

Original Article

Collateral circulation significantly improves prognosis in cerebral infarction: a meta-analysis

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Abstract: Objective: To systematically evaluate the association between collateral circulation and prognosis in patients with cerebral infarction through a meta-analysis. Methods: A comprehensive literature search was conducted across multiple databases to identify studies examining the relationship between collateral circulation and outcomes in cerebral infarction. Studies were screened based on predefined inclusion and exclusion criteria. Data were extracted and pooled using standard meta-analytic techniques. Results: A total of 41 studies encompassing 10,510 patients were included. Meta-analysis revealed that good collateral circulation was significantly associated with a favorable prognosis (pooled odds ratio [OR] = 1.67, 95% confidence interval [CI]: 1.35-2.07; $P < 0.001$). Subgroup analyses confirmed this association across different geographic regions and sample sizes. Conclusion: Collateral circulation is a critical determinant of prognosis in cerebral infarction. Enhancing collateral circulation may serve as a promising therapeutic strategy to improve clinical outcomes in affected patients.

Keywords: Collateral circulation, cerebral infarction, prognosis, meta-analysis

Introduction

Cerebral infarction is a major cerebrovascular disorder characterized by high incidence, disability, and mortality rates, posing a serious threat to human health and quality of life. Despite continuous advancements in medical technology and the widespread application of treatments such as intravenous thrombolysis and endovascular intervention, many patients with acute cerebral infarction still experience poor prognoses and varying degrees of neurological impairment. Therefore, identifying key prognostic factors and developing precise, individualized treatment strategies have become critical and urgent areas of research in the field of neuroscience.

Collateral circulation has garnered increasing attention for its pivotal role in the onset and progression of cerebral infarction. It refers to the physiological compensatory mechanism wherein, in cases of major cerebral artery stenosis or occlusion, alternative vascular pathways maintain perfusion to ischemic brain tis-

sue [1]. Numerous studies have demonstrated a strong association between collateral status and clinical outcomes in cerebral infarction. For example, Gao et al. [2] reported a significant correlation between collateral circulation scores and the recurrence of acute cerebral infarction, suggesting that robust collateral flow may effectively lower recurrence risk. Similarly, Zhang et al. [3] found that well-developed collateral networks contribute to long-term cognitive improvement, underscoring the enduring neuroprotective effects of adequate collateral circulation.

Recent evidence has elucidated the multifactorial mechanisms through which collateral circulation influences prognosis. Studies [4] indicate that beyond improving perfusion, collateral pathways help regulate the metabolic microenvironment of ischemic tissue, mitigate the accumulation of neurotoxic substances, and support neuronal survival and repair. Furthermore, other investigations [5, 6] suggest that strong collateral circulation enhances responsiveness to treatment, improving thrombolytic efficacy

and reducing the risk of hemorrhagic transformation.

However, inconsistencies in study populations, collateral assessment methods, follow-up durations, and outcome measures have led to heterogeneous conclusions regarding the prognostic value of collateral circulation in cerebral infarction. To address these discrepancies, this meta-analysis employs rigorous statistical methodologies to comprehensively evaluate the true relationship between collateral status and clinical outcomes. By synthesizing available data, this study aims to provide robust, evidence-based insights to inform clinical practice. Ultimately, the findings may clarify the prognostic significance of collateral circulation, support its role as a therapeutic target, and contribute to enhanced management strategies for cerebral infarction.

Materials and methods

Literature search strategy

A comprehensive literature search was conducted in electronic databases including PubMed, Embase, Web of Science, and the Cochrane Library, covering publications from database inception to December 2024. Search terms included “collateral circulation”, “cerebral infarction”, “stroke”, “prognosis”, “outcome”, along with relevant synonyms and Medical Subject Headings (MeSH). In addition, the reference lists of all included studies were manually screened to ensure thorough identification of relevant literature. This study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42025639536).

Inclusion and exclusion criteria

Inclusion criteria: (1) Studies involving patients clinically diagnosed with cerebral infarction; (2) Evaluation of collateral circulation using objective imaging modalities such as digital subtraction angiography (DSA), computed tomography angiography (CTA), or magnetic resonance angiography (MRA); (3) Prognosis as a primary outcome, including indicators such as neurological recovery (e.g., NIH Stroke Scale [NIHSS], Modified Rankin Scale [mRS]), Barthel Index (BI), mortality, recurrence, or long-term disability ra-

tes; (4) Study design: prospective or retrospective cohort studies; (5) Sufficient data reported to calculate the odds ratio (OR) and 95% confidence interval (CI) based on multivariate analysis, or data that allowed such estimates to be derived.

Exclusion criteria: (1) Animal studies, review articles, conference abstracts, and case reports; (2) Studies lacking a clear investigation of the relationship between collateral circulation and prognosis, or studies with insufficient data for analysis; (3) Duplicate publications (in such cases, the most complete and recent study was retained).

Data extraction

Two independent, trained reviewers extracted data from the included studies. Extracted information included: Study characteristics (first author, publication year, region, study design); Participant details (sample size, age, sex); Method and results of collateral circulation assessment; Prognostic indicators and corresponding outcomes. Discrepancies or missing data were resolved by consulting the original articles, contacting authors, or involving a third reviewer.

Quality assessment

The quality of included cohort studies was assessed using the Newcastle-Ottawa Scale, which evaluates studies based on three domains: selection of study participants, comparability of groups, and assessment of outcomes. The maximum score is 9, with higher scores indicating higher methodological quality.

Statistical analysis

Meta-analysis was performed using RevMan 5.3 software. Heterogeneity among studies was assessed using the I^2 statistic. If $I^2 \leq 50\%$, a fixed-effect model was used. If $I^2 > 50\%$, indicating substantial heterogeneity, a random-effects model was applied.

Sources of heterogeneity were explored via subgroup analyses.

Pooled ORs with corresponding 95% CIs were calculated to assess the association between collateral circulation and cerebral infarction prognosis.

