PROGNOSTIC IMAGING MARKERS AND REPERFUSION STRATEGIES IN ACUTE ISCHEMIC STROKE

Ph.D. Thesis

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"We learn neurology stroke by stroke"

C. Miller Fisher

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1. LIST OF ABBREVATIONS

ADC	Apparent diffusion coefficient
BAO	Basilar artery occlusion
CI	Confidence interval
CT	Computed tomography
DWI	Diffusion-weighted imaging
EVT	Endovascular thrombectomy
FLAIR	Fluid-attenuated inversion recovery
GRADE	Grading of recommendations, assessment, development, and evaluation
GRE	Gradient-recalled echo
HT	Hemorrhagic transformation
IVT	Intravenous thrombolysis
LKN	Last known normal
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRS	Modified Rankin scale
MTICI	Modified thrombolysis in cerebral infarction
NIHSS	National Institute of Health Stroke Scale
NPV	Negative predictive value
OR	Odds ratio
PICO	Patient, Intervention, Comparison, Outcome
PPV	Positive predictive values
PRISMA	Preferred reporting items for systematic reviews and meta-analyses

PWI	Perfusion-weighted imaging
QUIPS	Quality in prognostic studies
ROBINS-I	Risk of bias in non-randomized studies of interventions
RTPA	Recombinant tissues plasminogen activator

2. STUDENT PROFILE

2.1. Vision, mission, and specific goals

My vision is a future in which stroke no longer represents a leading cause of death and long-term disability. My mission is to contribute to the optimization of stroke care by promoting timely diagnosis, refining acute treatment strategies, and improving the overall quality of care delivered to patients with stroke.

I aim to investigate the impact of different imaging strategies, treatment workflows, and therapeutic approaches on patient selection and treatment outcomes. Through this work, I aim to create clinically meaningful evidence that informs guideline-based practice and ultimately improves stroke care.

2.2. Scientometrics

Number of all publications:	8
Cumulative IF:	21
Average IF/publication:	2.33
Ranking (SCImago):	D1: (3), Q1: (3), Q2: (2)
Number of publications related to the subject of the thesis:	2
Cumulative IF:	8.3
Average IF/publication:	4.15
Ranking (SCImago):	D1: (1), Q1: (1)
Number of citations on Google Scholar:	233
Number of citations on MTMT (independent):	101
H-index:	3

The detailed bibliography of the student can be found on pages 83-86.

2.3. Future plans

My plan is to further engage in stroke research, focusing on the optimization of acute stroke care pathways and generating evidence that can be directly applied to clinical practice. In parallel, I aim to advance my clinical training in neurology, with a dedicated focus on stroke medicine. I think that establishing myself as a stroke neurologist will enable me to better identify unmet clinical needs and formulate research questions that are grounded in clinical practice. My ultimate goal is to dedicate my career to advancing stroke care through research that is firmly integrated within high-quality patient care.

3. SUMMARY OF THE THESIS

Acute ischemic stroke remains a leading cause of mortality and long-term disability worldwide. Despite major advances in reperfusion therapies, there are many uncertainties regarding prognostic imaging markers and the optimal therapeutic interventions. High-quality evidence synthesis is therefore essential to guide clinical decision-making and support the implementation of evidence-based therapeutic strategies.

This thesis is based on two systematic reviews and meta-analyses addressing key questions in acute stroke care. The first study investigates the prognostic role of fluid-attenuated inversion recovery (FLAIR) positivity in patients with acute ischemic stroke treated with intravenous thrombolysis (IVT) within the standard time window. The second study evaluates the effectiveness and safety of bridging IVT with endovascular treatment (EVT) versus direct EVT in patients with basilar artery occlusion (BAO).

The first study demonstrates that FLAIR positivity is associated with less favorable functional outcomes and a trend toward a higher risk of hemorrhagic transformation following IVT. While FLAIR positivity may provide additional prognostic information and support individualized patient management, it should not be considered a contraindication to IVT in otherwise eligible patients. The second study shows that bridging IVT with EVT in patients with BAO is associated with higher rates of functional independence and lower 90-day mortality compared to direct EVT, without an increased risk of symptomatic intracranial hemorrhage. The observed benefit was consistent across examined subgroups.

In conclusion, this thesis highlights the importance of imaging-based prognostic markers and optimized reperfusion strategies in acute ischemic stroke in clinical decision-making, while emphasizing the need for further prospective research.

4. GRAPHICAL ABSTRACT

Association of FLAIR Positivity and Worse Outcomes After Intravenous Thrombolysis in Known-Onset Strokes:
A Systematic Review and Meta-Analysis

Clinical Question Framework	
P	Acute stroke patients treated with IVT within 4.5h
I	FLAIR-positive lesions
C	FLAIR-negative lesions
O	Hemorrhagic transformation
	Less favorable functional outcome (mRS ≥ 1)

Number of articles screened	9,912
Embase	7,001
PubMed	2,632
CENTRAL	279

Outcomes	N of studies	N of patients	Odds ratio	95% CI	*p*-value
Hemorrhagic transformation	4	804	3.47	0.51 – 23.57	0.131
Less favorable functional outcome	3	405	2.14	1.01 – 4.55	0.049

Zhubi E. et al, 2025. Journal of Clinical Medicine; doi: 10.3390/jcm14228031

Bridging Therapy Versus Direct Endovascular Thrombectomy in Basilar Artery Occlusion Stroke:
A Systematic Review and Meta-Analysis

Clinical Question Framework	
P	Patients with acute basilar artery occlusion
I	EVT + IVT
C	EVT
O	Functional independence (90-day mRS 0–2)
	Independent ambulation (90-day mRS 0–3)
	Successful recanalization rate (mTICI ≥2b)
	Symptomatic intracranial hemorrhage
	Any intracranial hemorrhage
	Mortality (90-day mRS 6)

Number of articles screened	6,274
Embase	1,100
PubMed	375
CENTRAL	87
Scopus	3,626
Web of Science	543

Outcomes	Odds ratio	95% CI	*p*-value
90-day mRS 0–2	1.46	1.22 – 1.76	<0.001
90-day mRS 0–3	1.27	1.07 – 1.52	0.009
mTICI ≥2b	0.97	0.79 – 1.18	0.707
sICH	0.88	0.65 – 1.18	0.330
Any ICH	1.07	0.66 – 1.74	0.746
90-day mRS 6	0.63	0.49 – 0.82	0.002

Zhubi E. et al, 2025. GeroScience; doi: 10.1007/s11357-025-01887-0

5. INTRODUCTION

5.1. Burden of acute ischemic stroke and advances in reperfusion therapy

Acute ischemic stroke remains a leading cause of mortality and long-term disability worldwide and represents a major public health challenge (1). Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA) is the established treatment for eligible patients presenting within 4.5 h of symptom onset (2). The proportion of patients treated with IVT has increased over the years, due to improved prehospital stroke recognition, centralized stroke care pathways, broader access to advanced neuroimaging, and the implementation of tissue-based rather than strictly time-based patient selection paradigms (3, 4). Despite recent advances in stroke care, IVT remains underutilized in routine clinical practice, and concerns regarding treatment-related complications continue to influence clinical decision-making (5).

5.2. Safety of IVT in acute ischemic stroke

Although current guidelines recommend intravenous administration of rtPA to patients with acute ischemic stroke within 4.5 hours of symptom onset (2, 6), substantial concern persists regarding the risk of hemorrhagic transformation and subsequent neurological deterioration, even among patients treated within this standard time window (7). According to randomized trials and large registries, such as the European Cooperative Acute Stroke Study (ECASS) III or Safe Implementation of Treatments in Stroke–Monitoring Study (SITS-MOST), symptomatic intracerebral hemorrhage occurred in approximately 6–8% of IVT-treated patients, while any radiological hemorrhagic transformation has been observed in up to one-third of cases (8, 9). Established clinical predictors of hemorrhagic transformation include advanced age, arterial hypertension, diabetes mellitus, atrial fibrillation, prior stroke, higher baseline National Institutes of Health Stroke Scale (NIHSS) scores, and delayed treatment initiation (10, 11). Imaging-based markers, such as larger infarct core volume on diffusion-weighted imaging (DWI) and extensive cerebral small vessel disease, further increase bleeding risk (12).

5.3. MRI-based tissue characterization and the role of FLAIR imaging

Magnetic resonance imaging (MRI) has become integral to acute stroke diagnostics, particularly in patients with unknown symptom onset (13). The diffusion-weighted imaging–fluid-attenuated inversion recovery (DWI–FLAIR) mismatch concept has been utilized as a valid imaging surrogate for symptom onset within 4.5 h in patients with wake-up or unknown-onset stroke, supporting IVT eligibility in appropriately selected cases (13, 14).

However, FLAIR hyperintensity is not limited to late-presenting or unknown-onset strokes and it is thought that FLAIR hyperintensity within areas of diffusion restriction reflects increased tissue water content, vasogenic edema, and evolving blood–brain barrier disruption (15). This observation suggests that FLAIR signal changes may reflect infarct progression and tissue vulnerability rather than stroke duration alone (15, 16).

5.4. Prognostic role of FLAIR positivity in IVT-treated patients

Several observational studies have reported that FLAIR-positive strokes are associated with worse functional outcomes, higher rates of dependency, and increased mortality compared with FLAIR-negative strokes (16, 17). From a pathophysiological perspective, reperfusion of more advanced ischemic tissue may increase the risk of blood–brain barrier disruption and predispose patients to hemorrhagic transformation following IVT (18, 19). Despite ongoing research, it remains uncertain whether FLAIR status plays a significant role in predicting clinical outcomes following IVT treatment, including functional recovery and the risk of hemorrhagic transformation (17, 20, 21). Clarifying the role of FLAIR imaging in outcome prediction following thrombolysis remains clinically relevant.

5.5. Posterior circulation stroke and basilar artery occlusion

Posterior circulation strokes represent approximately 20% of ischemic strokes, and differ from anterior circulation strokes in terms of vascular anatomy, collateral supply, and clinical presentation (22). They pose a significant diagnostic and therpeutic challenge due to their diverse and fluctuating clinical presentation, which can range from dizziness,

vertigo, diplopia, and dysarthria, to advancing brainstem dysfunction or coma at onset, particularly in cases of basilar artery occlusion (BAO) (23). Although BAO accounts for only 1–2% of all ischemic strokes, it is associated with devastating neurological deficits and mortality rates approaching 80% in the absence of successful reperfusion (24). Given its rarity and clinical heterogeneity, high-quality evidence guiding optimal management of BAO has generally been limited.

5.6. Evolution of EVT for basilar artery occlusion

Although several trials have demonstrated significant benefits of endovascular thrombectomy (EVT) on functional outcomes of large vessel occlusions in the anterior circulation (25), the effectiveness of EVT for BAO has been less evident until recently (26). Earlier randomized controlled trials, such as BEST and BASICS, failed to demonstrate a statistically significant advantage of EVT over best medical therapy (27, 28). However, more recent randomized controlled trials conducted in China, ATTENTION and BAOCHE, have demonstrated that EVT significantly improves functional outcomes compared to best medical management in carefully selected BAO patients treated within extended time windows of 0–12 h and 6–24 h, respectively (29, 30).

5.7. Bridging IVT prior to EVT in basilar artery occlusion

The theoretical benefits of bridging therapy include early partial recanalization, thrombus softening, and improved perfusion of perforating and branch arteries prior to mechanical thrombectomy, potentially leading to better neurological recovery (31). However, bridging IVT with EVT may also introduce significant risks in the posterior circulation, including clot fragmentation with distal embolization (32), increased procedural complexity, treatment delay, and a potentially higher risk of intracerebral hemorrhage in vulnerable brainstem structures (33). Current European Stroke Organisation (ESO) and European Society of Minimally Invasive Neurological Therapy (ESMINT) guidelines suggest that IVT should be administered before EVT in eligible patients with BAO presenting within 4.5 hours of symptom onset and having no contraindications, although

this recommendation is supported by relatively weak evidence (34). Therefore the application of bridging therapy in BAO remains a matter of ongoing debate, resulting in variability in treatment strategies across centers.

6. OBJECTIVES

6.1. Study I

The aim of this study was to evaluate whether FLAIR positivity was associated with worse clinical outcomes following IVT within 4.5 hours of symptom onset in patients with acute ischemic stroke. We hypothesized that the presence of a visible ischemic lesion on pre-treatment FLAIR MRI is associated with a lower likelihood of favorable functional outcome at 90 days and a higher risk of hemorrhagic transformation following IVT.

6.2. Study II

The aim of this study was to compare the clinical efficacy and safety of bridging IVT with EVT versus direct EVT in patients with acute ischemic stroke due to BAO. We hypothesized that bridging therapy was associated with improved functional outcomes and reduced mortality, without an increased risk of symptomatic intracranial hemorrhage.

7. METHODS

We conducted systematic review and meta-analysis for both of our studies, following the recommendations of the Cochrane Handbook (35) and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines (36). The study protocols (CRD42023486781 and CRD42024519161) were prospectively registered in PROSPERO, with full adherence throughout study conduct and analysis.

7.1. Study I

7.1.1. Eligibility criteria

Studies were eligible for inclusion if they met the following criteria: (a) inclusion of patients with known-onset ischemic stroke; (b) administration of IVT within the standard therapeutic time window (≤ 4.5 h); (c) availability of pre-treatment brain MRI including DWI and FLAIR sequences; (d) availability of follow-up imaging (MRI or CT) at 24 h after IVT; and (e) reporting of outcomes related to hemorrhagic transformation and/or functional outcome at 90 days. Both prospective and retrospective cohort studies were considered eligible. The first and corresponding authors were contacted for further data when the studies met the inclusion criteria but did not report the outcomes of interest.

7.1.2. Outcomes

This analysis was structured according to the Patient, Intervention, Comparison and Outcome (PICO) framework and aimed to compare outcomes of IVT administered within the standard treatment window in patients with FLAIR-positive versus FLAIR-negative acute ischemic lesions. FLAIR-positive lesions were defined as acute ischemic lesions visible on DWI with a corresponding hyperintense signal on FLAIR, as determined by visual assessment by physicians. In contrast, FLAIR-negative lesions were defined as DWI-visible acute ischemic lesions without a corresponding FLAIR signal.

The primary outcomes were hemorrhagic transformation following IVT and less favorable functional outcome at 90 days, assessed using the modified Rankin Scale (mRS). Hemorrhagic transformation was defined as the presence of any hemorrhagic changes on follow-up imaging (MRI or CT) performed 24 hours after IVT. An unfavorable functional outcome was defined as an mRS score ≥ 2 at 90 days.

In addition, diagnostic performance measures were evaluated as secondary outcomes to assess the prognostic value of FLAIR lesion status. These included sensitivity, specificity, positive predictive value, and negative predictive value. For this purpose, true positives, false positives, true negatives, and false negatives were extracted from individual studies and used to calculate diagnostic accuracy estimates.

