hemisphere, posterior	Within 4.5 h	9
16	Lee *et al.* 2020. USA [30]	T = 81 END = 28 Non-END = 53	END 70.8 Non-END 63.2	A prospective study	IVT	anterior circulation LVO as M1, M2, or carotid artery terminus (ICAT)	Within 4.5 h	7
17	Zhong *et al.* 2020. China [31]	T = 148 END = 21 Non-END = 127	END 56 (49–65) Non-END 61 (54–67)	A prospectively registered consecutive cohort study	Basilar EVT	BAO	Within 24 h	9
18	He *et al.* 2020. China [32]	T = 341 END = 65 Non-END = 276	END 67.14 ± 10.06 Non-END 64.87 ± 11.38	A prospectively study	IVT		Within 4.5 h	8

Table 1. Continued.

No.	Source (Author/Year/Country)	Sample size (Total, END, non-END)	Age, year	Study design	Interventions	Location lesion	Time of stroke onset	Quality score
19	Wang *et al*. 2020. China [33]	T (END) = 581 END = 50 No END = 531	END 59.5 (53.5–67.5) Non-END 62 (53–69)	Single center retrospectively study	IVT		Within 4.5 h	9
20	Soomro *et al*. 2020. USA [34]	T = 178 END = 26 Non-END = 152	END 60.5 (53–69) Non-END 63 (53–75)	Retrospective cohort	EVT	LVO	Within 6 h for anterior; 6 to 24 h for posterior	9
21	Gong *et al*. 2019. China [35]	T = 342 END = 86 No-END = 256	END 70.9 ± 11.4 Non-END 67.2 ± 12.7	Prospectively study	IVT (IVT+EVT)	proximal arte- rial occlusion	Within 4.5 h	9
22	Zhang *et al*. 2019. China [36]	T = 563 END = 83 Non-END = 480	END 69.1 ± 9.6 Non-END 66.2 ± 11.8	Multicenter, large prospective cohort study	IVT (IVT+EVT)		within 4.5 h	9
23	Mazya *et al*. 2018. Sweden [37]	T = 587 END = 53 Non-END = 534	END 67 (59–75) Non-END 67 (57–76)	Secondary data analysis on an ongoing, prospective, multinational centers cohort study	IVT	occlusion of large proximal and distal cerebral arteries		9
24	Seners *et al*. 2017. France [38]	T = 120 END = 22 Non-END = 98	END 75.7 ± 11.4 Non-END 68.0 ± 15.8	Secondary analysis on a prospective cohort study	IVT	MCA	Within 4.5 h	9

Table 1. Continued.

No.	Source (Author/Year/Country)	Sample size (Total, END, non-END)	Age, year	Study design	Interventions	Location lesion	Time of stroke onset	Quality score
25	Simonsen *et al*. 2016. Denmark [39]	T = 569 END = 33 Non-END = 536	END 66 (61–74) 73 (60.5–80.75) Non-END 66 (57–74)	A single center prospective cohort study	IVT	Small vessel disease, Large vessel disease	Less than 3 hours, extended to 4.5 hours	10
26	Zinkstok *et al*. 2014. The Netherlands [40]	T = 640 END = 31 Non-END = 609	END 71.1 ± 12.4 Non-END 66.7 ± 13.5	A prospective, multi-center, randomized controlled trial	IVT (Asprin + standard treatmetn)		113 (85–150) 115 (85–165)	9
27	Mori *et al*. 2012. Japan [41]	T = 566 END = 56 Non-END = 510	END 71.5 ± 9.3 Non-END 72.0 ± 11.9	A retrospective, multicenter, observational cohort study	IVT	AIS, ICA	Within 3 h	10
28	Seners *et al*. 2014. France [42]	T = 309 END = 23 Non-END = 276	END 73.1 ± 12.6 Non-END 68.6 ± 14.7	A retrospective cohort	IVT	Anterior circulation (MCA)	Within 4.5 h	9
29	Saqqur *et al*. 2007. Canada [43]	T = 374 END = 44 Non-END = 330 T = 374	END 66.1 ± 14.7 Non-END 68.8 ± 13.3	A retrospective study	IVT	M1, M2, ICA, BA	Within 3 h	9

3.4 Publication Bias and Heterogeneity

We detected the publication bias by combining visual funnel plots inspection with the symmetry distributions and the quantitative analysis of Egger's test and Peters test ($p > 0.05$), showing no sign of publication bias for all except age (**Supplementary Figs. 2,3** and Appendix III).