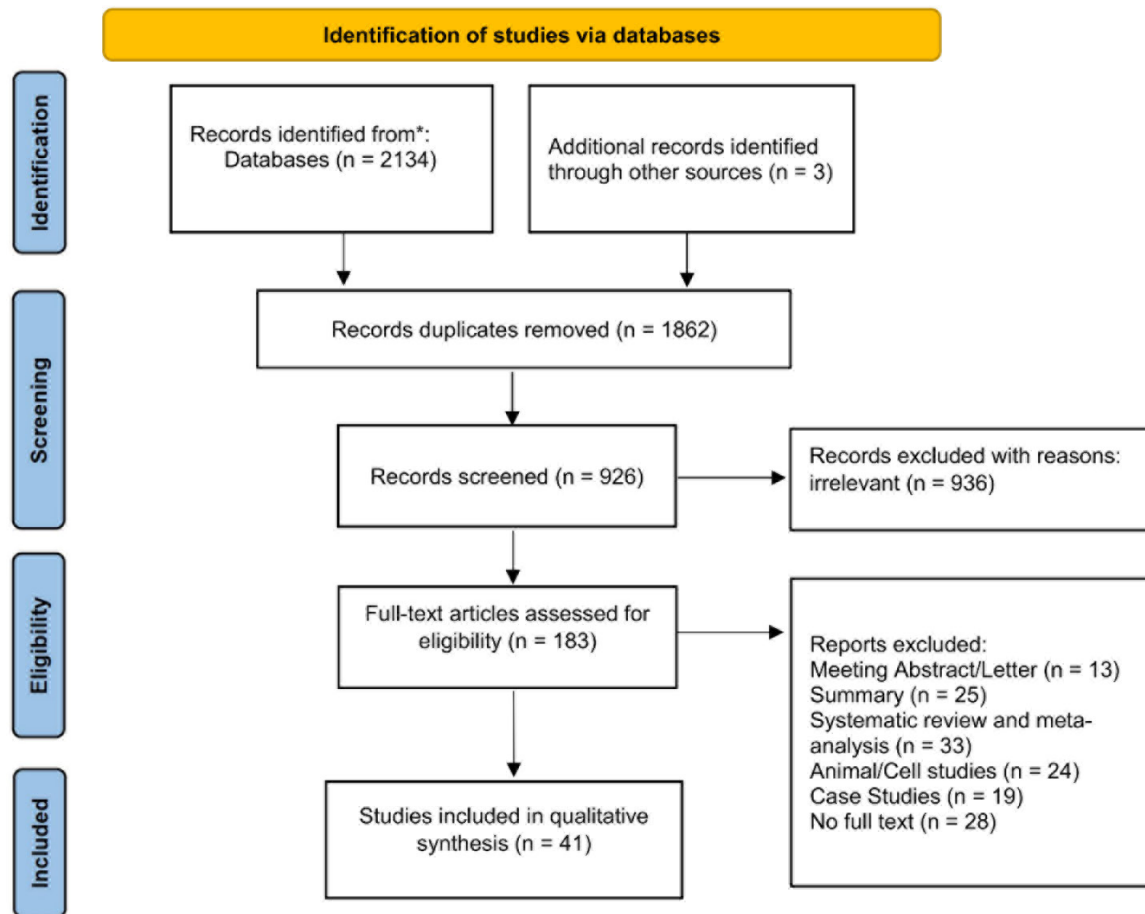


Figure 1. The literature screening process.

Subgroups were defined based on collateral circulation assessment method (e.g., DSA, CTA, MRA, transcranial Doppler), study region (e.g., Asia, Europe/North America) and sample size (categorized into large or small based on the median value).

Within each subgroup, heterogeneity was re-evaluated and effect sizes recalculated to determine differences in associations and assess potential sources of heterogeneity.

To test result robustness, sensitivity analysis was conducted by sequentially removing individual studies and observing changes in the pooled effect size and heterogeneity. If heterogeneity markedly decreased without significant changes in the pooled OR, the removed study was considered a potential source of heterogeneity.

Both funnel plots and Egger's test were used to assess publication bias. Funnel plots were

visually inspected for symmetry. A symmetric funnel shape suggests minimal publication bias, whereas asymmetry may indicate its presence. Egger's test, a linear regression-based approach, assessed funnel plot asymmetry. The standard normal deviate (effect size divided by standard error) was regressed against the standard error. A P -value < 0.05 for the intercept term indicated potential publication bias.

Results

Literature search results

A total of 183 articles were initially retrieved. After screening titles, abstracts, and full texts based on inclusion and exclusion criteria, 41 eligible studies were included in the final analysis [7-47], comprising a total of 10,510 patients with cerebral infarction. The detailed study selection process is illustrated in **Figure 1**.

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Table 1. Basic characteristics of the included studies

Number	Author/year	Area	Study type	Sample size	Male	Ag (years)	Collateral circulation assessment	NOS
[7]	Kucinski 2003	Germany	Retrospective	111	84	13-76	DSA	8
[8]	Mangiafico 2014	Italy	Prospective	103	55	71 (60-77)	CCS	7
[9]	Sperti 2023	Italy	Retrospective	520	215	Mean 75.04 (SD 14)	dichotomic Menon scale	7
[10]	Cuccione 2016	Italy	Retrospective	182	-	-	4D CTA-CS	7
[11]	Liu 2022	China	Prospective	58	-	-	ASL	7
[12]	de Havenon 2017	America	Retrospective	38	19	Mean 61 (SD 20)	ASL	7
[13]	Wu 2023	China	Retrospective	55	-	-	ASL	7
[14]	Bang 2011	America/South Korea	Retrospective	222	119	Mean 65	ASITN/SIR	8
[15]	van der Hoeven 2016	Netherlands	Prospective	149	98	Mean 65 (SD 15)	PC-CS	7
[16]	Alves 2018	Netherlands	Retrospective	195	119	-	MR CLEAN trial	7
[17]	Jeon 2024	Korea	Prospective	214	-	-	4D CTA-CS	6
[18]	Kim 2020	Korea	Prospective	154	99	69±13	MAC	6
[19]	Yeo 2015	Singapore	Retrospective	200	137	63 (35-92)	Miteff System	7
[20]	Lee 2023	Korea	Prospective	148	96	68±13	ASL	6
[21]	Park 2018	Korea	Retrospective	119	60	72.9±11.9	LMC score	7
[22]	Lima 2010	America	Prospective	196	85	69±17	LMC score	6
[23]	García-Tornel 2016	Canada	Retrospective	108	47	69.6±13	mCTA	7
[24]	Otani 2023	Korea	Retrospective	81	49	Mean 70.3	tomography angiography score and posterior circulation collateral score	7
[25]	Cao 2019	China	Retrospective	34	19	71.1±11.5	4D CTA	7
[26]	Yu 2021	China	Prospective	40	27	60.12±11.84	CTA-MIP	7
[27]	Gong 2024	China	Retrospective	338	-	-	Tan scale	6
[28]	Miteff 2009	Australia	Prospective	92	39	Mean 75	CTA	6
[29]	Derraz 2021	France	Prospective	326	170	Mean 68.5	FLAIR sequence	7
[30]	van den Wijngaard 2015	Netherlands	Retrospective	70	36	Mean 68 (SD 14)	Tan Collateral grading system	6
[31]	Cao 2024	China	Retrospective	126	-	-	4D CTA	7
[32]	Chen 2024	China	Retrospective	80	48	Median 66.00	CTA	6
[33]	Broocks 2019	Germany	Retrospective	176	102	Median 76	5-point scoring system	7
[34]	Cappellari 2022	Italy	Prospective	95	44	70.6 (11-6)	-	6
[35]	Rocha 2014	Portugal	Prospective	230	122	Median 72	ASPECTS	7
[36]	Xin 2024	China	Prospective	62	32	69.63±5.00	MRA	6
[37]	Flores 2015	Spain	Prospective	82	-	65.1±13.83	mCTA	6
[38]	JU 2019	China	Retrospective	73	-	-	CTA	7