7.1.3. Search and selection

The search was conducted in January 2024 in three databases (Medline – via PubMed, Embase, and Cochrane Controlled Register of Studies – CENTRAL) using a search key composed of three domains: *("stroke" OR ("cerebral" AND "infarction") OR ("brain" AND "infarction")) AND (("intravenous" AND "thrombolysis") OR "IVT" OR ("thrombolytic" AND "therapy") OR ("tissue" AND "plasminogen" AND "activator") OR "rTPA" OR "alteplase" OR ("intravenous" AND "alteplase")) AND (("magnetic" AND "resonance") OR "MRI" OR "fluid-attenuated inversion recovery" OR "FLAIR" OR ("DWI" AND "FLAIR" AND "mismatch"))*. No restrictions were imposed on the type of publications to be included, nor was the search limited by language or other criteria.

All retrieved articles were imported into a reference management software (EndNote version 20.1, Clarivate Analytics, Philadelphia, PA, USA) and duplicates were manually removed by one author. Duplicate records were removed based on overlapping publication year, authors, and title. Screening and selection were conducted independently by two authors, initially by title and abstract, followed by full-text evaluation. Any disagreements were resolved through discussion with the corresponding author. Interrater agreement was assessed using Cohen's kappa coefficient (κ) at both

screening levels. A reference search was performed using the CitationChaser tool (37).

7.1.4. Data extraction

Data extraction was done in duplicate by two independent authors. All data were recorded in a pre-designed and standardized Microsoft Excel spreadsheet (Microsoft Excel 2019, Microsoft Corp., Redmond, WA, USA). The variables collected included first author, year of publication, basic demographic characteristics (number of patients, number of females, age), number of patients in FLAIR-positive and FLAIR-negative groups, number of events in each group, follow-up duration, and the outcomes of interest when available.

7.1.5. Risk of bias and quality of evidence assessment

The risk of bias in the included studies was assessed by two independent authors using the Quality in Prognostic Studies (QUIPS) tool, with any disagreements resolved by the third author. The certainty of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework (38), implemented through GRADEpro GDT 2015 software (McMaster University and Evidence Prime, Hamilton, Canada).

7.1.6. Statistical synthesis

We used forest plots to summarize the findings of the studies and show the pooled result. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used as the primary effect measure. Study-specific ORs were either extracted directly or calculated from the reported numbers of patients and events in each group. A random-effects model was applied due to an expectation of significant between-study heterogeneity.

To estimate the heterogeneity variance measure τ^2, the maximum likelihood method was used. Heterogeneity was quantified using Higgins and Thompson's I^2 statistic (39). Sensitivity and specificity were pooled using a bivariate model (40, 41). Prediction intervals were calculated for the main outcomes to estimate the probability that future

studies would yield similar results in comparable settings. Analyses were done in R (R Core Team 2023, v4.2.3) using the meta (v6.5.0) package and dmetar (v0.0.9000) for meta-analysis calculations. Publication bias/outlier/influential could not be performed due to low number of studies.

7.2. Study II

7.2.1. Eligibility criteria

Studies were eligible for inclusion if they met the following criteria: (a) enrollment of patients with acute BAO; (b) treatment with either bridging therapy (IVT prior to EVT) or direct EVT; and (c) reporting of at least one outcome of interest, including functional independence at 90 days (mRS 0–2), independent ambulation at 90 days (mRS 0–3), successful recanalization (modified Thrombolysis in Cerebral Infarction [mTICI] grade 2b–3), hemorrhagic complications, or 90-day mortality. Both prospective and retrospective cohort studies were considered eligible. The first and corresponding authors were contacted for further data when the studies met the inclusion criteria but did not report the outcomes of interest.

7.2.2. Outcomes

This analysis was structured according to the Patient, Intervention, Comparison, and Outcome (PICO) framework and aimed to compare the efficacy and safety of bridging therapy (IVT prior to EVT) versus direct EVT in patients with basilar artery occlusion. The primary outcome was functional independence at 90 days, defined as a mRS score of 0–2. Secondary outcomes included independent ambulation at 90 days (mRS 0–3), successful recanalization defined as a mTICI grade of 2b–3, symptomatic intracranial hemorrhage, any intracranial hemorrhage, and mortality at 90 days.

Post hoc subgroup analyses were performed for occlusion site, stroke severity, treatment window, and study site to explore potential effect modifiers on functional independence. Differences between subgroups were evaluated using p-values, without adjustment for multiple comparisons, reflecting the hypothesis-generating nature of these analyses.

7.2.3. Search and selection

The literature search was conducted in March 2024 across five databases (Medline – via PubMed, Embase, Cochrane Controlled Register of Studies – CENTRAL, Scopus and

World of Science) using a search key composed of four domains: *("stroke" OR ("cerebral" AND "infarction") OR ("brain" AND "infarction")) AND (("posterior" AND "circulation") OR "PCS" OR ("basilar" AND "artery") OR "BAO") AND (("thrombectomy" OR ("endovascular" AND "treatment") OR "EVT")) AND (("intravenous" AND "thrombolysis") OR "IVT" OR ("thrombolytic" AND "therapy") OR ("tissue" AND "plasminogen" AND "activator") OR "rtPA" OR "alteplase" OR ("intravenous" AND "alteplase"))*. No restrictions were applied regarding publication type, language, or other search limits.

All retrieved articles were imported into a reference management software (EndNote version 20.1, Clarivate Analytics, Philadelphia, PA, USA) and duplicates were manually removed by one author. Duplicate records were removed based on overlapping publication year, authors, and title. Screening and selection were conducted independently by two reviewers, initially by title and abstract, followed by full-text evaluation. Any disagreements were resolved through discussion with the corresponding author. Interrater agreement was assessed using Cohen's kappa coefficient (κ) at both screening levels. A reference search was performed using the CitationChaser tool (37).

7.2.4. Data extraction

Data extraction was done in duplicate by two independent authors. All data were recorded in a pre-designed and standardized Microsoft Excel spreadsheet (Microsoft Excel 2019, Microsoft Corp., Redmond, WA, USA). The variables collected included first author, year of publication, basic demographic characteristics (number of patients, number of females, age), numbers of patients treated with bridging therapy (EVT + IVT) or direct EVT, event counts for each outcome in both groups, duration of follow-up, and the outcomes of interest.

7.2.5. Risk of bias and quality of evidence assessment

The risk of bias in the included studies was assessed by two independent authors using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool (42) with

any disagreements resolved by a third author. The certainty of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework (38), implemented through GRADEpro GDT 2015 software (McMaster University and Evidence Prime, Hamilton, Canada).

7.2.6. Statistical synthesis

We used forest plots to summarize the findings of the studies and show the pooled result. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used as the primary effect measure. Study-specific ORs were either extracted directly or calculated from the reported numbers of patients and events in each group. A random-effects model was applied due to an expectation of significant between-study heterogeneity. Subgroup analyses were performed using mixed-effects models, and differences between subgroups were assessed using the Cochrane Q test at a 5% significance level. Statistical significance was defined by CIs not crossing unity.

To estimate the heterogeneity variance measure τ^2, the maximum likelihood method was used. Heterogeneity was quantified using Higgins and Thompson's I^2 statistic (39). Small-study effects were evaluated by visual inspection of funnel plots and, when at least 10 studies were available per outcome, by Peters' modified Egger test for raw data outcomes or the classical Egger test otherwise, with p values <0.10 indicating potential bias. Prediction intervals were calculated for the main outcomes to estimate the probability that future studies would yield similar results in comparable settings. Analyses were done in R (R Core Team 2023, v4.2.3) using the meta (v6.5.0) package and dmetar (v0.0.9000) for meta-analysis calculations.

8. RESULTS

8.1. Study I

8.1.1. Systematic search, selection, and study characteristics

The database search initially yielded 9,912 records, of which six studies comprising 951 patients met the eligibility criteria for inclusion in the final analysis. Full-text selection demonstrated substantial agreement, with a Cohen's kappa (κ) of 0.64 and 82.35% concordance. Four studies were included in the meta-analysis of hemorrhagic transformation, and three in the meta-analysis of less favorable 90-day functional outcomes. The eligible studies were published between February 2012 and July 2021, with 246 patients (25.9% of the total) exhibiting FLAIR-positive lesions. Four studies were prospective cohort studies, whereas two were retrospective cohort studies.The complete study selection process is summarized in the PRISMA diagram (**Figure 1**), and the detailed characteristics of the included studies are provided in **Table 1**.

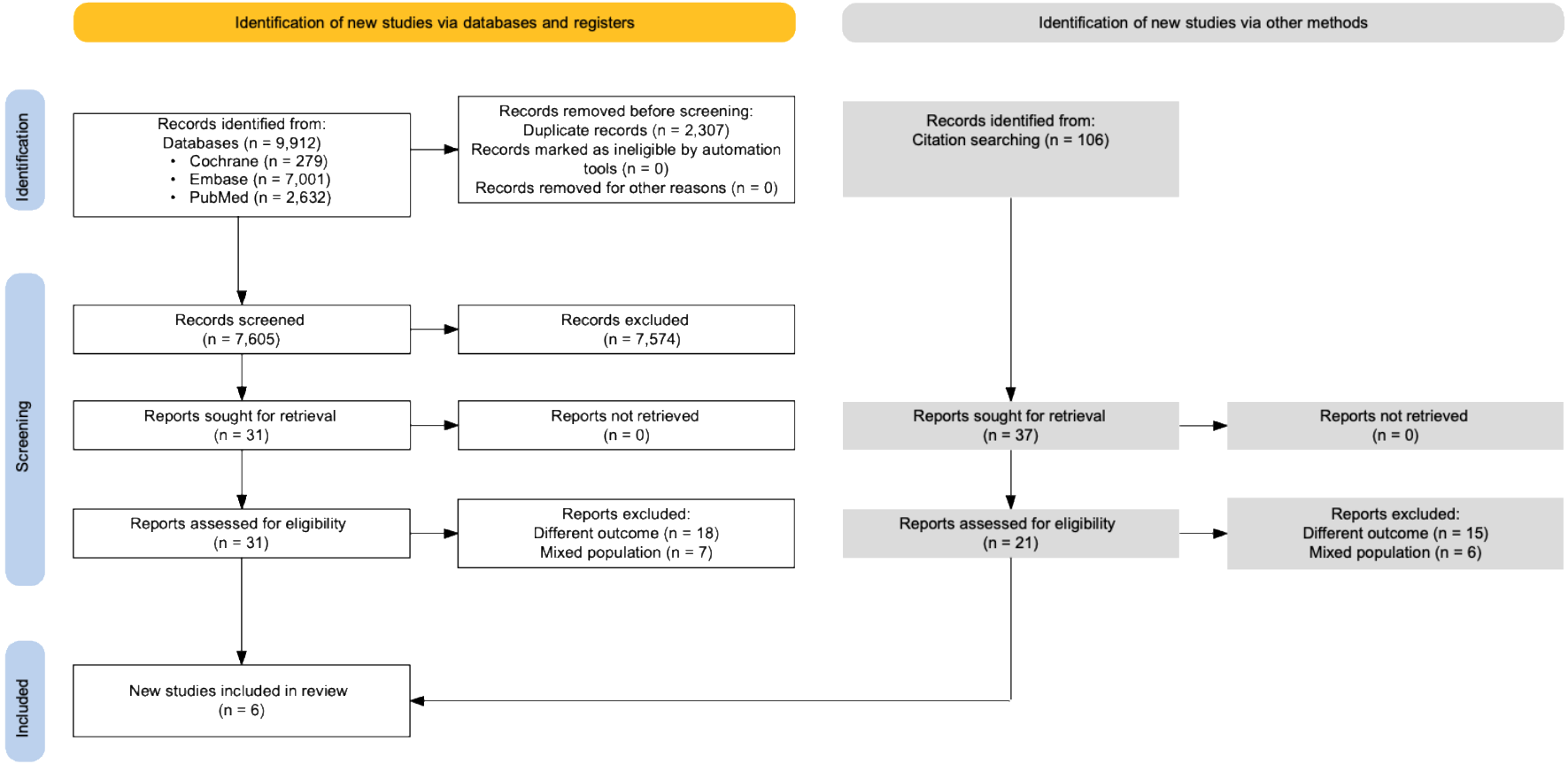

Figure 1. PRISMA Flowchart representing the study search and selection process.

Table 1. Basic characteristics of included studies.

Author (year)	Study site	Study design	No. of patients (female)	Age (year) ‡	Outcome	MRI protocol	Follow-up imaging	NIHSS FLAIR+ ‡	NIHSS FLAIR- ‡	LKN-to-IVT FLAIR+ (min) ‡	LKN-to-IVT FLAIR- (min) ‡
Ebinger 2012 (43)	Germany	Prospective cohort	44 (48.88%)	72.0 (65-81)	90-day functional outcome	DWI, FLAIR, MRA	NA	NA	5 (3.5-8)	ND	130 (108-154)
Kufner 2012 (44)	Germany	Prospective cohort	60 (55.04%)	71.3 (±12.5)	HT	DWI, FLAIR, T2* (PWI, MRA)	MRI	10 (6-17)	6 (4-11)	120 (95-165)	124 (98-152)
Hobohm 2014 (45)	Germany	Retrospective cohort	42 (43.29%)	70.7 (±11.7)	HT	DWI, FLAIR, T2*, PWI, ToF MRA	CT	14.9 (±6.9)	12.7 (±7.1)	ND	ND
Emeriau 2015 (46)	France	Retrospective cohort	36 (42.85%)	64.0 (50-75)	90-day functional outcome	DWI, FLAIR	NA	14 (10-20)	14 (9-19)	190 (160-201)	162 (140-190)
El Nawar 2019 (47)	France	Prospective cohort	145 (48.17%)	71.3 (±15.9)	HT	DWI, FLAIR, T2*, ADC, ToF MRA	CT/MRI	ND	ND	ND	ND
Kim 2021 (16)	USA	Prospective cohort	143 (48.14%)	70.0 (59-83)	HT; 90-day functional outcome	DWI, FLAIR, ADC, GRE, MRA	MRI	7 (4-13)	6 (3-15)	169 (120-208)	142 (107-188)

‡ Parameters represented as mean with standard deviation, or median with range (minimum and maximum);

(ADC, apparent diffusion coefficient; CT, computed tomography; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; GRE, gradient-recalled echo; HT, hemorrhagic transformation; IVT, intravenous thrombolysis; LKN, last known normal; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NA, not applicable; ND, not defined; NIHSS, National Institute of Health Stroke Scale; PWI, perfusion-weighted imaging; T2*, T2-star; ToF MRA, time-of-flight magnetic resonance angiography).

8.1.2. Main outcomes

Four of six included studies (16, 44, 45, 47) reported hemorrhagic transformation rates among 186 participants with FLAIR-positive and 618 participants with FLAIR-negative lesions. Across the studies involved, hemorrhagic transformation was defined as evidence of hemorrhage in the lesion at follow-up imaging 24 h after the IVT. Patients with FLAIR-positive lesions who underwent IVT within the standard treatment window had a non-significantly higher odds of hemorrhagic transformation compared to the patients with FLAIR-negative lesions (OR, 3.47; 95% CI, 0.51–23.57; $p = 0.131$; **Figure 2**). There was substantial heterogeneity across the included studies (p for heterogeneity < 0.001; I^2 = 83%), which might reflect differences in definitions of hemorrhagic transformation across studies, variability in imaging protocols, as well as differences in patient characteristics such as stroke severity and anticoagulation status.