Considering the high heterogeneity emerged at predictors of initial NIHSS, SBP, etiology of atherosclerosis, serum glucose, ASPECT, location of intracranial occlusion_IVT, and successful recanalization (Figs. 3,4), a sensitivity analysis was performed to detect which study resulted in such high heterogeneity. No high risk of bias for the studies were identified the other predictors [22,26]. All the aforementioned results are shown in **Supplementary Fig. 4**.

4. Discussion

The main findings from this meta-analysis focused on investigating the predictors of END occurrence in AIS patients who receiving reperfusion treatments. Elderly, systolic blood pressure, glucose levels at admission, treatment onset, history of previous diseases (i.e., hypertension, diabetes mellitus, arterial fibrillation), internal carotid artery occlusion, and middle cerebral artery M2 occlusion significant associated with END in AIS patients who experienced overall reperfusion therapy. In addition, elderly, SBP, glucose level at admission, OTT, history of hypertension, DM, AF, large artery atherosclerosis, internal carotid artery occlusion, middle cerebral artery M2 occlusion and bridging therapy associated with END in patients who experienced IVT, and four risk factors including SBP, history of hypertension and internal carotid artery occlusion were found to be related with END in patients witnessed EVT.

The definition of END was not clear in existing studies because of the degree of symptom worsening and the time frame of the deterioration. Some literature adopted an increase of $\geq$2 points of the NIHSS score within the predefined time frame (ΔNIHSS $\geq$2) as the definition of END. View the fact that ΔNIHSS equals 2 seems to be too small changes in NIHSS out of a total score of 42 points and reflects inadequate reliability of the score itself rather than real symptom worsening, especially for severe stroke with high scores [44,45]. We used ΔNIHSS $\geq$4 as the definition of END in this systematic review and meta-analysis, which was consistent with most studies on END. In terms of the time frame for END, although a number of END cases caused by malignant edema tended to occur beyond the first 24 hours, we adopted within 24 hours as the timeframe of END, which was consistent with most of the studies.

Within the currently acceptable timeframe and degree of worsening of END, multiple risk factors identified in this study were in line with several previous studies. Age has been identified as a risk factor for END onset in Birschel's study [46]. In our study, the pooled data analysis showed that older AIS patients were at higher risk of END after revascularization treatment, especially more obviously presented underwent IVT treatment in the subgroup analysis, whereas no significant association between age and the occurrence of END was observed in patients receiving EVT treatment. This result might relate to a small number of studies included in the EVT group, limited by the number of patients. In addition, another reason might be that patients receiving EVT treatment have a more strict age restrictions and a smaller age span. Initial NIHSS score is used widely to measure a level of consciousness on admission, specifically, a larger initial NIHSS score indicated a declined consciousness which is related to a greater chance of END achieved [47]. However, in our analysis, the initial NIHSS score was not statistically significant in predicting the occurrence of END. In previous studies, the initial NIHSS score was a significant predictor of END24, both of which used a liberal definition of END24 (worsening of Scandinavian Stroke Scale, which might be more sensitive than NIHSS, and ΔNIHSS $\geq$1, respectively). Since a severe neurological deficit strongly predicts sICH and malignant oedema. In contrast, another study [41] using a more conservative definition (namely, ΔNIHSS $\geq$4) found the inverse association, that is, less severe deficits predicted END24, which might be explained by a 'ceiling effect' such that higher admission scores are less likely to further increase. Thus, the risk of END24 associated with admission to NIHSS might depend on the definition of END, including whether absolute or relative changes are considered. This is consistent with the definition of END in the included studies in our analysis, so the results are similar. Systolic blood pressure is a significant predictor of increased END risk in our meta-analysis. In both overall and subgroup analyses, in AIS patients treated with IVT or EVT, higher SBP was associated with a greater incidence of END. Augmented systolic blood pressure has been mentioned to predict early neurological deterioration in the preceding study [48]. The exact cause is not yet clear, but it may be related to the fact that high blood pressure can easily aggravate cerebral edema, which occurs after acute cerebral infarction, particularly in patients with extensive oligaemia due to proximal occlusion. This hypothesis has not been directly tested so far. Serum Glucose is a significant predictor of increased END risk.