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[39]	Wang 2017	China	Retrospective	40	-	-	DSA	7
[40]	Zhang 2023	China	Retrospective	4483	-	-	CTA	7
[41]	Gao 2021	China	Prospective	187	147	60 (range: 23-80)	ACGS-BAO	7
[42]	van den Wijngaard 2016	Netherlands	Prospective	61	34	median 67	dynamic CTA	7
[43]	Luo 2018	China	Prospective	69	57	Mean 59	ASPECTS	7
[44]	Wang 2022	China	Retrospective	100	80	63.0±10.7	-	8
[45]	Wang 2018	China	Retrospective	115	-	-	rLMC	8
[46]	Boers 2018	Netherlands	Prospective	442	-	66 (54-76)	CTA	8
[47]	Zhang 2022	China	Retrospective	258	-	72.90±12.41	-	7

CTA: Computed Tomography angiography; mCTA: multiphase CTA; 4D CTA-CS: four-dimensional computed tomography angiography; DSA: digital subtraction angiography; ASL: arterial spin labeling; MIP: maximum intensity projection; TOF: time-of-flight; MRA: MR angiography; PC-CS: posterior circulation collateral score; MR: Multicenter Randomized; CLEAN: Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands; MAC: MR acute ischemic stroke collateral; ASITN: American Society of Interventional and Therapeutic Neuroradiology; SIR: Society of Interventional Radiology; ASPECTS: Alberta Stroke Program Early CT; ACGS-BAO: angiographic collateral grading system for BAO; LMC: Leptomeningeal Collateral; rLMC: regional leptomeningeal; CCS: Collateral Circulation Scale; FLAIR: Fluid-Attenuated Inversion Recovery; NOS: Newcastle-Ottawa.

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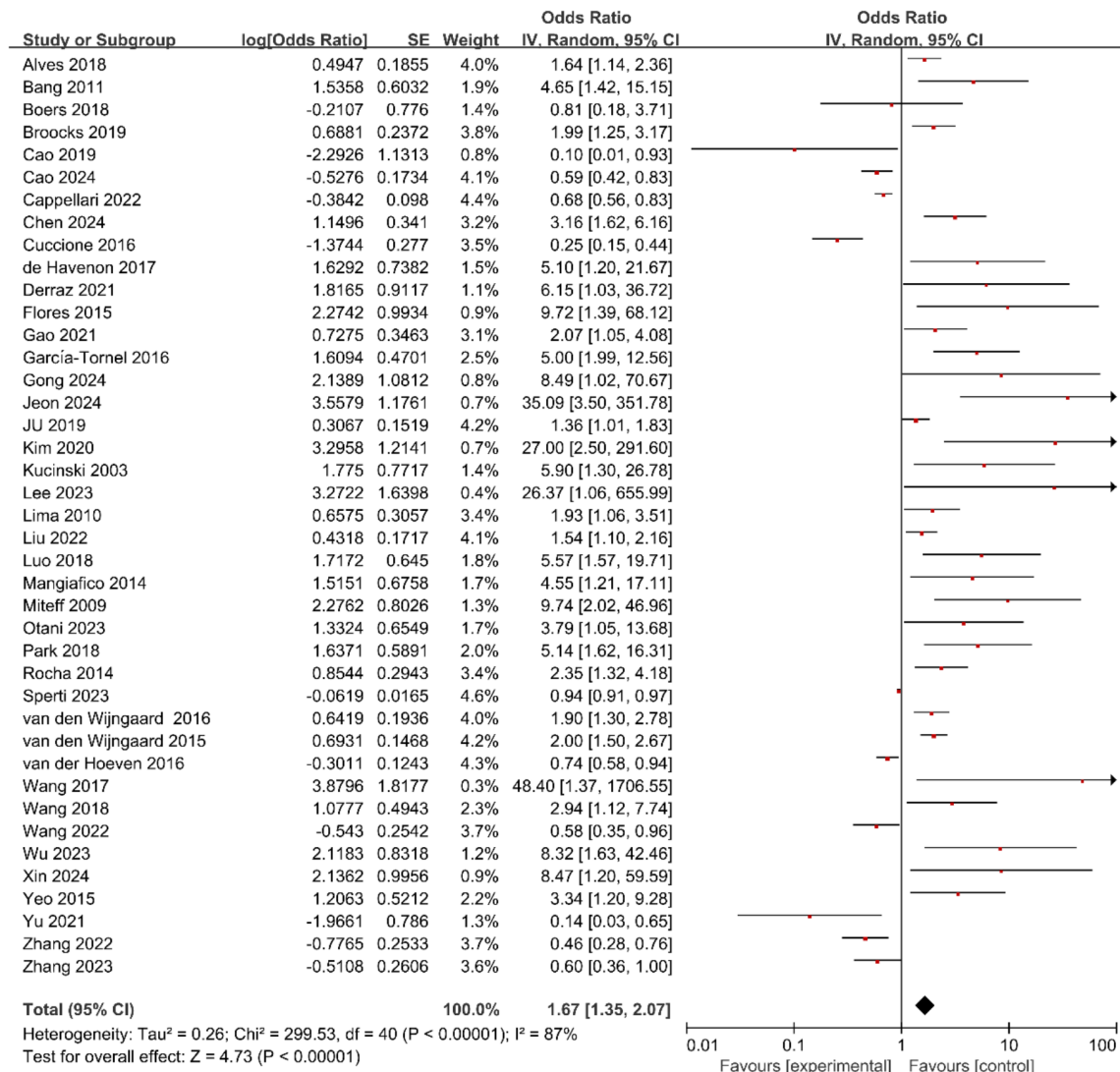


Figure 2. Forest map of the correlation between collateral circulation and prognosis of cerebral infarction.

Basic characteristics of included studies

The basic characteristics of the included studies are summarized in **Table 1**. These studies were conducted across various countries and regions worldwide. Of the 41 studies, 18 were prospective cohort studies and 23 were retrospective cohort studies.

Collateral circulation was assessed using diverse methods, grouped as follows:

Imaging modalities (10 types): including CTA, 4D CTA, four-dimensional CTA with contrast score, multiphase CTA, dynamic CTA, DSA, time-of-flight MRA, CTA-MIP (maximum intensity projection), Fluid-Attenuated Inversion Recovery sequence, and arterial spin labeling (ASL).

Scoring systems (10 types): including the 5-point grading system, angiographic collateral grading system for basilar artery occlusion, MR Acute Ischemic Stroke Collateral (MAC) score, CT angiography score, posterior circulation collateral score (PC-CS), leptomeningeal collateral score, Alberta Stroke Program Early CT, Tan scale, and Tan collateral grading system.