We identified Hobohm et al. (45) as an outlier study in the hemorrhagic transformation analysis, primarily due to the inclusion of patients with more severe strokes, reflected by higher baseline NIHSS scores (mean 13.2 ± 7.1 overall; 14.9 ± 6.9 in the FLAIR-positive group). In a subgroup analysis restricted to patients with moderately severe strokes (median baseline NIHSS 6–10), the FLAIR-positive group showed a non-significantly increased risk of hemorrhagic transformation, although with a smaller effect size (OR, 1.89, 95% CI 0.51–7.05, $p = 0.174$).

Three of six studies (16, 43, 46) reported 90-day functional outcome among 95 participants with FLAIR-positive and 310 participants with FLAIR-negative lesions. A less favorable functional outcome was defined as a mRS score of ≥ 2 by Kim et al., (16) and Emeriau et al. (46). Ebinger et al. (43) defined this outcome as an mRS score > 2. Patients with FLAIR-positive ischemic lesions who underwent IVT within the standard treatment window had significantly higher odds of having a less favorable 90-day functional outcome compared to patients with FLAIR-negative lesions (OR, 2.14; 95% CI, 1.01–4.55; $p = 0.049$; **Figure 3**). There was no significant heterogeneity among the included studies (p for heterogeneity = 0.555; $I^2 = 0\%$).

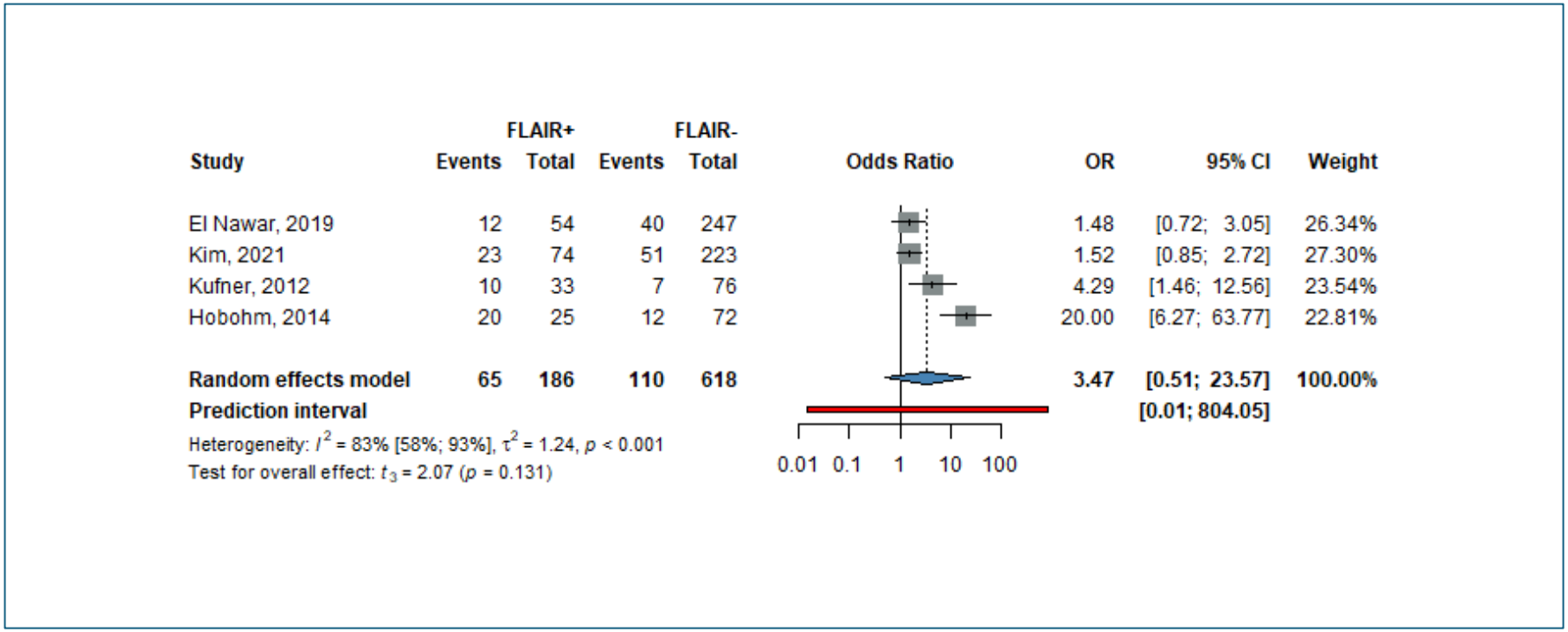

Figure 2. Forest plot representing the odds ratio (OR) of hemorrhagic transformation in FLAIR-positive patients compared to FLAIR-negative patients (FLAIR, fluid-attenuated inversion recovery).

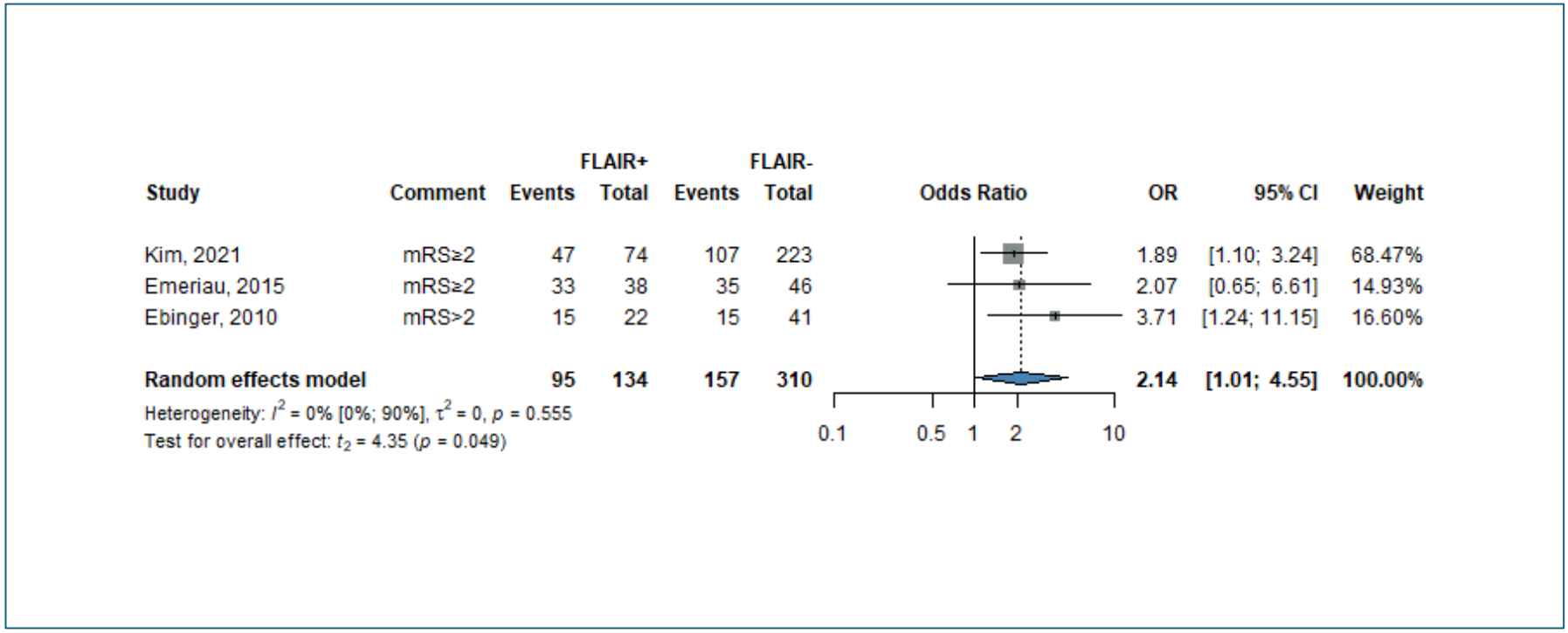

Figure 3. Forest plot representing the odds ratio (OR) of a less favorable 90-day functional outcome in FLAIR-positive patients compared to FLAIR-negative patients (FLAIR, fluid-attenuated inversion recovery).

8.1.3. Other outcomes

The pooled sensitivity of FLAIR-positive lesions for hemorrhagic transformations was 41.2% (95% CI, 25.5–58.9%), and the pooled specificity of FLAIR-negative lesions for hemorrhagic transformations was 82.1% (95% CI, 75–87.6%) (**Figure 4**). The pooled positive predictive value of FLAIR-positive lesions for hemorrhagic transformation was 39% (95% CI, 12–76%), and the pooled negative predictive value of FLAIR-negative lesions for hemorrhagic transformation was 83% (95% CI, 74–90%).

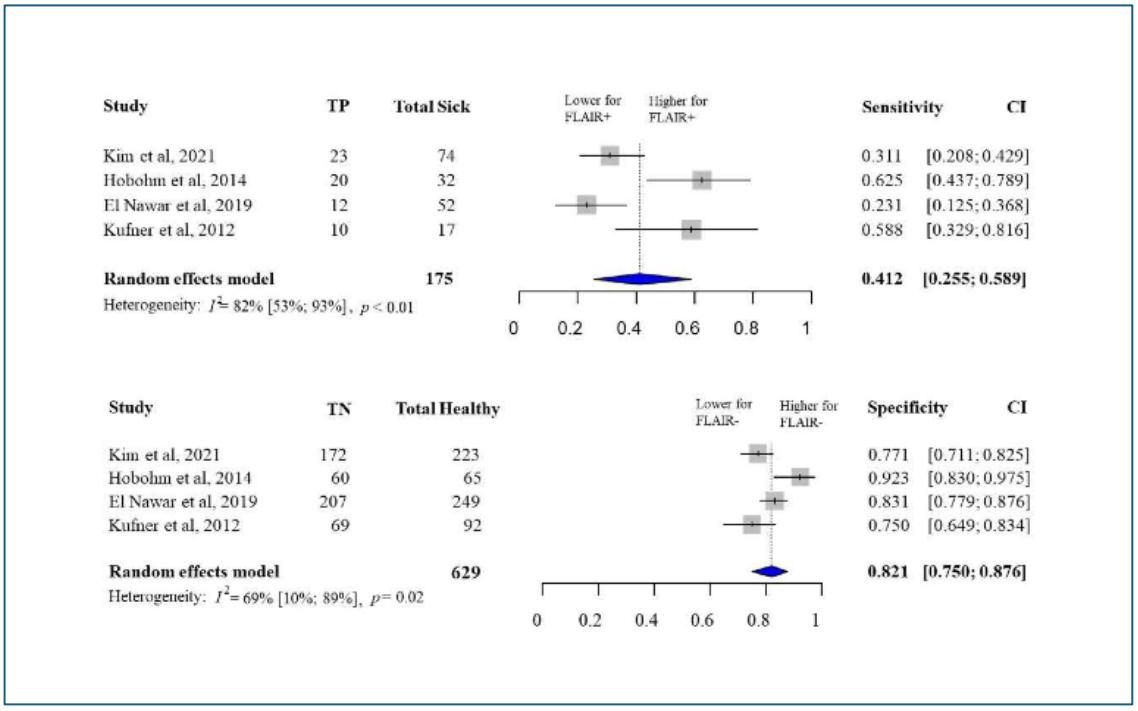

Figure 4. The pooled sensitivity and specificity of FLAIR status for hemorrhagic transformation (FLAIR, fluid-attenuated inversion recovery).

The pooled sensitivity of FLAIR-positive lesions for less favorable 90-day functional outcome was 40.9% (95% CI, 30.1–52.6%), and the pooled specificity of FLAIR-negative lesions was 78.1% (95% CI, 69.1–85.1%) for less favorable 90-day functional outcome (**Figure 5**). The pooled positive predictive value of FLAIR-positive lesions for less favorable 90-day functional outcome was 73% (95% CI, 39–92%), and the pooled negative predictive value of FLAIR-negative lesions for less favorable 90-day functional

outcome was 46% (95% CI, 13–82%).

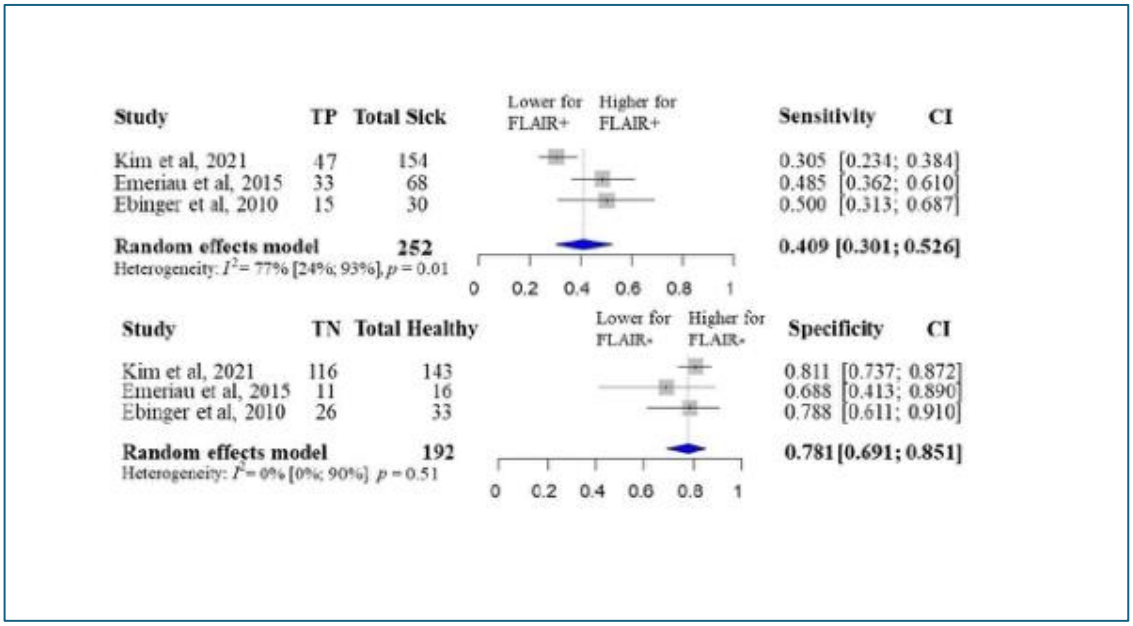

Figure 5. The pooled sensitivity and specificity of FLAIR status for less favorable 90-day functional outcome (FLAIR, fluid-attenuated inversion recovery.

8.1.4. Risk of bias assessment

Most of the included studies were assessed as having a moderate risk of bias. Among the six studies included in the meta-analysis, two (33.3%) were rated as high risk, and one (16.6%) as low risk, based on the QUIPS tool. The main concerns were incomplete reporting and unclear outcome measurement (**Table 2**).

8.1.5. Level of evidence

GRADE assessment was applied to our analyses, which included only cohort studies. Consequently, the certainty of evidence was rated as low for both outcomes.