History of diabetes mellitus is associated with a higher risk of END occurring [49,50]. Notably, the poor neurological outcome (i.e., END) has resulted from persistently high level of serum glucose following reperfusion treatments [51]. One potential mechanism could be that it increased blood-brain barrier disruption and promoted sICH. However, hyperglycaemia might also facilitate neuronal damage. OTT (Onset to Treatment Time) was another significant predictor of increased END risk in our meta-analysis. Patients with longer OTT were more likely to have END, which is consistent with the concept of "time is brain" that we have known before. In the subgroup analysis, it was

more obviously found in the IVT group, but in the EVT group, the association between age and the occurrence of END was not statistically different. We speculated that the reason was the large heterogeneity in OTT among patients receiving EVT. With the improved concept of thrombectomy, many AIS patients beyond the time window with salvage of brain tissue still received EVT. This might be the reason why OTT time did not fully predict the occurrence of END in EVT patients.

In addition, Kwan's study [52] found atrial fibrillation aggrandized the risk of END attained, which was also a significant predictor of increased END risk in our meta-analysis. It might be due to the stroke etiology in patients with atrial fibrillation was cardiogenic embolism. The occlusion site was usually large vessel, with less collateral compensation and a larger infarct size. However, in another study [53], which focused on non-thrombolysis mild strokes, the incidence of END24 was 9% in lacunar infarcts as compared with 31% and 23% in large atherosclerosis and cardioembolic strokes, respectively, which showed a non-significant difference. Since stroke was caused by many reasons, the mechanism of END in various subtypes of stroke was completely different, yet remains largely unknown. Proximal arterial occlusion was observed more frequently in patients with END in our meta-analysis. One possible explanation for this association would posit that proximal occlusion predicts stroke severity, and therefore also END through its association with sICH and malignant oedema.

There are a few limitations in this meta-analysis that ought to be considered when interpreting the findings. Although we performed the meta-analysis for AIS cases with EVT, a sufficient subgroup analysis providing reliable results in the EVT group equivalent to IVT and total group may not be possible as scarce EVT studies are included. Due to insufficient data of re-occlusion and collateral circulation reported, it was difficult to analyze these two factors in this meta-analysis. Nevertheless, re-occlusion has been recognized as one of the important prognoses of END by clinical physicians [15], as well as playing a predominant role to improve the neurological functions for stroke patients. Another mechanism of END focuses on the insufficient collaterals with the adverse metabolic consequences among AIS patients in clinical practice [54]. Accordingly, collateral status described a linear relationship of the NIHSS score, implicating such the mechanism moderating symptoms in the hyperacute and post-therapeutic acute stroke phase [22]. Despite the ASPCT score contributing a lot to END occurring [1], we were not able to find a significant association of END as assigning the ASPECT score may vary by different physician.

The strength of this meta-analysis is that several large sample studies were involved to conduct the meta-analysis, providing convincing evidence of the associations, as well as depicting a complete picture to predict END occurring in stroke patients with medical or reperfusion therapies in clinical practice. We not only focused on END occurrence after EVT, but we also determined that the site of occlusion was linked with END after EVT.

5. Conclusions

This study contains some implications in clinical practice. END at 24 hours was associated with poor outcomes, hinting toward needs of the concentration on neurological deficit management. Understanding and monitoring older age, elevated systolic blood pressure, high levels of serum glucose, hypertension, diabetes mellitus and atrial fibrillation may elevate the early neurological worsening and achieve a satisfactory prognosis. Apart from this, other unmentioned factors, including collateral circulation, ASPECT score, CE stroke, are supposed to be thought about in decision-making protocols before reperfusion therapy conducting. Further studies ought to look into END occurring after EVT deeply because the exact proportion of END onset following EVT, and short-term/long-term prognosis still remain unclear at this stage.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. PRISMA checklist is shown in supplementary materials.

Author Contributions

JL and WJJ take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualizing and designing the study—JL, HXS, CL and YQZ. Extracting, analyzing and interpreting the data—All authors. Drafting the study—HXS, CL and JL. Conducting meta-analysis—JL, HXS, CL, YQZ, XL, AFL,YEL. Critical revision of the study for important intellectual content—All authors. Obtaining funding—WJJ. Supervision—JL and WJJ.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.jin2202052.