Specific rating scales (3 types): including the dichotomized Menon scale, Miteff system, and Collateral Circulation Scale.

Trial-based/organizational criteria (2 types): including the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands trial and

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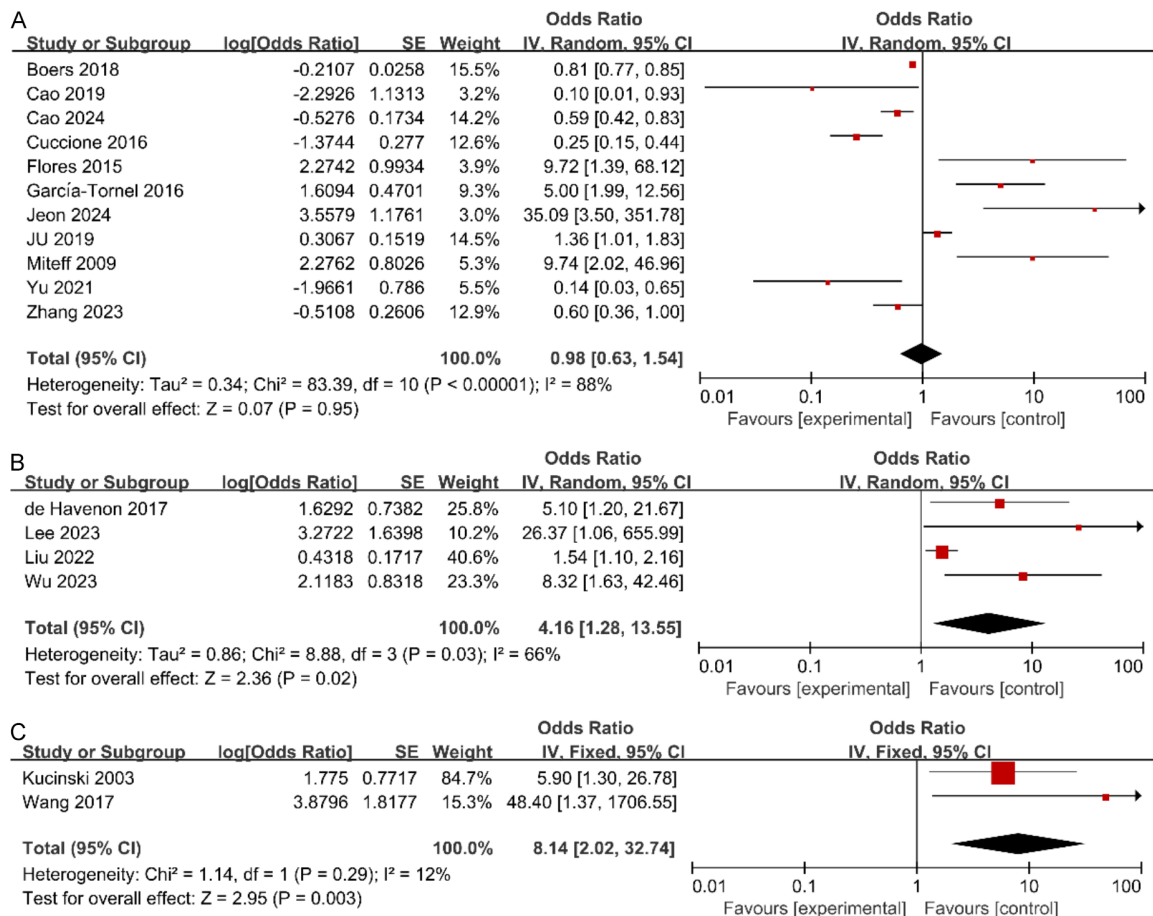


Figure 3. Forest plot of subgroup analysis by evaluation method. A. Computed Tomography angiography (CTA). B. Arterial spin labeling (ASL). C. Digital subtraction angiography (DSA).

American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology collateral grading system.

All included studies had a Newcastle-Ottawa Scale score ≥ 6 , indicating good methodological quality.

Meta-analysis results: association between collateral circulation and cerebral infarction prognosis

(1) Overall association: Meta-analysis of the 41 studies demonstrated that collateral circulation was significantly associated with favorable outcomes in patients with cerebral infarction (pooled OR = 1.67, 95% CI: 1.35-2.07, $P < 0.001$), indicating that better collateral status increases the likelihood of a good prognosis. See **Figure 2**.

(2) Subgroup analyses: By evaluation method: Studies were stratified by the method used to assess collateral circulation into CTA, ASL, and

DSA groups. Subgroup analysis (**Figure 3**) revealed no statistically significant association between collateral circulation and prognosis in the CTA group (both $P > 0.05$), whereas significant associations were observed in the ASL and DSA groups (both $P < 0.05$). Differences in pooled ORs among subgroups suggest that assessment method may influence the strength of the observed correlation.

By study region: Studies were categorized into two regional groups: Europe/North America and Asia. Both subgroups demonstrated a significant association between good collateral circulation and favorable prognosis ($P < 0.05$), with comparable pooled ORs (**Figure 4**), indicating consistent findings across geographic regions.

By sample size: Studies were divided into large-sample and small-sample groups based on the median sample size ($n = 119$). Both groups showed a significant association between col-