Table 2. Risk of bias assessment using Quality in Prognostic Studies (QUIPS) tool for a) hemorrhagic transformation; b) less favorable functional outcome.

a)

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis reporting	Overall risk of bias
El Nawar 2019	?	+	+	+	+	+	?
Hobohm 2014	+	?	+	+	?	+	?
Kim 2021	+	?	+	+	?	+	?
Kufner 2012	?	-	+	+	+	+	-

b)

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis reporting	Overall risk of bias
Ebinger 2012	-	?	+	+	?	?	-
Emeriau 2015	+	+	+	+	+	+	+
Kim 2021	+	?	+	+	?	+	?

8.2. Study II

8.2.1. Systematic search, selection, study characteristics

The database search initially yielded 6,274 records, of which 58 studies including more than 9,372 patients met the eligibility criteria for the final analysis. Of these, 35 studies involved patients with basilar artery occlusion (BAO), and 23 studies included patients with BAO and vertebral artery occlusion. Thirty-four studies contributed data to the analysis of functional independence, 24 to independent ambulation, 11 to successful recanalization, 8 to symptomatic intracranial hemorrhage, 7 to any intracranial hemorrhage, and 13 to 90-day mortality. Full-text selection showed substantial agreement, with a Cohen's kappa (κ) of 0.62 and 82.35% concordance. The included studies, published between 2014 and 2024, consisted of 38 prospective and 20 retrospective cohort studies. The complete study selection process is summarized in the PRISMA diagram (**Figure 6**), and the detailed characteristics of the included studies are presented in **Table 3**.

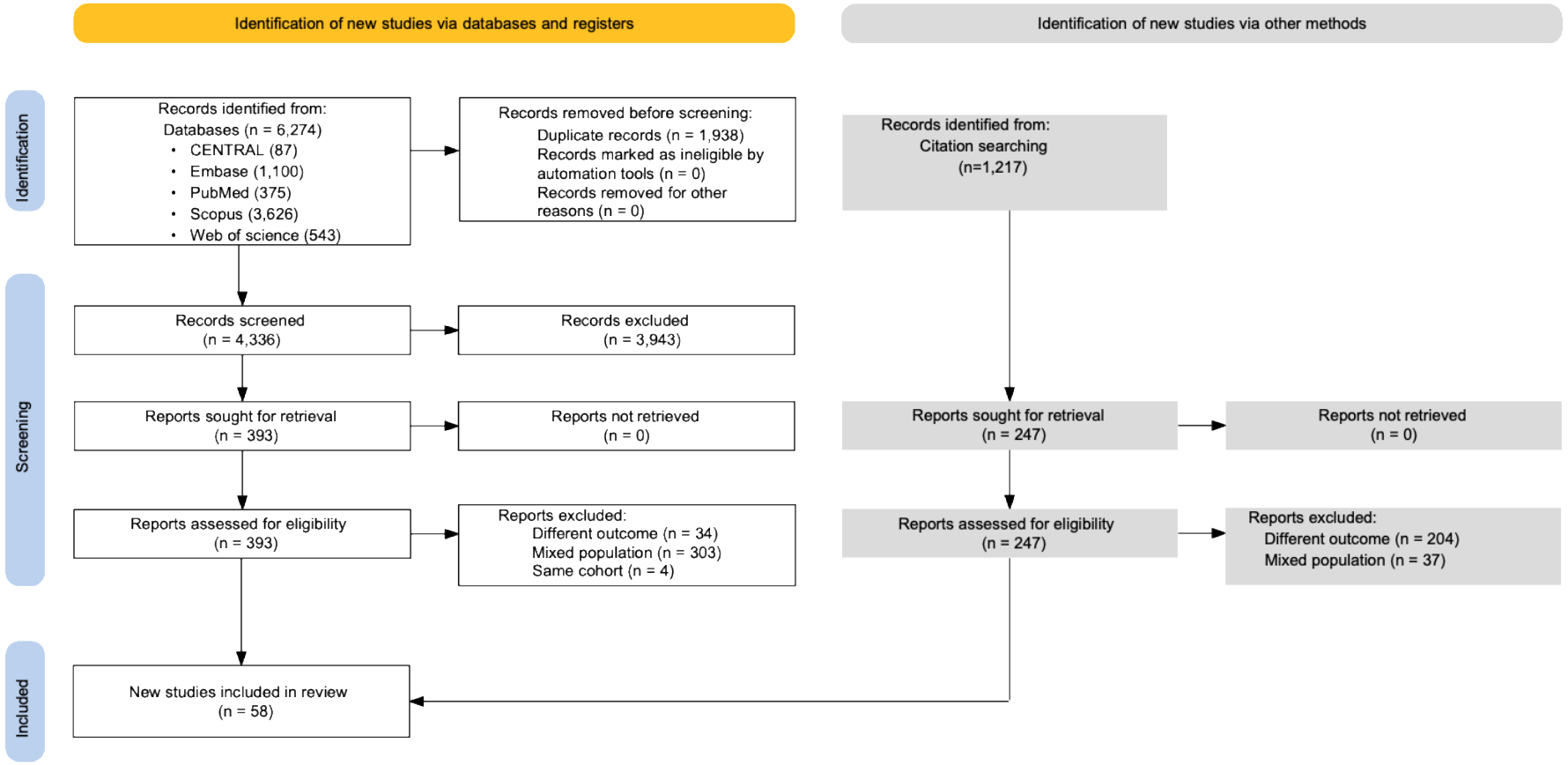

Figure 6. PRISMA Flowchart representing the study search and selection process.

Table 3. Basic characteristics of included studies.

Study	Study design	Study period	Study site	No. of patients ‡	No. of females (%)	Age ‡	Outcomes	NIHSS at admission ‡
BASILAR ARTERY OCCLUSION								
Abbas 2023 (48)	Retrospective cohort	Jan/14-Mar/22	USA	74	33 (44.6%)	62.7 (±16.6)	Independent ambulation; Successful recanalization	16 (9-26)
Baek 2014 (49)	Retrospective cohort	Dec/10-Dec/12	South Korea	25	11 (44%)	68	Functional independence	11 (3-25)
Brissette 2024 (50)	Retrospective cohort	Jan/12-Dec/19	Canada, Ireland, Belgium (6 centers)	279	109 (39.1)	65 (8-96)	Independent ambulation	Not specified
Cao 2021 (51)	Retrospective cohort	Jan/13-Sep/19	China	101	18 (18.6%)	62.2 (±12.91)	Functional independence; Mortality	30 (22.5–36.5)
Carneiro 2015 (52)	Retrospective cohort	Jan/12-Dec/14	Portugal	24	7 (29%)	57 (±14)	Functional independence	23 (8)
Dornak 2015 (53)	Retrospective cohort	Jan/06-Nov/13	Czech Republic (multicenter)	72	21 (29.2%)	59.1 (±13.3)	Independent ambulation	20.8 (±8.8)
Feil 2023 (54)	Prospective cohort	Jun/15-Dec/19	Germany	640	277 (43.3%)	72.2 (±13.3)	Functional independence; Successful recanalization; Mortality	17 (8-27)

Giorgianni 2018 (55)	Retrospective cohort	Jan/10-Dec/15	Italy (12 centers)	102	37 (36.3%)	68 (57-76)	Functional independence	17
Gory 2018 (56)	Prospective cohort	Mar/10-Apr/17	France (3 centers)	117	70 (59.8%)	67.7 (12.9) vs 62.9 (16.2) (dead vs alive)	Mortality	22 (14–41) vs 12 (8–21) (dead vs alive)
Guenego 2021 (57)	Prospective cohort	Jan/12-May/19	France (multicenter)	50	17 (34%)	63 (54-75)	Functional independence	≤6
Hu 2017 (58)	Retrospective cohort	Jan/13-Aug/16	South Korea	24	11 (45.8%)	65.7 (32–85)	Functional independence; Successful recanalization	13.9 (2–21) vs 15.3 (6–34) (successful vs not successful recanalization)
Kaneko 2021 (59)	Retrospective cohort	Jan/15-Mar/19	Japan (12 centers)	73	26 (35.6%)	77 (68-84)	Functional independence	24 (13-30)
Kang 2018 (60)	Retrospective cohort	Jan/11-Aug/17	South Korea	212	92 (43.4%)	71 (64–78)	Functional independence	17 (10–23.75)
Karadeli 2023 (61)	Retrospective cohort	2016-2021	Turkey	22	10 (45.5%)	61.7 (±11.3)	Functional independence; Mortality	20 (6-28) vs 18 (8–25) (dead vs alive)
Karamchandani 2021 (62)	Retrospective cohort	Jan/17-Jan/20	USA	65	28 (43%)	67 (57–77)	Functional independence	16 (6–28)
Kim 2019 (63)	Prospective cohort	Jan/12-Jan/18	South Korea	45	13 (29.9%)	69 (57–78)	Functional independence	16.5 (±8.4)
Lee 2018 (64)	Prospective cohort	Jan/10-Mar/17	South Korea	194	78 (40.2%)	68.8 (±11.8) (21–92)	Functional independence	16 (7–25)
Li 2018 (65)	Prospective cohort	Jan/14-Dec/16	China	68	9 (13.2%)	57.9 (±11.8)	Independent ambulation	24.5 (15–30)
Liu 2023	Retrospective	Dec/19-	China	55	11 (20%)	68 (60–75)	Independent	20 (9–35)

(66)	cohort	Jul/21					ambulation	
Liu 2023 (67)	Retrospective cohort	Jan/12-Dec/18	China	116	20 (17.2%)	59.1 (±11.7)	Independent ambulation	19 (12–26)
Mierzwa 2024 (68)	Retrospective cohort	Jan/15-Dec/21	USA	444	198 (44.5%)	66 (±15)	Independent ambulation; sICH; any ICH	13 (6–24) vs 21 (12–28) (good vs poor clinical outcome)
Mourand 2014 (69)	Prospective cohort	Nov/09-Mar/11	France	31	16 (52%)	61.2 (16.9)	Functional independence	14 (7–38)
Nappini 2021 (70)	Prospective cohort	2011-2017	Italy	464	161 (35%)	67.7 (±13.28)	Functional independence; Mortality	18 (10–30)
Neuberger 2019 (71)	Prospective cohort	Jan/12-Sep/17	Germany	101	42 (41.5%)	70.3±13.4 vs 72.5±12.4 (ICH vs no ICH)	sICH; any ICH	30 (20–37.5) vs 26 (11–35) (ICH vs no ICH)
Ouyang 2022 (72)	Retrospective cohort	Jan/18-Jun/21	China	55	8 (14.6%)	64 (57–75)	Functional independence	35 (20–35)
Pasarikovski 2020 (73)	Prospective cohort	Jan/13-Mar/19	Canada	43	17 (39%)	67 (57–97)	Independent ambulation	18 (6–28)
Pop 2023 (74)	Prospective cohort	Jan/14-May/19	France (18 centers)	195	77 (39.5%)	65 (16)	Independent ambulation	17 (22)
Ramazanoglu 2023 (75)	Retrospective cohort	Jan/18-Mar/21	Turkey	57	21 (36.8%)	64.1 (±14.5)	Mortality	16 (2 – 26)
Ritvonen 2021 (76)	Retrospective cohort	Jun/95-Dec/19	Finland	103	40 (38.8%)	73 (63–79)	Independent ambulation	Not specified
Ryu 2023 (77)	Retrospective cohort	Jan/12-Jul/22	South Korea	42	19 (45.2%)	70.3 (±11.2)	Independent ambulation	17 (12–24) vs. 8 (6–15)

Singer 2015 (78)	Retrospective cohort	Jan/11-Jun/13	Germany	148	52 (35%)	71 (61–77)	Functional independence	20 (9–28)
Siow 2022 (79)	Prospective cohort	Jan/15-Dec/19	Belgium, Germany, Greece, UK, Sweden, Singapore, Taiwan	322	116 (36%)	67.5 (±14.1)	Functional independence; Independent ambulation; sICH; Successful recanalization	16 (8–25)
Son 2016 (80)	Retrospective cohort	Mar/11-Dec/14	South Korea	19	9 (47.3%)	65.7 (±9.3) / 68 (47–83)	Functional independence	17.9 (±8.9) / 14 (5–34)
Uno 2017 (81)	Retrospective cohort	Oct/11-Sep/16	Japan	34	11 (32%)	72 (66–77)	Functional independence	29 (14–33)
Yoon 2015 (82)	Retrospective cohort	Dec/10-Feb/15	South Korea	50	24 (48%)	71 (63–77)	Functional independence	10.5 (7.75–16.00)
VERTEBRO-BASILAR ARTERY OCCLUSION								
Abdelrady 2023 (83)	Prospective cohort	Jan/15-Dec/19	France	139	48 (35%)	69 (61-76)	Functional independence; Successful recanalization; Mortality	15 (9-24)
Alexandre 2021 (84)	Retrospective cohort	Jan/16-Jul/19	France, Switzerland, Italy (10 centers)	191	61 (31.9%)	68.3 (±13.97)	Functional independence; Successful recanalization	12 (7–20)
Chen 2022 (85)	Prospective cohort	Jan/14-May/19	China (47 centers)	644	163 (25.31%)	64 (56-73)	Independent ambulation	27 (17-33)
Guo 2024 (86)	Retrospective cohort	Jan/14-May/19	China	647	164 (25.3%)	64 (56–73)	Functional independence; Independent	27 (17-33)

							ambulation; Mortality; sICH; Successful recanalization	
Hirai 2023 (87)	Retrospective cohort	Dec/13-Feb/21	Japan (multicenter)	86	33 (38.4%)	73.5 (67-81)	Independent ambulation	21 (9-32)
Huang 2022 (88)	Retrospective cohort	Dec/15-Dec/18	China (21 centers)	508	147 (28.4%)	61.4 (±14.5)	Functional independence; Independent ambulation	15 (10–23)
Ishiwada 2023 (89)	Retrospective cohort	Dec/13-Feb/21	Japan (multicenter)	100	34 (34%)	73 (66-82)	Independent ambulation	20 (9-33)
Jiang 2021 (90)	Retrospective cohort	Jan/12-Dec/17	China	67	23 (34.3)	63(57-68)	Independent ambulation	13(10-22)
Lee 2020 (91)	Retrospective cohort	Jan/11-Feb/16	South Korea	71	30 (42%)	67 (±11)	Functional independence	16.5 (9–22.25) vs 22.0 (15.0–27.5) (good vs poor)
Lee 2 2020 (92)	Retrospective cohort	Mar/10-Dec/17	South Korea	40	9 (22.5%)	66.4 (±9.24) vs 67.1 (±13.2) (good vs poor clinical outcome)	Functional independence	10.0 (±4.64) vs 14.8 (±13.2) (good vs poor outcome)
Liao 2023 (93)	Prospective cohort	Jan/14-May/19	China (47 centers)	585	143 (24.4%)	64 (56–73)	Independent ambulation	27 (17–33)
Liu 2021 (94)	Retrospective cohort	Jun/12-Mar/18	China	107	25 (14%)	60 (52–68)	Independent ambulation	20 (12–27)
Maier 2023	Prospective	Jan/15-	France	246	85	66.7 (16.0)	Functional	14 (14) vs 13