Appendix

Appendix I: Detailed Search strategy

Pubmed

Free Text
Initial search performed on 3 August 2021
Search updated on 7 December 2022
English language limit applied

#	Search Term	No. of Results
1	'neurological deterioration' or 'neurological deficit' or 'neurological decline'	724054
2	'thrombolysis' or 'thrombolytic treatment' or 'thrombolytic therapy' or 'IV-rtPA' or 'endovascular treatment' or 'endovascular therapy' or 'mechanical thrombectomy' or 'medical treatment' or 'medical management'	3697171
3	'acute ischemic stroke' or 'acute cerebral ischaemia' or 'proximal vessel occlusion' or 'proximal artery occlusion' or 'large artery occlusion' or 'large vessel occlusion' or 'vertebrobasilar artery occlusion' or 'basilar artery occlusion' or 'middle cerebral artery occlusion' or 'internal cerebral artery occlusion'	127348
4	#1 AND #2 AND #3	3648

Web of Science

Free Text
Initial search performed on 2 August 2021
Search updated on 6 December 2022
English language limit applied

#	Search Term	No. of Results
1	'neurological deterioration' or 'neurological deficit' or 'neurological decline' ALL	64510
2	'thrombolysis' or 'thrombolytic treatment' or 'thrombolytic therapy' or 'IV-rtPA' or 'endovascular treatment' or 'endovascular therapy' or 'mechanical thrombectomy' or 'medical treatment' or 'medical management' ALL	3459585
3	'acute ischemic stroke' or 'acute cerebral ischaemia' or 'proximal vessel occlusion' or 'proximal artery occlusion' or 'large artery occlusion' or 'large vessel occlusion' or 'vertebrobasilar artery occlusion' or 'basilar artery occlusion' or 'middle cerebral artery occlusion' or 'internal cerebral artery occlusion' ALL	79075
4	#1 AND #2 AND #3	2547

EBSCO

Free Text
Initial search performed on 16 August 2021
Search updated on 10 December 2022
English language limit applied

#	Search Term	No. of Results
1	'neurological deterioration' or 'neurological deficit' or 'neurological decline' ALL	31183
2	'thrombolysis' or 'thrombolytic treatment' or 'thrombolytic therapy' or 'IV-rtPA' or 'endovascular treatment' or 'endovascular therapy' or 'mechanical thrombectomy' or 'medical treatment' or 'medical management' ALL	102745
3	'acute ischemic stroke' or 'acute cerebral ischaemia' or 'proximal vessel occlusion' or 'proximal artery occlusion' or 'large artery occlusion' or 'large vessel occlusion' or 'vertebrobasilar artery occlusion' or 'basilar artery occlusion' or 'middle cerebral artery occlusion' or 'internal cerebral artery occlusion' ALL	46257
4	#1 AND #2 AND #3	638

Appendix II. Quality score

The quality score is composed of 5 items, and each item was allocated 0, 1 or 2 points. This allowed a total score between 0 and 10 points, 10 representing the highest quality. The following items are included in the score:

Objective

0 for no study objectives mentioned
1 for study objectives reported but non-specific
2 for specific study objectives reported

Design

0 for cross sectional studies
1 for case-control studies
2 for longitudinal studies (retrospective or prospective) or interventional studies

Population

Observational studies
0 if n <100
1 if n 100 to 500
2 if n >500

Outcome (see table below)

0	**1**	**2**
If not MRI or CT confirmation of AIS	MRI or CT confirmation with clear location of lesions or stroke onset time	With both clear location of lesions and stroke onset time

Adjustments

0 if findings are not controlled** for at least age and gender
1 if findings are controlled for age and gender

2 If findings are additionally controlled for covariates:

*** 'Controlled for' here refers to: adjusted for in the statistical analyses (e.g. with multiple regression); stratified for in the analyses (e.g. males and females separately)*

Appendix III Publication bias

Variables	Egger test/Peters test					
	Total		IVT		EVT	
	Z score	*p*	Z score	*p*	Z score	*p*
Age	–3.44	0.002	–3.80	0.001	–0.86	0.423
Initial NIHSS	–1.80	0.077	–1.15	0.264	–0.79	0.459
Systolic BP	–0.43	0.670	–0.48	0.634	–0.17	0.873
Serum Glucose	1.56	0.207	1.34	0.190	NA	
OTT	–0.20	0.840	–0.34	0.741	0.21	0.851
ASPECT	–0.74	0.672	–4.50	0.056	–0.17	0.807
HTN	9.34	0.003	9.80	0.002	1.21	0.273
Diabetes Mellitus	8.57	0.431	8.04	0.076	2.84	0.285
ET-atherosclerosis	5.23	0.209	5.87	0.098	–0.25	0.660
AF	5.68	0.180	5.31	0.287	3.71	0.531
SR	–0.71	0.799	–0.78	0.657	–0.37	0.803
Bridging	–0.53	0.612	–7.78	0.065	–0.178	0.135
ICA	0.109	0.912	4.10	0.419	1.21	0.510
M2	–3.09	0.553	–1.98	0.912	–3.87	0.199
90DmRS (0–2)	–3.50	0.781	–6.80	0.097	NA	

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