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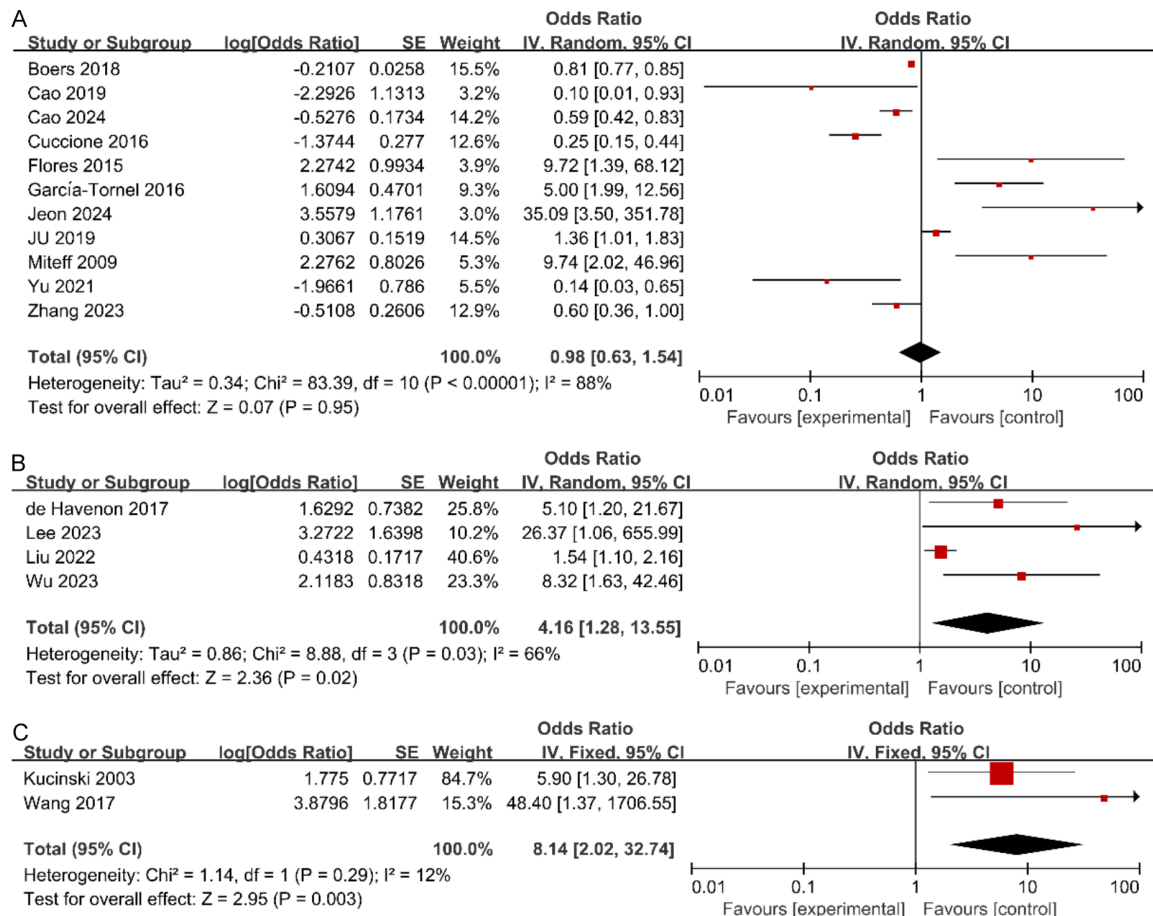


Figure 4. Forest plot of subgroup analysis by study region. A. European and American region group. B. Asian region group.

lateral circulation and favorable prognosis ($P < 0.05$; **Figure 5**). Notably, the pooled OR in the large-sample group was more stable, suggesting higher reliability in larger studies.

Sensitivity analysis

Sensitivity analysis was performed by sequentially removing individual studies to assess the impact on heterogeneity and overall effect size. Results showed that exclusion of certain studies reduced heterogeneity without significantly altering the pooled OR, indicating those studies may have contributed to heterogeneity. Overall, the findings remained stable and robust (**Figures 6-9**).

Assessment of publication bias

Funnel plot analysis and Egger's test were conducted to evaluate publication bias. The funnel plot appeared symmetric, and all studies were evenly distributed (**Figure 10**). Egger's test yi-

ielded a P value of 0.264 (> 0.05), suggesting no significant publication bias.

Discussion

This meta-analysis of 41 studies systematically investigated the association between collateral circulation and the prognosis of cerebral infarction, offering important implications for both research and clinical practice. The key finding is that good collateral circulation is significantly associated with favorable clinical outcomes. This is consistent with previous studies [48], as adequate collateral blood flow during ischemia can reduce infarct size, preserve neurological function, and increase the likelihood of recovery. Collateral circulation serves as an "emergency channel" for the brain, helping to sustain physiological function under critical conditions.

Subgroup analyses revealed notable differences based on the evaluation method. No signi-

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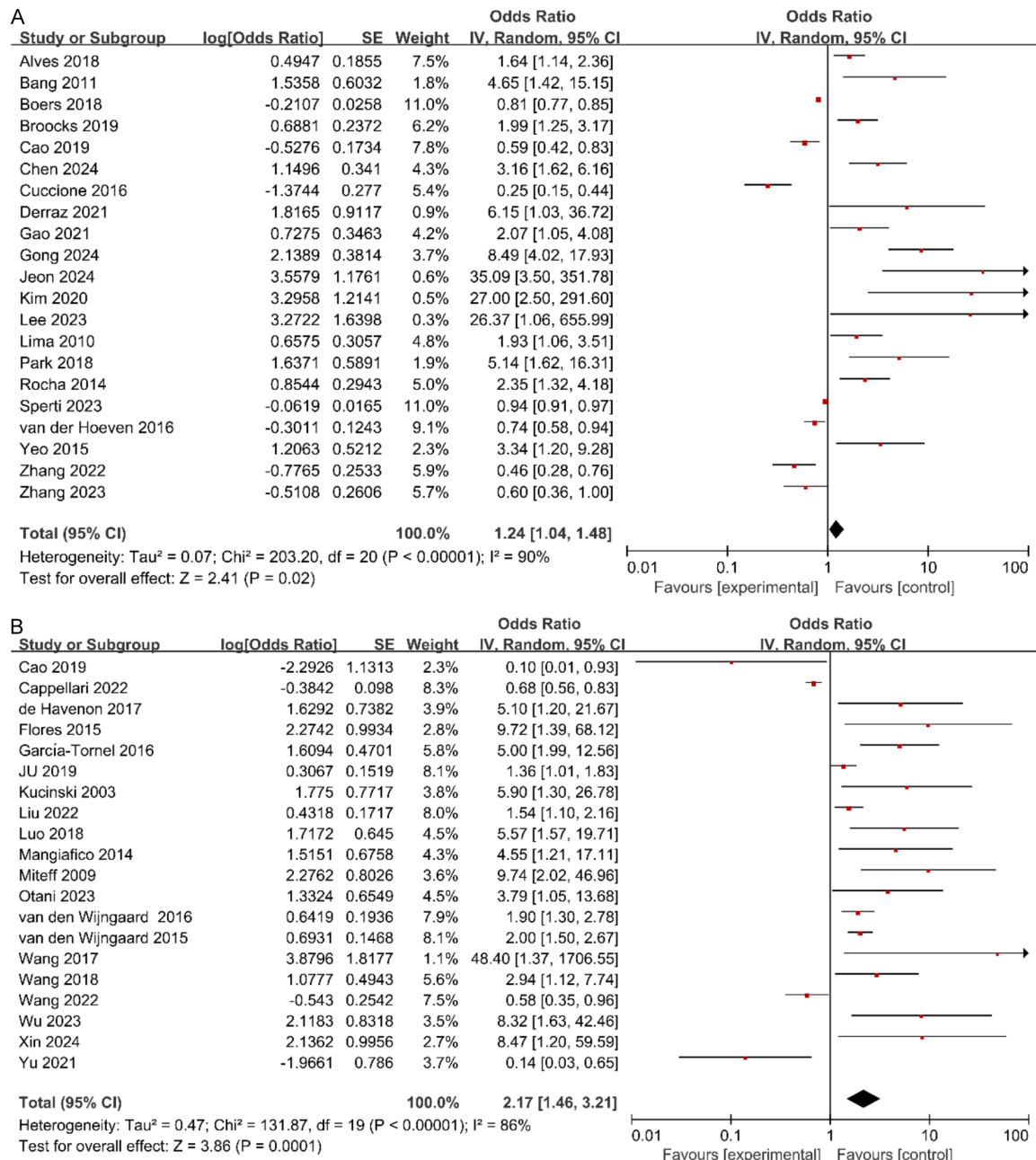