(95)	cohort	Dec/21	(21 centers)		(34.5%)	vs 66.8 (15.0) (bridging vs no bridging)	independence; Independent ambulation; Mortality; sICH; any ICH; Successful recanalization	(11)
Nie 2022 (96)	Prospective cohort	Jul/18-Oct/20	China	310	70 (22.58%)	61.39±10.92	Functional independence; Mortality; sICH; ICH; Successful recanalization	21 (11–27)
Rentzos 2018 (97)	Retrospective cohort	Jan/91-Dec/15	Sweden	110	36 (33%)	62 (±13)	Functional independence	31 (13-31)
Sang 2019 (98)	Prospective cohort	Jan/16-Jul/18	China	48	12 (25%)	70.5 (62-80)	Independent ambulation	22 (12.5-26)
Sun 2019 (99)	Retrospective cohort	Jan/12-Jul/18	China	187	30 (16%)	60 (±10)	Functional independence; Independent ambulation; sICH; any ICH; Mortality; Successful recanalization	22 (10–34)
Sun 2023 (100)	Retrospective cohort	Jul/20-Nov/21	China	65	10 (15.4%)	64(55–68)	Independent ambulation	17(12–27)
Sun 2	Prospective	Nov/17-	China	347	72	64 (54–72)	Independent	22 (11–35)

2023 (101)	cohort	Mar/19			(20.7%)		ambulation	
Werner 2016 (102)	Retrospective cohort	Nov/08-Jul/13	Spain	28	13 (31.8%)	60.5 (50–75)	Functional independence; Mortality	24 (11.5–31.25)
Wu 2021 (24)	Prospective cohort	Dec/12-Dec/18	China	177	33 (18.6%)	59.7 (±11.8)	Independent ambulation	22 (14–32)
Wu 2 2021 (103)	Retrospective cohort	Jan/14-Dec/19	China	100	23 (23%)	62 (±11)	Mortality	26 (17–29)
Zhang 2019 (104)	Retrospective cohort	Apr/12-Feb/18	China	103	14 (13.6%)	58.56 (±9.08)	Functional independence	20.26± 10.15

‡ Parameters represented as mean with standard deviation, or median with range (minimum and maximum);

(EVT, endovascular thrombectomy; ICH, intracranial hemorrhage; IVT, intravenous thrombolysis; NIHSS, National Institute of Health Stroke Scale; sICH, symptomatic intracranial hemorrhage)

8.2.2. Functional independence

Thirty-four studies reported 90-day functional independence among more than 1355 patients treated with bridging therapy and more than 3,336 patients treated with direct EVT. Functional independence was defined across studies as a 90-day mRS from 0 to 2. Patients who underwent bridging therapy were more likely to have functional independence at 90 days compared to the patients who underwent direct EVT (OR, 1.46; 95% CI, 1.22–1.76; $p < 0.001$, **Figure 7**). There was a low heterogeneity among the included studies (p for heterogeneity = 0.071; $I^2 = 28\%$).

8.2.3. Independent ambulation

Twenty-four studies reported 90-day independent ambulation among more than 1244 patients treated with bridging therapy and more than 3500 patients treated with direct EVT. Independent ambulation was defined across studies as a 90-day mRS from 0 to 3. Patients who underwent bridging therapy were more likely to have independent ambulation at 90 days compared to the patients who underwent direct EVT (OR, 1.27; 95% CI, 1.07–1.52; $p = 0.009$, **Figure 8**). There was a low heterogeneity among the included studies (p for heterogeneity = 0.174; $I^2 = 21\%$).

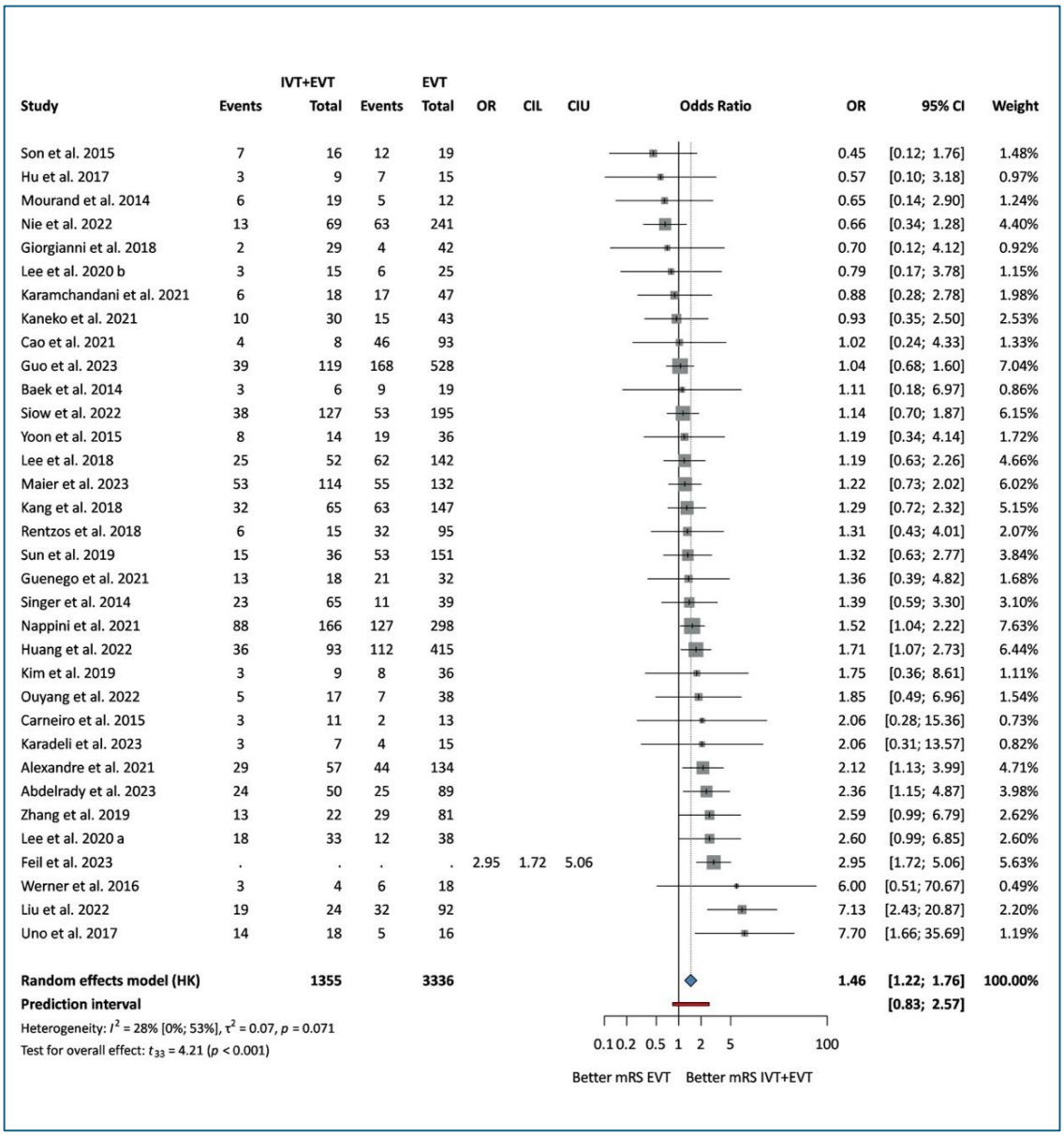

Figure 7. Forest plot representing the odds ratio (OR) of 90-day functional independence (modified Rankin Scale 0–2).

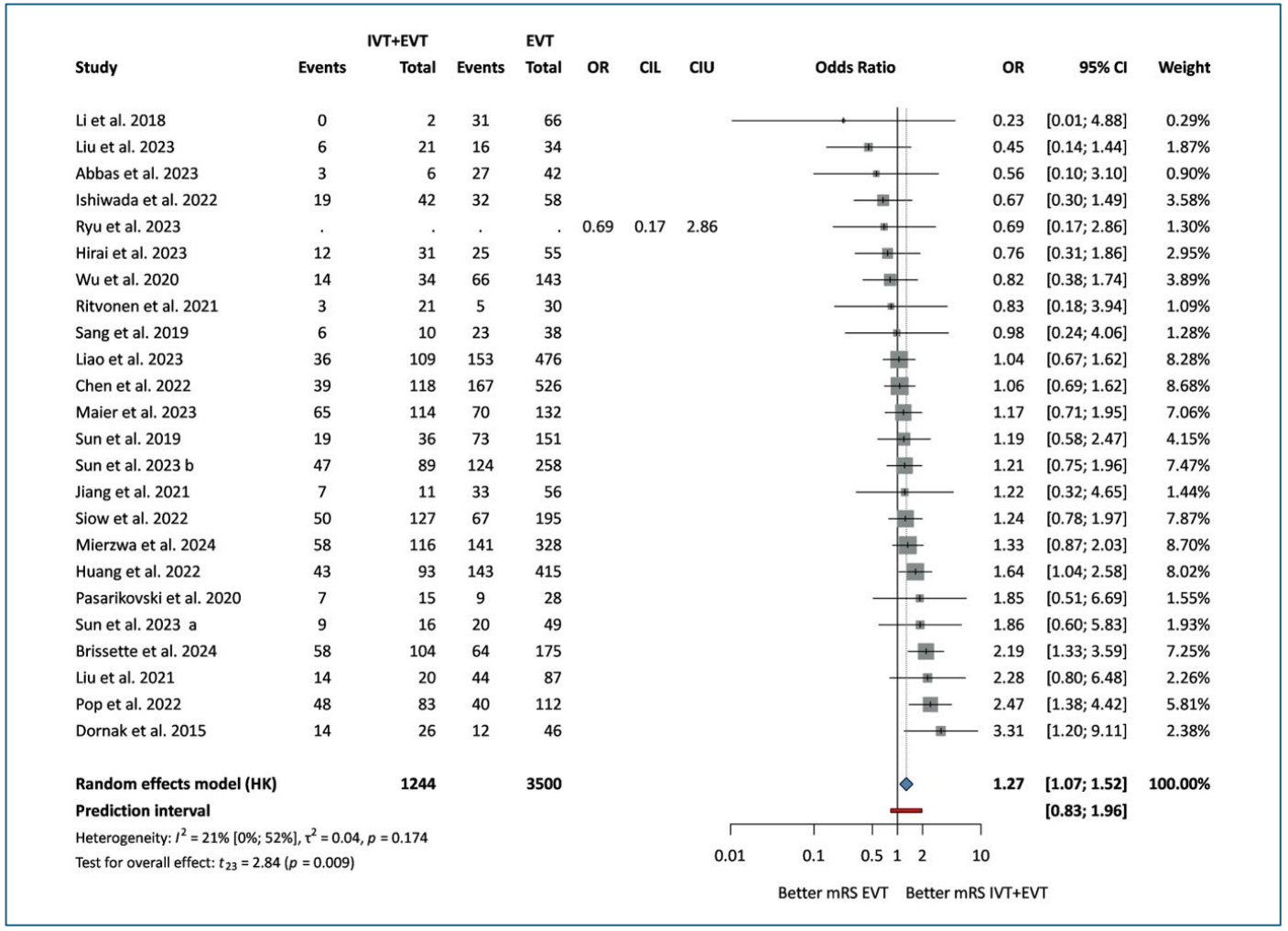

Figure 8. Forest plot representing the odds ratio (OR) of 90-day independent ambulation (modified Rankin Scale 0–3).

8.2.4. Successful recanalization rate

Eleven studies reported successful recanalization rates among 905 patients who underwent bridging therapy and 1938 patients who underwent direct EVT. Successful recanalization was defined across studies as a mTICI of 2b (substantial perfusion, ≥ 50% of the territory) to 3 (complete recanalization). There were no significant differences between patients who underwent bridging therapy and those who underwent direct EVT in terms of successful recanalization rate (OR, 0.97; 95% CI, 0.79–1.18; $p = 0.707$; **Figure 9**). There was a low heterogeneity among the included studies (p for heterogeneity = 0.747; I^2 =0%) .

8.2.5. Symptomatic intracranial hemorrhage

Eight studies reported symptomatic intracranial hemorrhage among 920 patients who underwent bridging therapy and 1,757 patients who underwent direct EVT. Across studies, symptomatic intracranial hemorrhage was defined as intracerebral hemorrhage clinically manifested by neurological deterioration and visible on imaging up to 48 h after treatment. There were no significant differences between patients who underwent bridging therapy and those who underwent direct EVT in terms of the occurrence of symptomatic intracranial hemorrhage (OR, 0.88; 95% CI, 0.65–1.18; $p = 0.330$; **Figure 10**). There was low heterogeneity among the included studies (p for heterogeneity = 0.905; $I^2 = 0\%$).

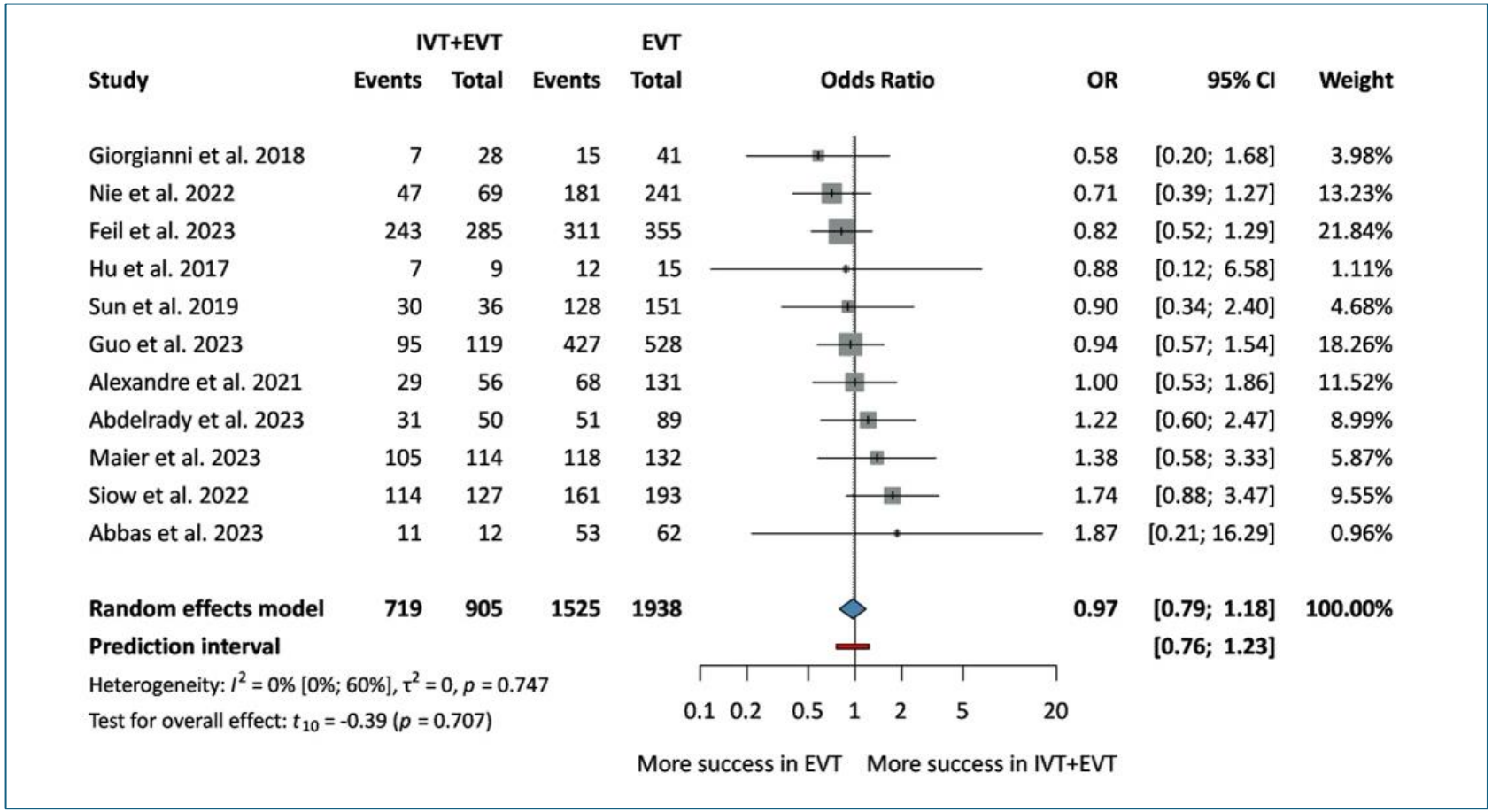

Figure 9. Forest plot representing the odds ratio (OR) of successful recanalization (mTICI ≥2b).

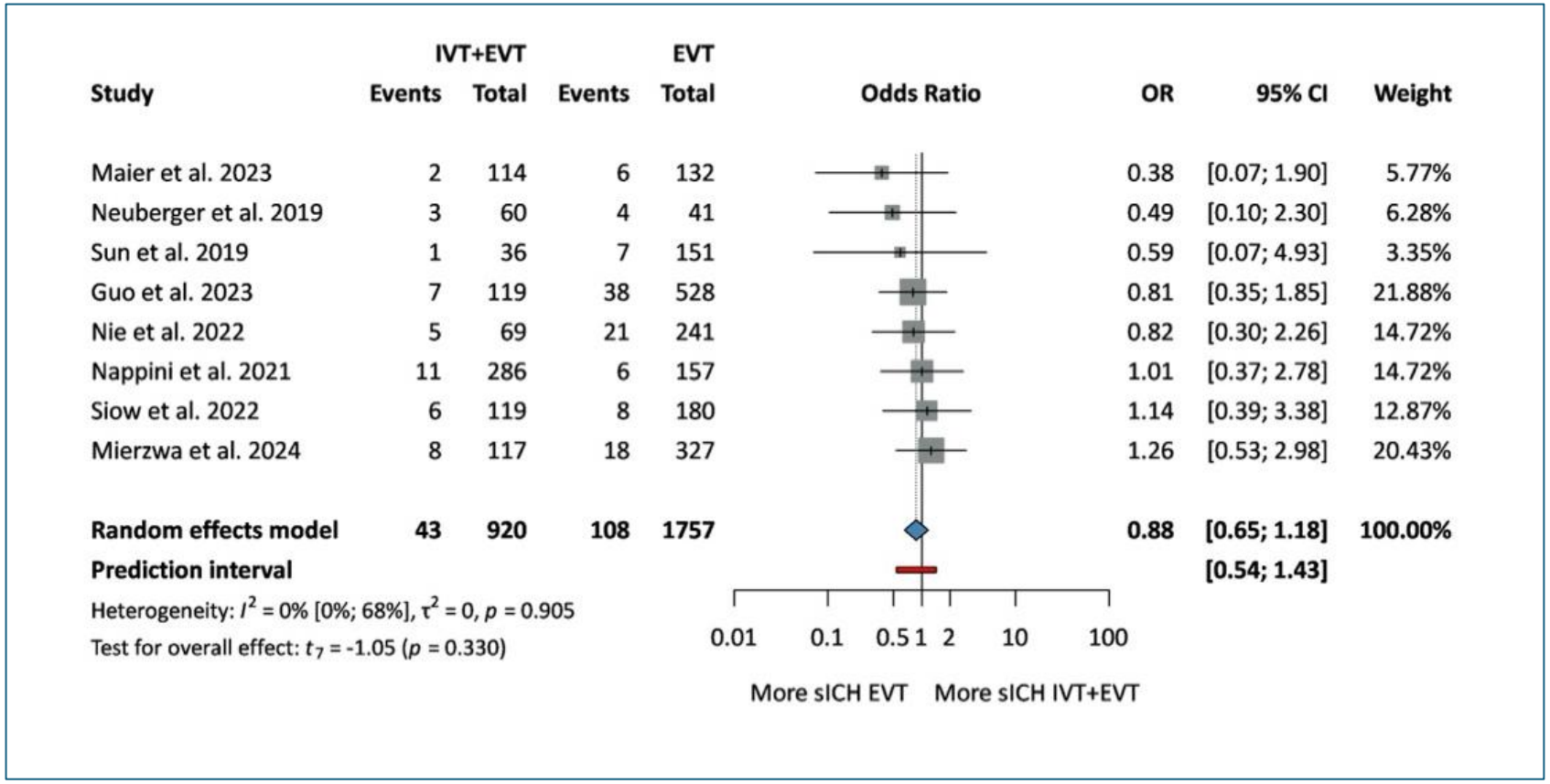

Figure 10. Forest plot representing the odds ratio (OR) of symptomatic intracranial hemorrhage.

8.2.6. Any type of intracranial hemorrhage

Seven studies reported any type of intracranial hemorrhage among 649 patients who underwent bridging therapy and 1,346 patients who underwent direct EVT. Intracranial hemorrhage was defined across studies as hemorrhage visible on imaging up to 48 h after treatment. There were no significant differences between patients who underwent bridging therapy and those who underwent direct EVT in terms of the occurrence of any type of intracranial hemorrhage (OR, 1.07; 95% CI, 0.66–1.74; p = 0.746; **Figure 11**). There was moderate heterogeneity among the included studies (p for heterogeneity = 0.134; I^2 = 39%).

8.2.7. Mortality

Thirteen studies reported 90-day mortality among 653 patients who underwent bridging therapy and 1758 patients who underwent direct EVT. Across studies, mortality was defined as death reported up to 90 days after treatment. Bridging therapy was associated with reduced 90-day mortality (OR, 0.63; 95% CI, 0.49–0.82; p = 0.002; **Figure 12**). There was low heterogeneity among the included studies (p for heterogeneity = 0.245; I^2 = 20%).

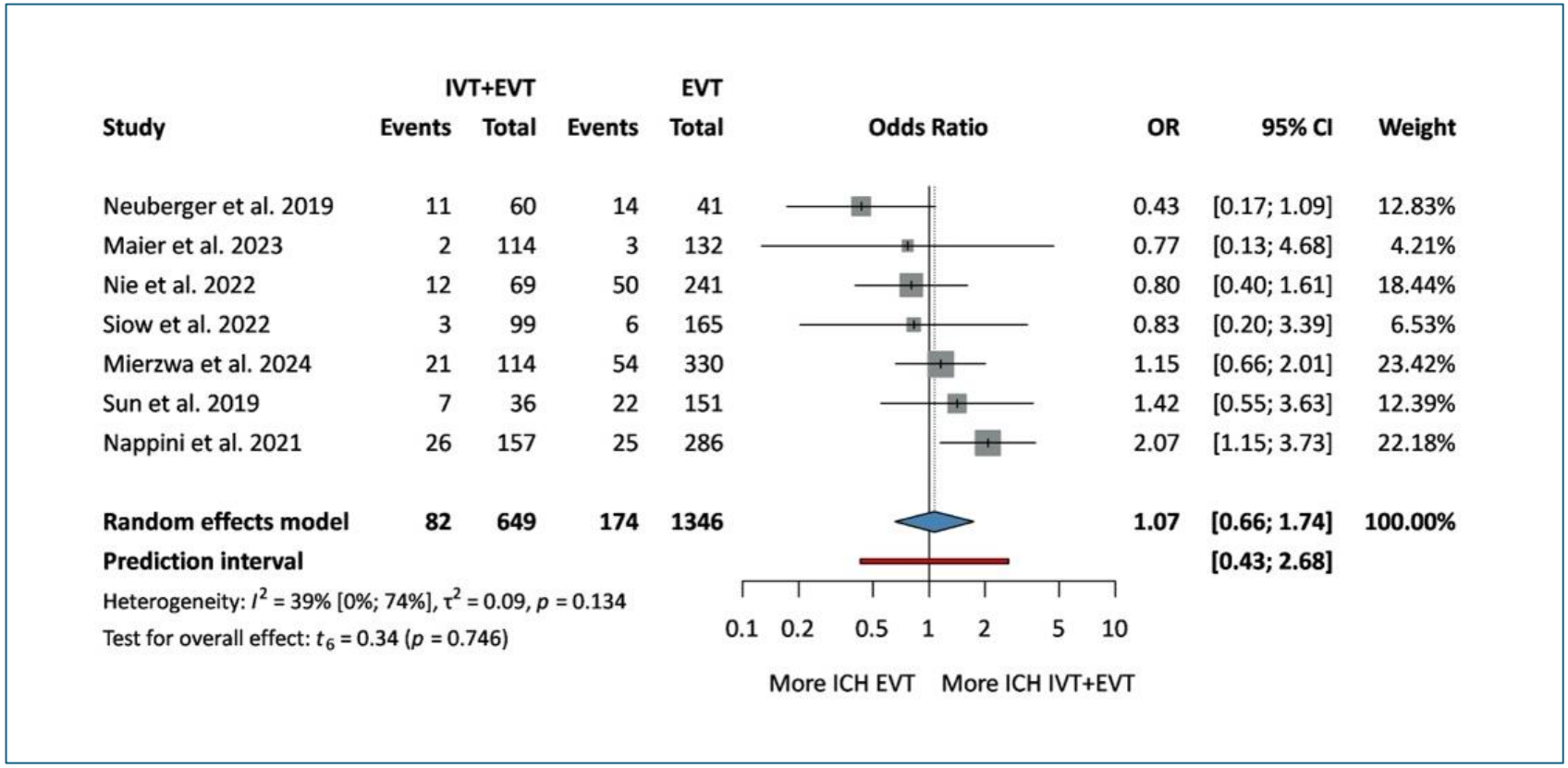

Figure 11. Forest plot representing the odds ratio (OR) of any intracranial hemorrhage.

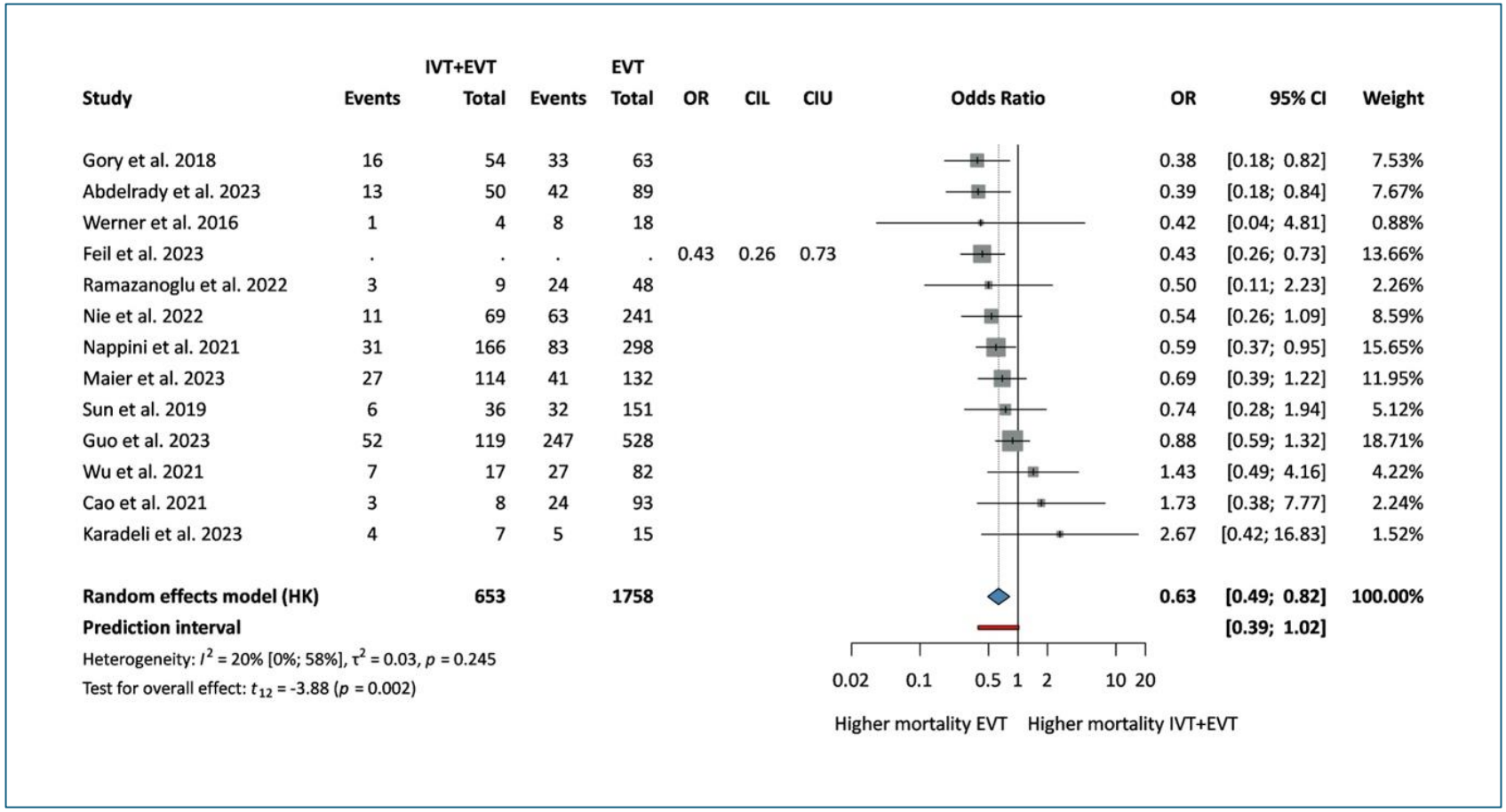

Figure 12. Forest plot representing the odds ratio (OR) of 90-day mortality.

8.2.8. Subgroup analysis

Post hoc subgroup analyses were performed to explore potential effect modifiers, with differences evaluated using *p* values for tests of subgroup interaction. No adjustments for multiple comparisons were applied, reflecting the exploratory, hypothesis-generating nature of these analyses. The subgroup analyses identified several characteristics associated with treatment effects.

Among patients with milder strokes (NIHSS 5–15), bridging therapy was associated with significantly higher odds of independent ambulation (OR 1.52; 95% CI 1.11–2.07; *p* for subgroup difference = 0.028), whereas no significant differences across subgroups were observed for functional independence (OR 1.52; 95% CI 1.17–1.66; *p* = 0.765). With increasing stroke severity, the estimated ORs for both functional independence and independent ambulation decreased, although this trend did not reach statistical significance for functional independence. Patients receiving bridging therapy within 24 hours of symptom onset showed comparable odds of functional independence (OR 1.32; 95% CI 1.11–1.58; *p* for subgroup difference = 0.709) and independent ambulation (OR 1.25; 95% CI 1.07–1.45; *p* = 0.076) compared with those treated within 12 hours.