Figure 5. Forest plot of subgroup analysis by sample size. A. Large-sample group (≥ 119). B. Small-sample group (< 119).

ficant association was observed in studies using CTA, whereas significant correlations were found in those using ASL and DSA, albeit with slightly varying pooled ORs. While CTA is widely used for visualizing vascular anatomy due to its speed and accessibility, it has limited capacity to assess hemodynamic status and tissue perfusion [49]. In contrast, ASL, a perfusion MRI technique, provides quantitative cerebral blood flow measurements [50], and DSA remains the gold standard for detailed visualization of vas-

cular anatomy and collateral pathways [51]. Therefore, the choice of collateral evaluation method in both clinical and research settings should be tailored to the diagnostic objective to ensure accurate assessment.

Subgroup analysis by geographic region showed consistent findings across both European/American and Asian populations, with similar pooled ORs. This suggests that the protective role of collateral circulation is likely driven by

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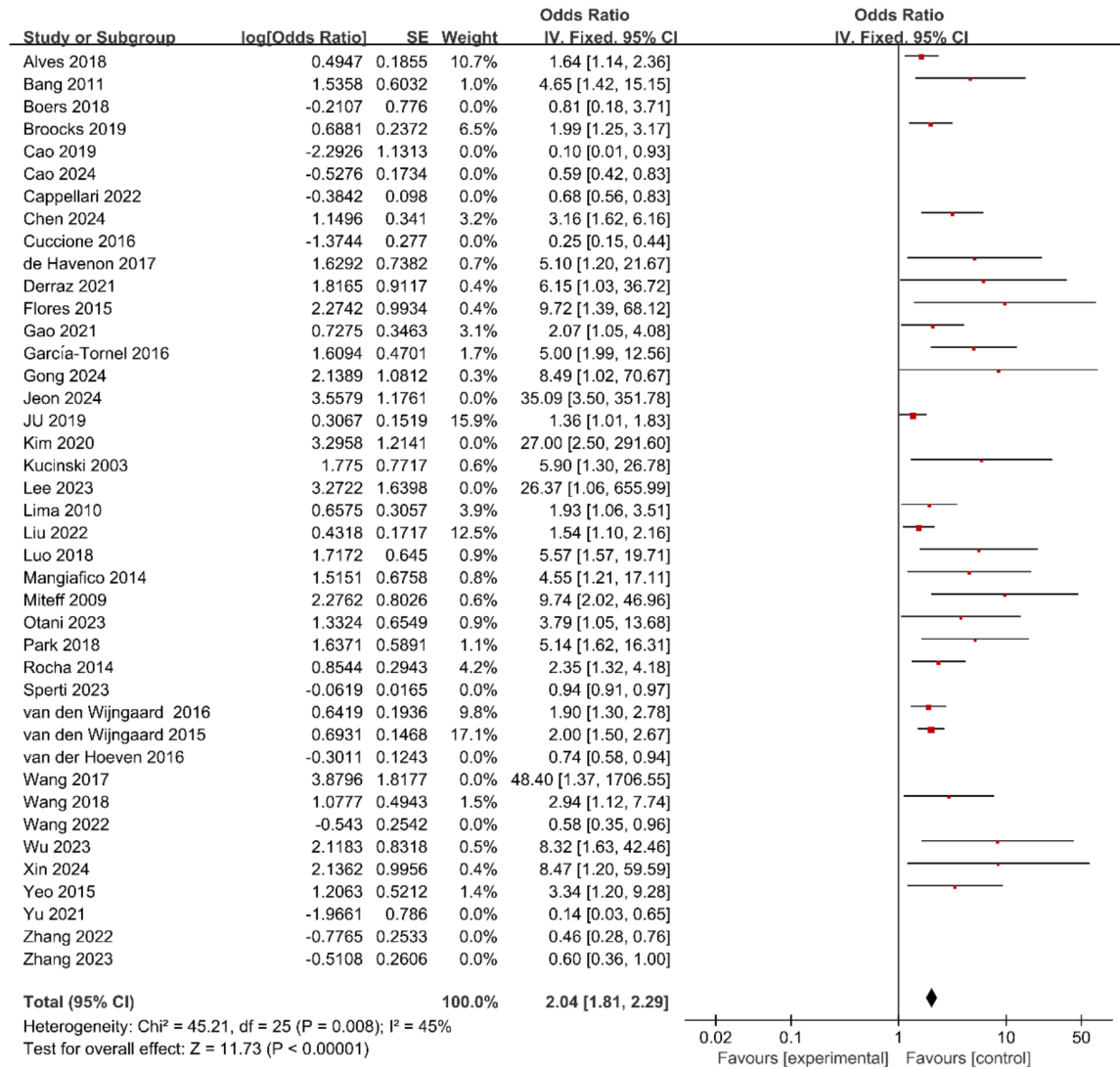
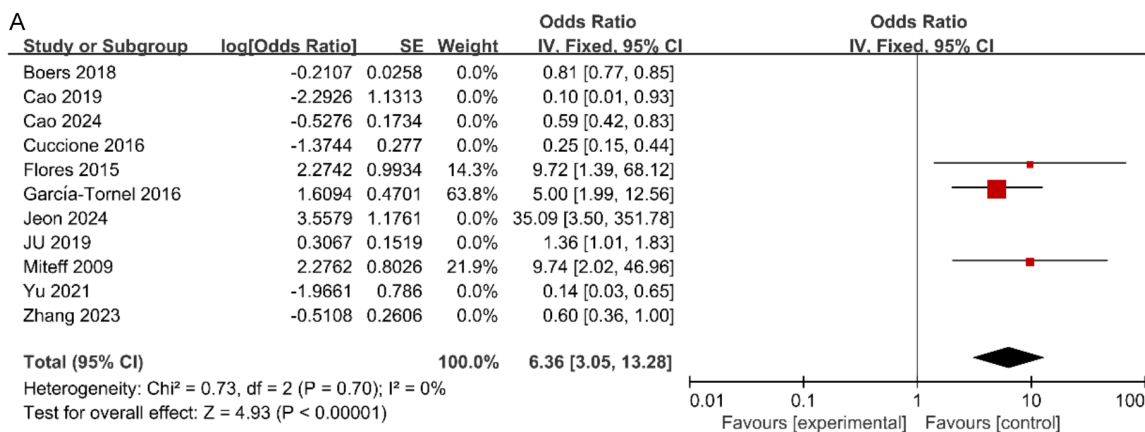


Figure 6. Sensitivity analysis of the correlation between collateral circulation and the prognosis of cerebral infarction.