Consistent benefits of bridging therapy over direct EVT for functional independence were observed in studies conducted in Asia (OR 1.39; 95% CI 1.02–1.91) as well as in Europe and North America (OR 1.66; 95% CI 1.33–2.08), with no significant differences between regions (*p* for subgroup difference = 0.308). Similar treatment effects were noted in studies including patients with basilar artery occlusion alone and those including both basilar and vertebral artery occlusion. Only four studies provided poolable adjusted ORs, and no significant differences between treatment strategies were observed in these analyses. A comprehensive overview of all subgroup analyses for functional independence is presented in **Figure 13**.

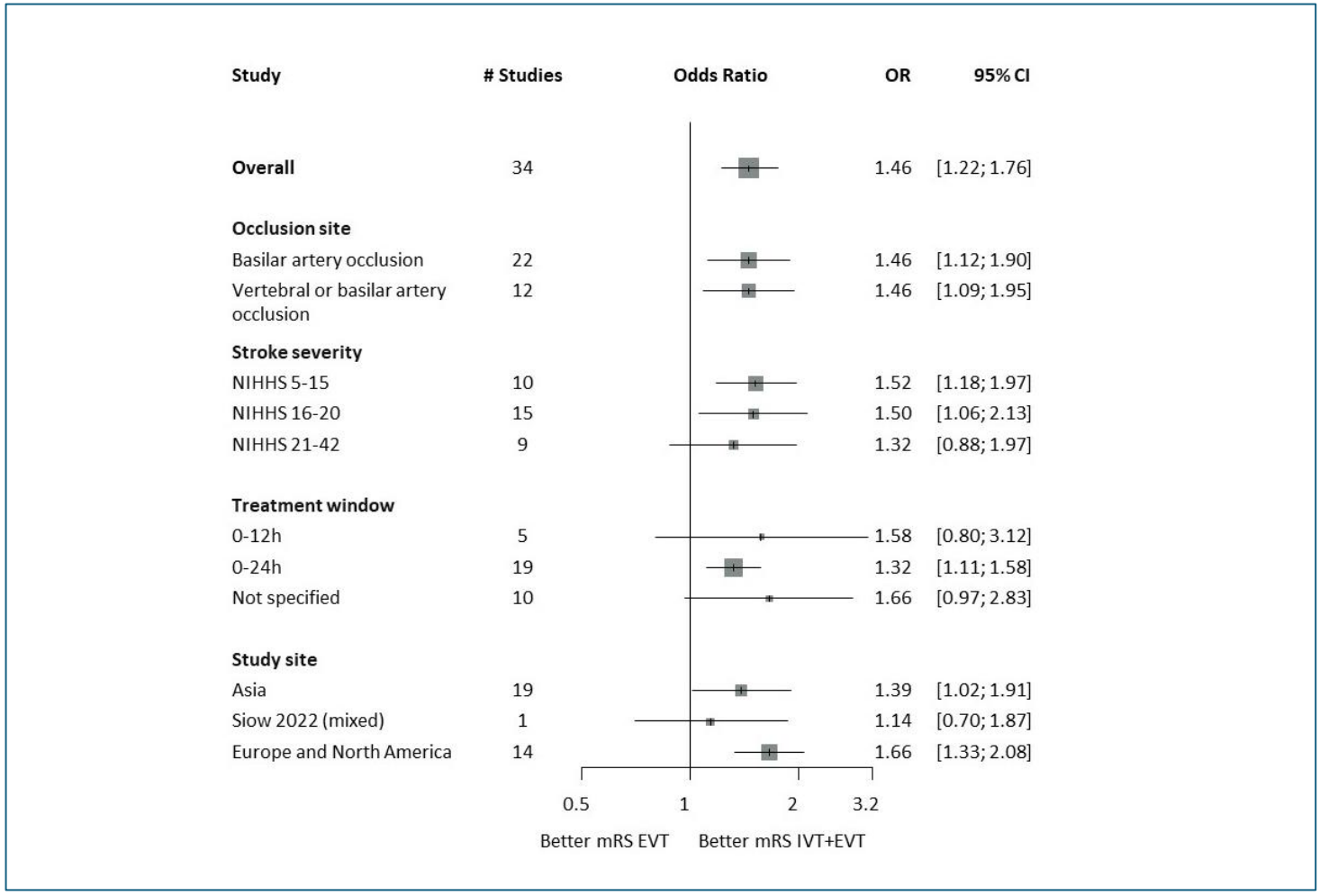

Figure 13. Summary plot of all subgroup analysis for the outcome of functional independence (90-day modified Rankin Scale 0–2).

8.2.9. Risk of bias assessment

Overall, the majority of included studies were estimated to have a moderate risk of bias. Of the 58 studies included in the meta-analysis, three studies (5.17%) were assessed as having a high risk of bias**,** largely attributable to substantial methodological limitations, while the remaining 55 studies (94.83%) were classified as having a moderate risk of bias (**Figure 14**).

8.2.10. Level of evidence

Given that only cohort studies were included, the overall certainty of evidence was assessed as moderate to high across all evaluated outcomes. However, the generally large sample sizes, consistency of effect estimates, and precision of outcome measurements contributed to higher certainty assessment for several outcomes.

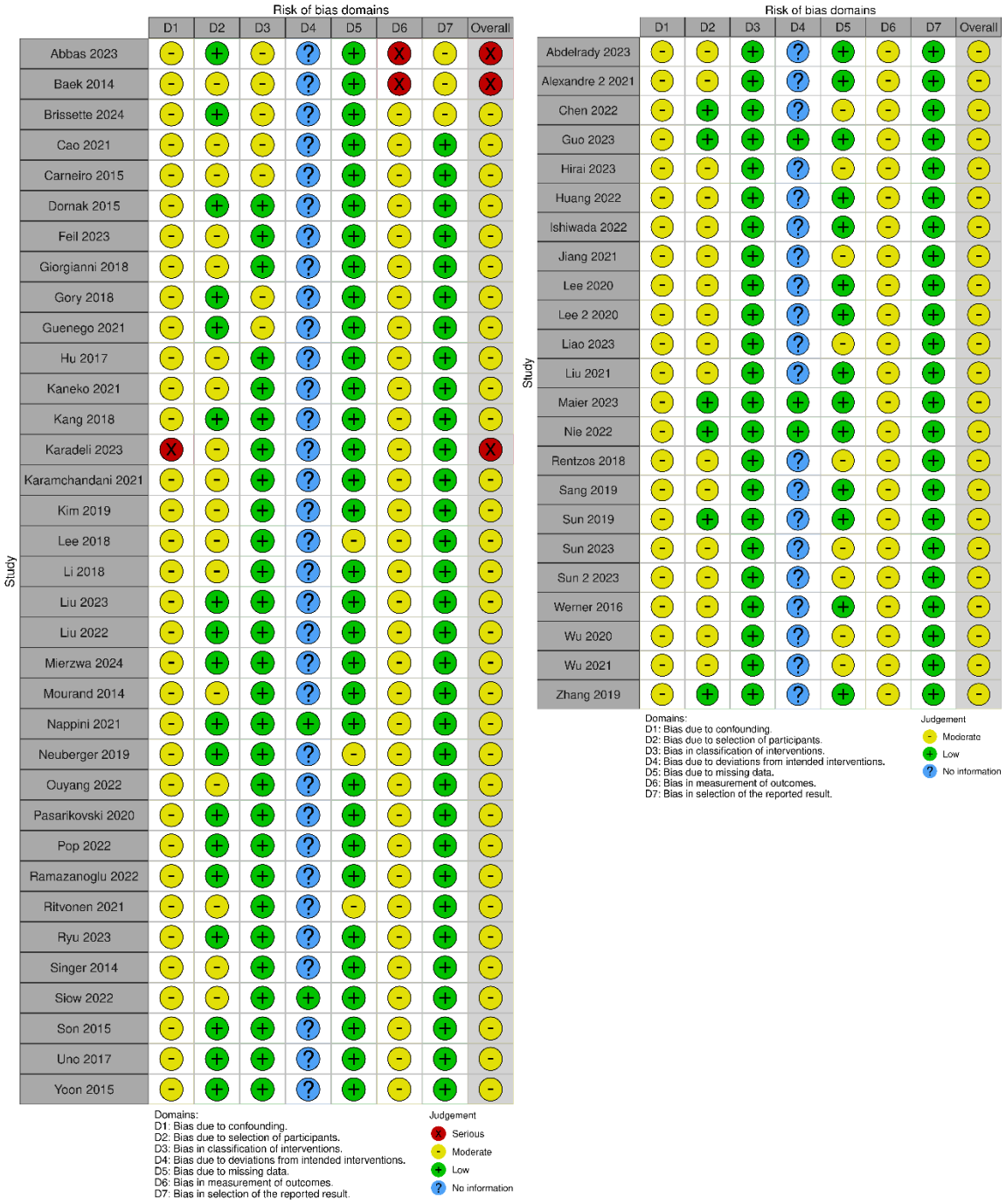

Figure 14. Risk of bias assessment using Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool.

9. DISCUSSION

9.1. Summary of findings and international comparisons (including all studies)

The first study investigated the association between FLAIR status and outcomes after IVT in known-onset acute ischemic stroke. Specifically, rates of hemorrhagic transformation and less favorable 90-day functional outcome were analyzed. Patients with FLAIR-positive acute ischemic lesions showed higher rates of hemorrhagic transformation and significantly worse 90-day functional outcomes compared to patients with FLAIR-negative lesions. While the difference in functional outcome reached statistical significance, the difference in hemorrhagic transformation did not. Importantly, more than one quarter of patients presenting within 4.5 hours of symptom onset already had FLAIR-positive lesions, indicating that FLAIR positivity does not exclude a recent stroke.

FLAIR imaging has been extensively used in the context of wake-up stroke (105). A DWI–FLAIR mismatch, defined as a DWI hyperintensity without a corresponding FLAIR lesion, suggests that ischemic changes have occurred recently, and the patient is likely to be within a time window for safe and effective thrombolysis (105-107). Although the present analysis demonstrated an association between FLAIR-positive lesions and poorer functional outcomes, the prognostic value of FLAIR status in early known-onset stroke remains limited. The modest sensitivity observed suggests that FLAIR status alone is unlikely to serve as a reliable predictor of outcome. Consequently, FLAIR positivity in early-presenting patients should prompt a careful risk–benefit assessment but should not be used to withhold IVT in otherwise eligible patients.

These findings are consistent with those of a previous meta-analysis, which has shown that FLAIR-positive acute ischemic lesions reflecting blood–brain barrier disruption, are associated with more severe strokes and a higher risk of vessel-wall failure, hemorrhagic transformation, and neurological deterioration (108). Other studies have reported that FLAIR-negative lesions are more frequently associated with early neurological improvement (109). Beyond conventional visual assessment, radiomics approaches incorporating FLAIR and other MRI sequences have demonstrated good performance in

predicting functional outcome after acute ischemic stroke (110, 111). More recently, synthetic FLAIR images generated from DWI using deep learning techniques have shown diagnostic performance comparable to conventional FLAIR, with the added advantage of substantially reducing MRI acquisition time (112, 113).

Several prognostic scores, including HAT, DRAGON, Stroke-TPI, SPAN-100, MSS, SEDAN, SITS-ICH, iScore, and ASTRAL, have been developed to estimate the risk of hemorrhagic transformation after IVT (114). However, these models primarily rely on clinical and CT-based radiological variables, and none incorporate MRI-derived parameters such as FLAIR status as key prognostic components (114). Similarly, CT perfusion has shown high sensitivity and moderate specificity for predicting hemorrhagic transformation, further highlighting that MRI-based markers remain underrepresented in established prognostic frameworks (115).

The second study was a meta-analysis comparing two treatment strategies in patients with BAO, bridging IVT prior to EVT versus direct EVT. Efficacy outcomes included 90-day functional independence, 90-day independent ambulation, and successful recanalization, while safety outcomes comprised symptomatic intracranial hemorrhage, any type of intracranial hemorrhage, and 90-day mortality. Bridging therapy was associated with higher rates of functional independence and lower mortality at 90 days compared to direct EVT. No significant differences were observed between the two treatment strategies regarding successful recanalization or hemorrhagic complications.

These results align with previous meta-analyses conducted in smaller cohorts, which similarly suggested that bridging IVT before EVT may improve functional outcomes and reduce mortality without increasing hemorrhagic risk (116-118). The updated ESO-ESMINT treatment guidelines for BAO recommend IVT before EVT for patients presenting within 4.5 h of symptom onset, and direct EVT for patients presenting from 4.5 to 24 h of symptom onset (34). However, there are insufficient data to support reperfusion therapy beyond standard treatment time for adults with BAO-related acute ischemic stroke based on advanced imaging evaluation (34).

Randomized controlled trials and large prospective registries have also compared EVT with best medical treatment in BAO (27-30). Notably, the BASICS trial reported higher rates of IVT use before EVT compared with the BAOCHE, ATTENTION, and BEST trials (27). These differences are largely explained by variations in treatment time windows: BASICS included patients within 6 h of estimated BAO onset, whereas BEST included patients within 8 h, ATTENTION included patients within 12 h, and BAOCHE included patients within 6 to 24 h of estimated BAO onset (27-30). Moreover, the BAOCHE, ATTENTION, and BEST trials involved patients from China, where IVT required upfront payment and potentially limited its use (28-30).

Bridging IVT prior to EVT offers several theoretical and practical benefits, including early microvascular reperfusion beyond the reach of thrombectomy devices, preservation of downstream microcirculation through fibrinogen-dependent platelet inhibition (119). Moreover, IVT can facilitate clot retrieval, and dissolution of distal perioperative clots (120, 121). Conversely, arguments against bridgin therapy include increased hemorrhagic risk, thrombus fragmentation, delayed initiation of EVT, limitations on antithrombotic therapy, and higher costs (122).

Evidence from randomized trials comparing bridging therapy and direct EVT in large vessel occlusion has been mixed. The DIRECT-SAFE trial failed to demonstrate non-inferiority of direct EVT and supported bridging therapy as the standard approach (122). Similarly, trials such as SWIFT DIRECT, SKIP, and MR CLEAN–NO IV showed neither superiority nor non-inferiority of direct EVT compared with bridging therapy (123-125). Only two trials from China, DEVT and DIRECT-MT, demonstrated non-inferiority of direct EVT (126, 127). Evidence from previous studies suggest that the therapeutic time window for BAO may be more flexible than in anterior circulation stroke, with a potential of the IVT treatment window to align more closely with the EVT window (29). More recent randomized evidence, such as the BRIDGE-TNK trial, demonstrated that IV tenecteplase administered before EVT within 4.5 hours improved functional independence compared with direct EVT in patients with LVO (128). Although only a small proportion of enrolled patients had vertebrobasilar occlusions, these findings

provide additional indirect support for the potential benefit of bridging IVT in posterior circulation stroke.