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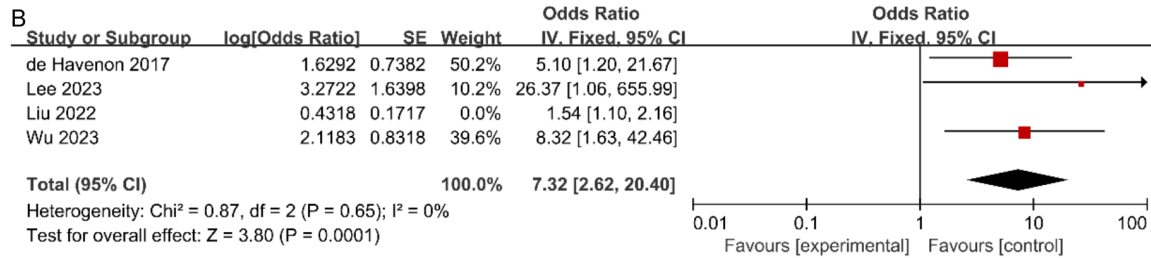


Figure 7. Sensitivity analysis of the subgroup by evaluation method. A. Computed Tomography angiography (CTA). B. Arterial spin labeling (ASL).

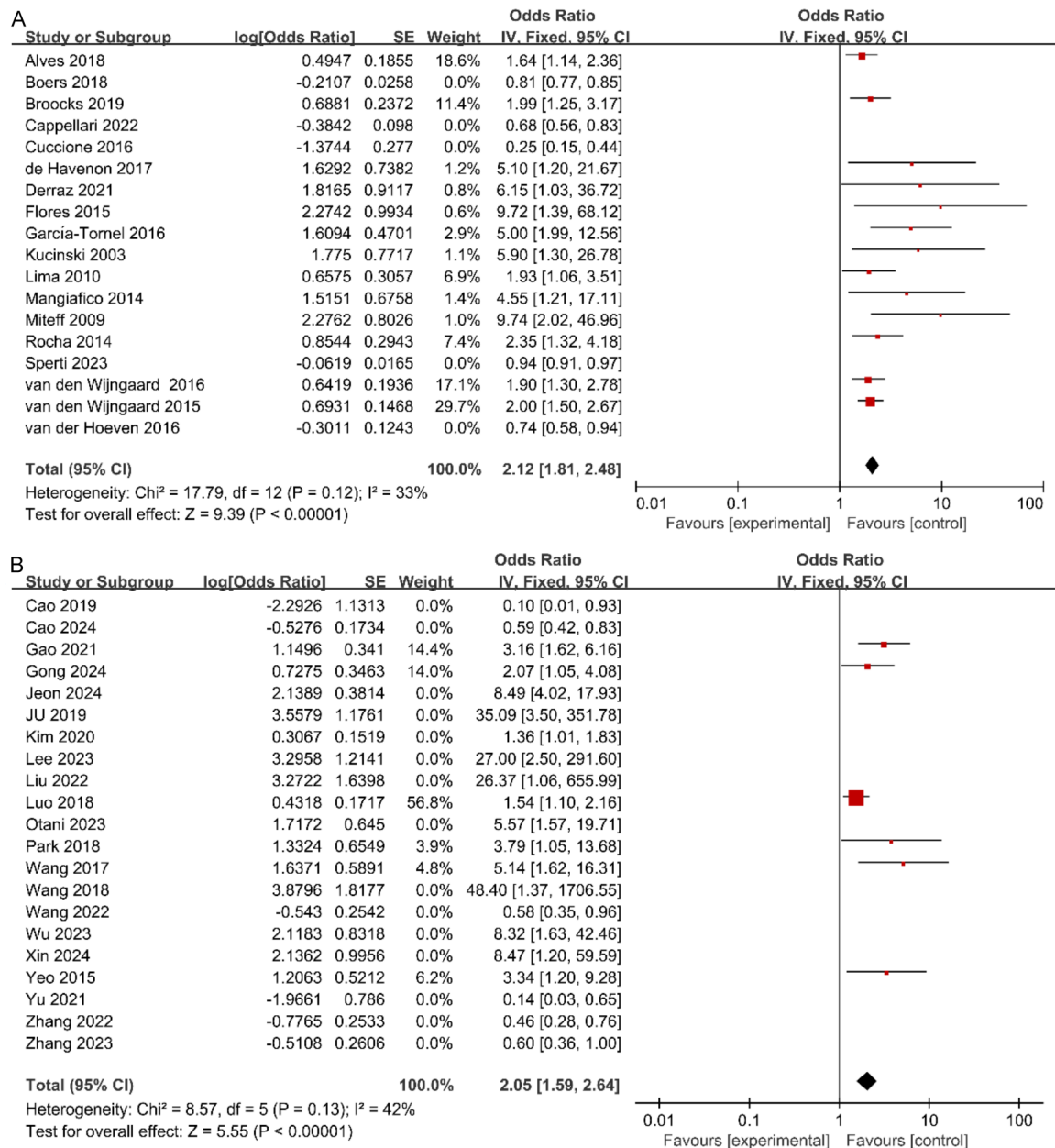


Figure 8. Sensitivity analysis of the subgroup by study region. A. European and American region group. B. Asian region group.

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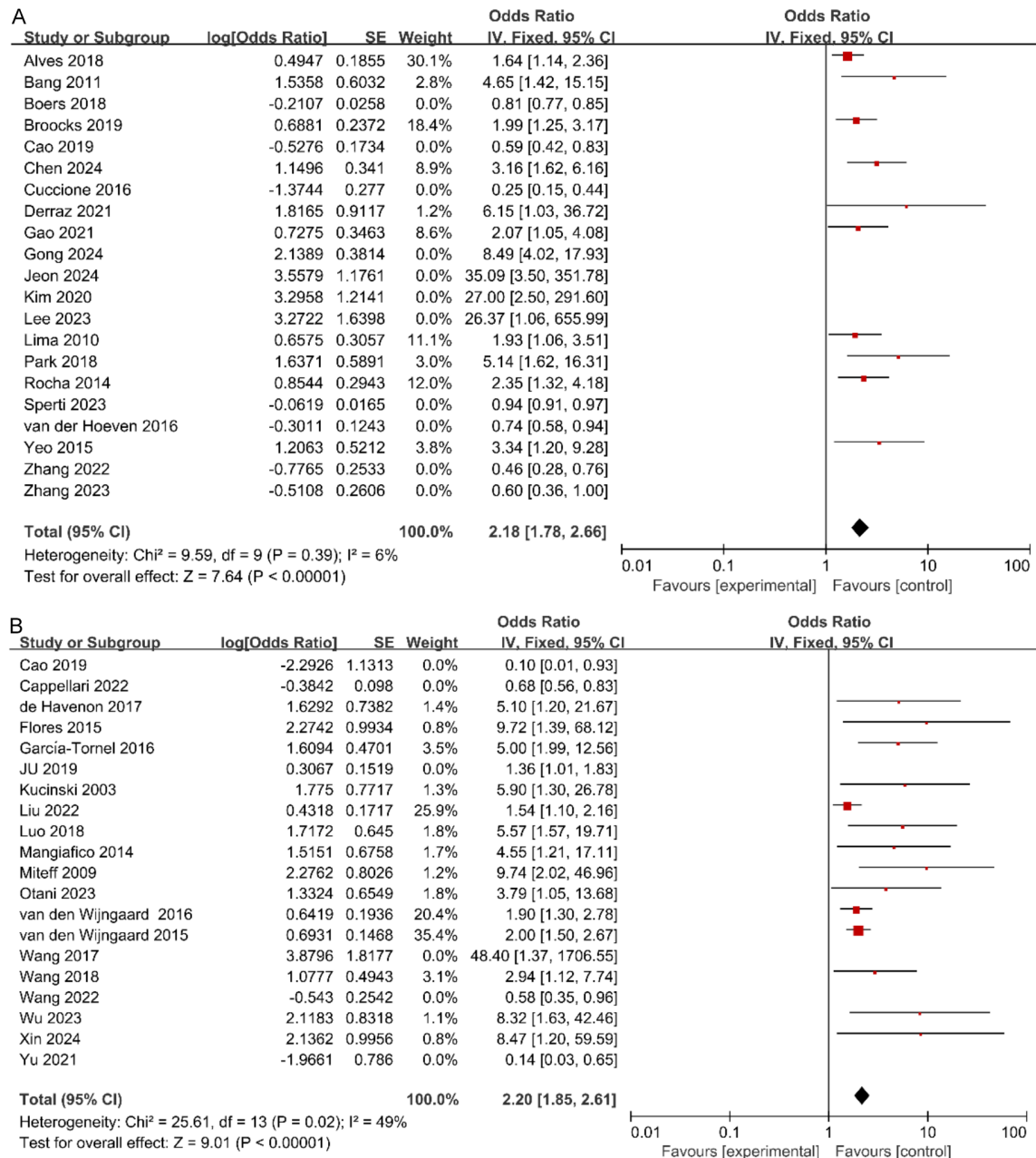


Figure 9. Sensitivity analysis of the subgroup by sample size. A. Large-sample group (≥ 119). B. Small-sample group (< 119).

common pathophysiological mechanisms, regardless of genetic, environmental, or healthcare differences [14]. These results support the global relevance of collateral circulation in ischemic stroke prognosis and emphasize the importance of incorporating collateral assessment into routine clinical protocols across regions.

Sample size-based subgroup analysis demonstrated significant associations in both large-

and small-sample studies, with more stable pooled ORs observed in the large-sample group. This highlights the methodological robustness of larger studies, which are better able to control for confounding variables and minimize random error [52]. Incorporating large-sample studies into meta-analyses enhances both precision and reliability of the findings.

Sensitivity analysis, performed by sequentially excluding individual studies, identified one stu-

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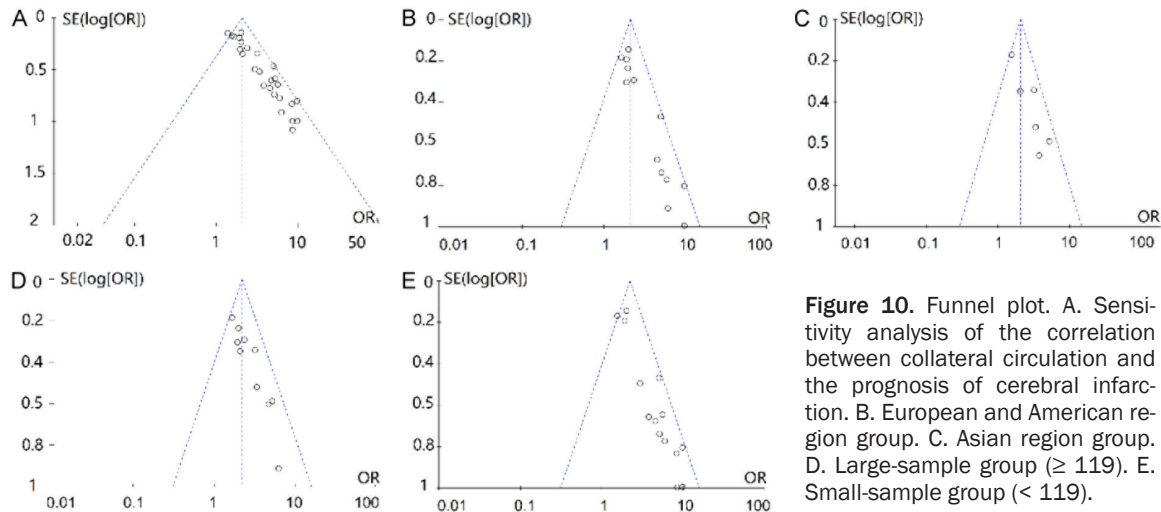


Figure 10. Funnel plot. A. Sensitivity analysis of the correlation between collateral circulation and the prognosis of cerebral infarction. B. European and American region group. C. Asian region group. D. Large-sample group (≥ 119). E. Small-sample group (< 119).

dy that contributed substantially to heterogeneity. Its exclusion notably reduced heterogeneity without markedly altering the pooled effect size, suggesting that the overall findings are robust and not driven by any single study. Additional subgroup-based sensitivity analyses (by evaluation method, region, and sample size) also demonstrated consistent results, underscoring the overall reliability and internal stability of the analysis [53].

Nevertheless, several limitations must be acknowledged. Operational variations in collateral evaluation methods and parameter settings across studies may have introduced bias. The regional categorization into only two broad groups (European/American vs. Asian) may have overlooked more granular ethnic, lifestyle, or healthcare system differences. Additionally, dividing sample sizes based solely on the median may not fully reflect the statistical power of each study. Although funnel plots and Egger's test showed no apparent publication bias, the presence of potential bias cannot be entirely excluded. Future research should adopt more refined designs and standardized methodologies to address these limitations.

Conclusion

This meta-analysis provides robust evidence that good collateral circulation is significantly associated with favorable outcomes in patients with cerebral infarction. Although evaluation methods, study regions, and sample sizes may influence the strength of this association, the

overall results are consistent and stable. Future studies should focus on optimizing collateral assessment techniques and conducting large-scale, multicenter trials to further elucidate the mechanisms by which collateral circulation affects prognosis. Enhanced international collaboration will be essential to advancing the global understanding and management of cerebral infarction.

Disclosure of conflict of interest

None.

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