Ongoing trials, such as the RESILIENT DIRECT-TNK trial (NCT05199194) in Brazil is evaluating whether intravenous tenecteplase administered prior to EVT improves clinical outcomes in patients with large-vessel occlusion presenting within 4.5 hours of symptom onset. Expanding the therapeutic time window, the POST-ETERNAL trial (NCT05105633) is investigating whether tenecteplase given up to 24 hours before EVT leads to superior functional outcomes in acute BAO compared with current standard care. Additionally, the ATTENTION-IV early trial (NCT05827042) in China is comparing direct EVT and bridging therapy within 4.5 hours in patients with acute BAO. Collectively, these trials are expected to provide important evidence to refine treatment strategies across varying time windows and stroke subpopulations.

9.2. Strengths

9.2.1. Study I

Our analysis strictly followed a pre-registered protocol, ensuring transparency and minimizing bias in our investigation of FLAIR positivity and post-IVT outcomes. The strength of our study lies in the conduction of univariate analysis, which provided a comprehensive and objective assessment of the predictive value of FLAIR positivity. A consistent and clear definition of FLAIR positivity across studies ensured uniformity and clarity in our analysis, increasing the reliability of our conclusions.

9.2.2. Study II

Our analysis strictly followed a pre-registered protocol, ensuring transparency and minimizing bias in our investigation of treatment strategies for BAO. The primary strength of this analysis is that it incorporates data from multiple cohort studies. The inclusion of a patient population larger than ever before (more than 9372 patients across 58 cohorts) allowed for a more generalized understanding of treatment effects. In

addition, the analysis highlighted significant outcomes, such as improved functional independence and lower mortality rates associated with bridging IVT and EVT, which are crucial for clinical decision-making in acute stroke management.

9.3. Limitations

9.3.1. Study I

One limitation of our study is the relatively low number of studies and patients involved, which potentially limited the generalizability of our findings on the predictive value of FLAIR positivity. Moreover, the majority of enrolled patients suffered moderate strokes based on the reported baseline NIHSS scores, restricting the applicability of our results to more severe stroke populations.

However, in the one study with more severe strokes (Hobohm et al.) (45), the odds for hemorrhagic transformation in FLAIR-positive patients were much higher than in the other studies with milder strokes, so we expect this association to become stronger with increasing stroke severity. In mild-to-moderate acute ischemic stroke, the prognostic impact of hemorrhagic transformation may be less pronounced than in severe cases. Nevertheless, hemorrhagic transformation remains clinically relevant, as it can lead to secondary neurological worsening, delay functional recovery, and influence post-thrombolytic management decisions. This relevance is further underscored by the recently introduced concept of the “leaky core,” which describes regions within the ischemic core where irreversible neuronal injury coincides with severe blood–brain barrier disruption, predisposing to hemorrhagic transformation and malignant edema after reperfusion (129).

We also acknowledge that using hemorrhagic transformation rather than symptomatic intracerebral hemorrhage as an outcome measure reduces direct clinical applicability. However, as most included studies did not consistently distinguish between symptomatic and asymptomatic hemorrhagic events, hemorrhagic transformation was used as the most uniformly reported endpoint. Despite this limitation, hemorrhagic transformation remains a relevant surrogate marker of tissue vulnerability and provides insight into the imaging

pathophysiological relationship between FLAIR positivity and secondary injury.

9.3.2. Study II

One limitation of our study is that all included prospective studies were observational and not randomized, and thus the potential for clinician selection bias in IVT decisions may have influenced the observed associations. There was a substantial clinical heterogeneity among studies due to differences in treatment protocols, imaging techniques, and inclusion criteria, which undermines and limits the generalizability of our findings.

Another limitation is the potential bias arising from the fact that all patients receiving bridging therapy were treated within 4.5 h of symptom onset, whereas those receiving direct EVT were treated up to 24 h. This discrepancy could partly account for the observed benefits in mortality and functional outcomes, as well as similar rates of symptomatic intracranial hemorrhage between the two treatment groups. Although not statistically significant, bridging therapy showed a lower rate of symptomatic intracranial hemorrhage. This counterintuitive trend may reflect selection bias, as patients eligible for IVT were generally less frail or had fewer contraindications. Center-level treatment preferences and residual confounding in observational data may also have influenced treatment allocation and safety outcomes.

Interestingly, patients treated with bridging therapy within 24 hours demonstrated similar odds of functional independence and independent ambulation compared with those treated within 12 hours. This finding may appear counterintuitive, as earlier reperfusion is typically associated with better outcomes. However, patients treated in the late window may represent “slow progressors” with favorable collateral circulation or imaging profiles, who were selectively identified using advanced imaging techniques. Differences in center-level imaging-based triage and residual confounding in subgroup analyses may also contribute to this observation.

Furthermore, Nappini et al. (70) found that patients treated with bridging therapy within 6 h had lower mortality rates than those receiving EVT alone within the same time frame. In addition, in cases without significant baseline ischemia (posterior circulation

ASPECTS ≥ 8), Strbian et al. (130) observed no significant association between onset-to-treatment time and poor outcomes. These findings suggest that although time is a critical factor, its impact may be nuanced by patient-specific factors and baseline ischemic burden, supporting the consideration of bridging therapy even within extended treatment windows.

In conclusion, treatment response and prognosis may vary by BAO site, with EVT showing greater benefit in proximal and mid-basilar versus distal “top-of-the-basilar” occlusions (34), but occlusion location was inconsistently reported among included studies. Similarly, intracranial atherosclerosis, which often requires intracranial percutaneous transluminal angioplasty (PTA) or stenting after thrombectomy, and additional antithrombotic therapy, was also inconsistently reported among included studies, potentially affecting procedural efficacy and safety outcomes.

10. CONCLUSION

10.1. Study I

Our first study showed that FLAIR positivity in acute ischemic stroke treated with IVT within the standard time window is associated with less favorable functional outcome and a trend toward higher hemorrhagic transformation risk. FLAIR positivity may be taken into account in treatment decisions and patient management but should not be regarded as a contraindication to IVT in otherwise eligible patients. Further prospective research is needed on the clinical significance of FLAIR positivity and its underlying mechanisms.

10.2. Study II

Our second study demonstrated that bridging IVT with EVT in patients with BAO leads to improved outcomes in terms of functional independence and lower mortality at 90 days compared to direct EVT without increasing the rate of symptomatic intracranial hemorrhage. The bridging therapy was shown to be beneficial across all subgroups. Our observational findings align with current guideline-based practice but should be interpreted with caution and considered hypothesis-generating rather than directive for clinical decision-making.

11. IMPLICATIONS FOR PRACTICE

11.1. Study I

While our findings show a significant association between FLAIR hyperintensity and less favorable functional outcome and a non-significantly higher odds for hemorrhagic transformation post-IVT, the clinical relevance of FLAIR status remains uncertain. Given the limited number of studies, high between-study heterogeneity, and the modest effect sizes, these findings should be interpreted with caution. FLAIR positivity should not be used as a standalone decision-making tool, and its presence should not be a reason to withhold treatment from otherwise eligible patients. Integrating FLAIR positivity assessment into clinical practice may improve prognostication and inform post-thrombolysis treatment and follow-up, e.g., timing of follow-up scans, timing of secondary prevention antithrombotic use, and extent of clinical monitoring.

11.2. Study II

Our findings support the continued use of bridging therapy in eligible patients with BAO presenting within the standard treatment window. In routine clinical practice, IVT should not be withheld in anticipation of EVT when no contraindications exist, as combined therapy was associated with improved functional outcomes and reduced mortality without an apparent increase in symptomatic intracranial hemorrhage. The consistency of benefit across patient subgroups further supports a broadly inclusive treatment approach rather than selective restriction.

12. IMPLICATIONS FOR RESEARCH

12.1. Study I

The study highlights the need for further research to validate and refine the predictive role of FLAIR positivity in stroke outcomes following IVT. Future studies should focus on prospective investigations to confirm the findings of this meta-analysis and clarify the underlying mechanisms that drive the association between FLAIR positivity and hemorrhagic transformation, possibly with the addition of perfusion data. Adjusted analyses are needed to determine whether FLAIR positivity has independent predictive value when accounting for other relevant clinical and imaging factors.

Additionally, research should assess the impact of FLAIR positivity on long-term recovery and its utility in post-thrombolysis management. The potential of artificial intelligence and radiomics to enhance the diagnostic and predictive value of FLAIR and other MRI markers should be explored. External validation of prognostic models, including FLAIR status, is also recommended. Overall, these findings should be interpreted with caution and viewed as a basis for further investigation rather than as definitive evidence for the clinical use of FLAIR positivity in acute stroke care.

12.2. Study II

Future research on bridging IVT and EVT for BAO should incorporate several key design improvements to address existing limitations. Implementing stratified randomization based on critical factors such as stroke severity, time from symptom onset to treatment, and collateral circulation status is essential to reduce selection bias and achieve balanced treatment groups. In addition, standardized and long-term follow-up (12–24 months) with comprehensive neurological assessment is essential for analyzing long-term outcomes of bridging therapy.

At the same time, advanced imaging can minimize inter-observer variability in evaluating imaging-based criteria and outcomes. To further mitigate confounding, researchers should

conduct multivariable analyses and sensitivity evaluations to account for critical variables such as pre-stroke disability, comorbidities, and variation in provided care. By incorporating these methodological improvements, future studies can provide more reliable evidence that informs optimized therapeutic strategies for BAO

13. IMPLICATIONS FOR POLICYMAKERS

13.1. Study I

Current evidence does not justify incorporating FLAIR positivity as a criterion to restrict access to IVT in otherwise eligible patients treated within the standard time window. Policymakers should therefore ensure that national and institutional stroke guidelines continue to prioritize timely IVT delivery based on established clinical and imaging eligibility criteria, without introducing FLAIR status as a contraindication.

At the same time, FLAIR positivity may have value as a prognostic and management-supportive marker rather than a treatment-limiting one. Policies that promote standardized MRI acquisition and reporting, including structured assessment of FLAIR hyperintensity, could facilitate more informed post-thrombolysis care, such as clinical monitoring, follow-up imaging strategies, and individualized timing of secondary prevention measures.

13.2. Study II

These findings support health policies that ensure timely and equitable access to bridging therapy for patients with BAO. Stroke units should prioritize rapid initiation of IVT within 4.5 hours of symptom onset, followed by prompt access to EVT when indicated. Delaying or withholding IVT in anticipation of EVT may exclude eligible patients who could benefit from combined treatment, particularly in time-critical posterior circulation strokes.

Accordingly, policy efforts should focus on reducing pre-hospital and in-hospital delays, strengthening regional stroke networks, and optimizing inter-facility transfer pathways to enable fast delivery of IVT and EVT. Until robust evidence supports selective restriction, bridging IVT plus EVT should remain broadly available to eligible BAO patients to maximize early reperfusion and improve clinical outcomes

14. FUTURE PERSPECTIVES

I aim to apply the scientific expertise developed during my PhD training to my future career as a stroke neurologist and clinical researcher. The training in study design, critical appraisal of evidence, and data interpretation has strengthened my ability to evaluate various treatments and translate findings into clinically meaningful improvements in acute stroke care, particularly in optimizing reperfusion strategies and patient outcomes. Ultimately, I aspire to combine patient-centered stroke care with active clinical research, contributing to the generation of new knowledge, educating future clinicians and researchers, and advancing the field of vascular neurology.

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16. BIBLIOGRAPHY

16.1. Publications related to the thesis

Zhubi Esra, Bissenov Azamat, Lengyel Anna Sára, Tóth Réka, Horváth András Attila, Kéri Szabolcs, Engh Marie Anne, Hegyi Péter, Gunda Bence

Association of FLAIR Positivity and Worse Outcomes After Intravenous Thrombolysis in Known-Onset Strokes: A Systematic Review and Meta-Analysis
JOURNAL OF CLINICAL MEDICINE 14 : 22 Paper 8031. 15 p. (2025)
Journal subject: Scopus – Medicine (miscellaneous) Rank: Q1
IF: 2.9

Zhubi Esra, Bissenov Azamat, Engh Marie Anne, Tóth Réka, Horváth András Attila, Hegyi Péter, Gunda Bence

Bridging therapy versus direct endovascular thrombectomy in basilar artery occlusion stroke: a systematic review and meta-analysis
GEROSCIENCE: OFFICIAL JOURNAL OF THE AMERICAN AGING ASSOCIATION (AGE) 2025 Paper: 22 p. (2025)
Journal subject: Scopus – Complementary and Alternative Medicine Rank: D1
Journal subject: Scopus – Veterinary (miscellaneous) Rank: D1
Journal subject: Scopus – Aging Rank: Q1
Journal subject: Scopus – Cardiology and Cardiovascular Medicine Rank: Q1
Journal subject: Scopus – Geriatrics and Gerontology Rank: Q1
IF: 5.4

16.2. Publications not related to the thesis

Zhubi Esra, Lehoczki Andrea, Tóth Péter, Lendvai-Emmert Dominika, Szalardy Levente, Gunda Bence

Intracerebral Hemorrhage in Aging: Pathophysiology, Clinical Challenges, and Future Directions

LIFE-BASEL 15 : 10 Paper: 1569 , 29 p. (2025)

Journal subject: Scopus – Ecology, Evolution, Behavior and Systematics Rank: Q1

Journal subject: Scopus – Paleontology Rank: Q1

Journal subject: Scopus – Biochemistry, Genetics and Molecular Biology (miscellaneous) Rank: Q2

Journal subject: Scopus – Space and Planetary Science Rank: Q2

IF: 3.4

Bissenov Azamat, **Zhubi Esra**, Engh Marie Anne, Gresits Orsolya, Tóth Réka, Terebessy Tamás

Concurrent validity of wearable IMUs for sagittal plane lower-limb range of motion

during walking and estimated ground reaction forces: a systematic review and meta-analysis

JOURNAL OF ORTHOPEDIC SURGERY AND RESEARCH 20 : 1 Paper: 891, 14p. (2025)

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Journal subject: Scopus – Surgery Rank: Q1

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Gunda Bence, Böjti Péter, Takács Tímea, **Zhubi Esra**, Bereczki Dániel, Varga Andrea, Kozák Lajos R.

Spontaneous intracerebral hemorrhage during computed tomography scanning—assessment of hyperacute hematoma growth

GEROSCIENCE: OFFICIAL JOURNAL OF THE AMERICAN AGING ASSOCIATION (AGE) (2025) Paper

Citing papers: 1 | Independent citation: 0 | Self citation: 1 | Unknown citation: 0 |

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Journal subject: Scopus – Veterinary (miscellaneous) Rank: D1
Journal subject: Scopus – Aging Rank: Q1
Journal subject: Scopus – Cardiology and Cardiovascular Medicine Rank: Q1
Journal subject: Scopus – Geriatrics and Gerontology Rank: Q1
IF: 5.4

Zeka Naim, Zeka Eris, **Zhubi Esra**, Hoxha Ilir

Case report: Diagnosis of a patient with Sifrim-Hitz-Weiss syndrome, development and epileptic encephalopathy-14, and medium chain acyl-CoA dehydrogenase deficiency
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Journal subject: Scopus – Pediatrics, Perinatology and Child Health Rank: Q2
IF: 2.0

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Journal subject: Scopus – Pollution Rank: Q2

Journal subject: Scopus – Public Health, Environmental and Occupational Health Rank: Q2

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