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Key prognostic risk factors linked to poor functional outcomes in cerebral venous sinus thrombosis: a systematic review and meta-analysis

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Abstract

Background Cerebral venous sinus thrombosis is a rare stroke with several clinical manifestations. Several studies have identified prognostic risk factors associated with poor functional outcomes and established predictive models. This systematic review and meta-analysis assessed the overall effect size of all prognostic risk factors.

Methods A systematic review was conducted to explore all prognostic risk factors in studies published from the initial to June 2024 among 5 Databases included PubMed / Medline, Scopus, EBSCOhost, Web of Science, and Cochran Library. The quality of the methodology was analyzed using the Newcastle–Ottawa Scale. Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 29.

Results Sixty-four studies involving 18,958 participants with a mean age of 38.46 years and females 63.03% were included in the quantitative meta-analysis. Functional outcomes were primarily measured using the Modified Rankin Scale (mRS), with scores ≥ 2 or ≥ 3 indicating poor outcomes in 35.00% and 60.00% of studies, respectively.

For general information, age (lnOR = 0.98, 95% CI 0.53–1.43), intracranial hemorrhage (OR = 3.79, 95% CI 2.77–5.20), and ischemic infarction (OR = 3.18, 95% CI 2.40–4.23) were associated with poor functional outcomes. For general and neurological symptoms, headache (OR = 0.22, 95% CI 0.17–0.29), seizure (OR = 2.74, 95% CI 1.76–4.27), focal deficit (OR = 4.72, 95% CI 3.86–5.78), coma (OR = 11.60, 95% CI 6.12–21.98), and consciousness alteration (OR = 7.07, 95% CI 4.15–12.04) were outstanding factors. The blood biomarkers of NLR (log OR = 1.72, 95% CI 0.96–2.47), lymphocytes (Cohen's d = -0.63, 95 CI -0.78—-0.47), and D-dimer (lnOR = 1.34, 95% CI 0.87–1.80) were the three most frequently reported factors. Parenchymal lesion (OR = 4.71, 95% CI 1.12–19.84) and deep cerebral venous thrombosis (OR = 6.30, 95% CI 2.92–13.63) in radiological images were two frequently reported factors. CVST patients with cancer (OR = 3.87, 95% CI 2.95–5.07) or high blood glucose levels (OR = 3.52, 95% CI 1.61–7.68) were associated with poor functional

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outcomes. In the meta-regression analysis, ischemic infarction ($P=0.032$), consciousness alteration ($P<0.001$), and NLR ($P=0.015$) were associated with mRS prediction.

Conclusions Pooled effect sizes revealed that ischemic infarction, headache, neurological focal deficit, lymphopenia, and cancer were significantly associated with poor functional outcomes, with low to moderate heterogeneity. Consciousness alterations/deterioration and deep cerebral venous thrombosis were also significant prognostic factors, albeit with substantial heterogeneity. The meta-regression analysis showed that the effect sizes of consciousness alterations/deterioration and NLR increased with worsening mRS scores. Other notable risk factors included age, intracranial hemorrhage, seizures, coma, D-dimer, parenchymal lesions, and hyperglycemia. This systematic review provides a comprehensive overview of the prognostic risk factors for poor functional outcomes in patients undergoing CVST, which can guide clinical decision-making and future research.

Trial registration This systematic review and meta-analysis has been registered with INPLASY (International Platform of Registered Systematic Review and Meta-analysis Protocols), and the registration number is INPLASY202480072. The registration period is 14 August 2024.

Keywords Cerebral venous sinus thrombosis, Stroke, Prognosis, Functional outcome

Background

Cerebral venous sinus thrombosis (CVST) is a special type of cerebrovascular disease, that was observed only in 9 patients out of a series of 70 cases (12%) in a prospective population-based clinical study for ischemic stroke of unusual cause in 2001 [1]. The CVST counted 0.5–3% of all stroke subtypes [2–4]. The estimated incidence rate of CVST varied and increased, according to the reference, from 3–4 / 1,000,000 / annually in 2014 [5] of the stroke guideline to 13.9–20.2 / 1,000,000 / annually in 2020 in a population-based cohort study in the USA [6]. A wide range of factors can lead to thrombotic occlusion of the dural venous sinuses or cerebral veins, resulting in the development of various neurological symptoms. Blocking the drainage of intracranial blood circulation can leads to focal cerebral edema, venous cerebral infarction, intracranial hypertension, or even intracranial hemorrhage [7]. The patients' presentations at the first onset of CVST varied from mild to severe, which challenged the accuracy and time of diagnosis [8]. The most frequently reported clinical manifestations include headache, seizures, neurological deficit, coma, consciousness/mental disorders, and even visual disorders provoked by clotting in the ophthalmic vein [9]. The median age at first onset was 41–50.9 years based on the latest nationwide or population-based research [10, 11]. Females, especially during pregnancy and postpartum or when taking contraceptive medication, were more likely to suffer from CVST than males [12], with a reported proportion of 75.3% [13]. There are different instrument tools for functional outcome measurement in CVST, including the Institutes of Health Stroke Scale (NIHSS), Modified Rankin Scale (mRS), Activities of Daily Living (ADL), and Glasgow Outcome Scale (GOS). The division scale of the dichotomy of functional outcome into good (favorable) and poor (unfavorable) was based on different studies. However, the epidemiology of CVST has demonstrated that the clinical or functional outcome of patients with CVST was 79%−91% in a favorable situation after long-term follow-up [5, 14]. Many studies have established models to identify potential risk factors for predicting functional outcomes of CVST during short- or long-term follow-up. Based on different research settings, sociodemographic backgrounds, complications involved, and perspectives, the output of the studies varied from one to another. However, systematic reviews, literature reviews, and meta-analyses that studied CVST mostly focused on diagnosis [15], different medical treatments [15, 16], incidence rate [11], or complications such as heparin-induced thrombocytopenia [17] /COVID-19 [18]. This systematic review and meta-analysis will help summarize all identified risk factors and provide a full perspective on CVST and functional outcome assessment.

Methods

This systematic review and meta-analysis followed the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement. The study protocol was registered in the INPLASY (International Platform of Registered Systematic Review and Meta-analysis Protocols) database (INPLASY202480072) [19].

Inclusion criteria

Studies that met the following criteria were included: (1) human studies were considered with patients aged ≥ 18 years. (2) patients diagnosed with CVST by any neuroradiological examination listed below (e.g., intra-arterial angiography (DSA), magnetic resonance imaging

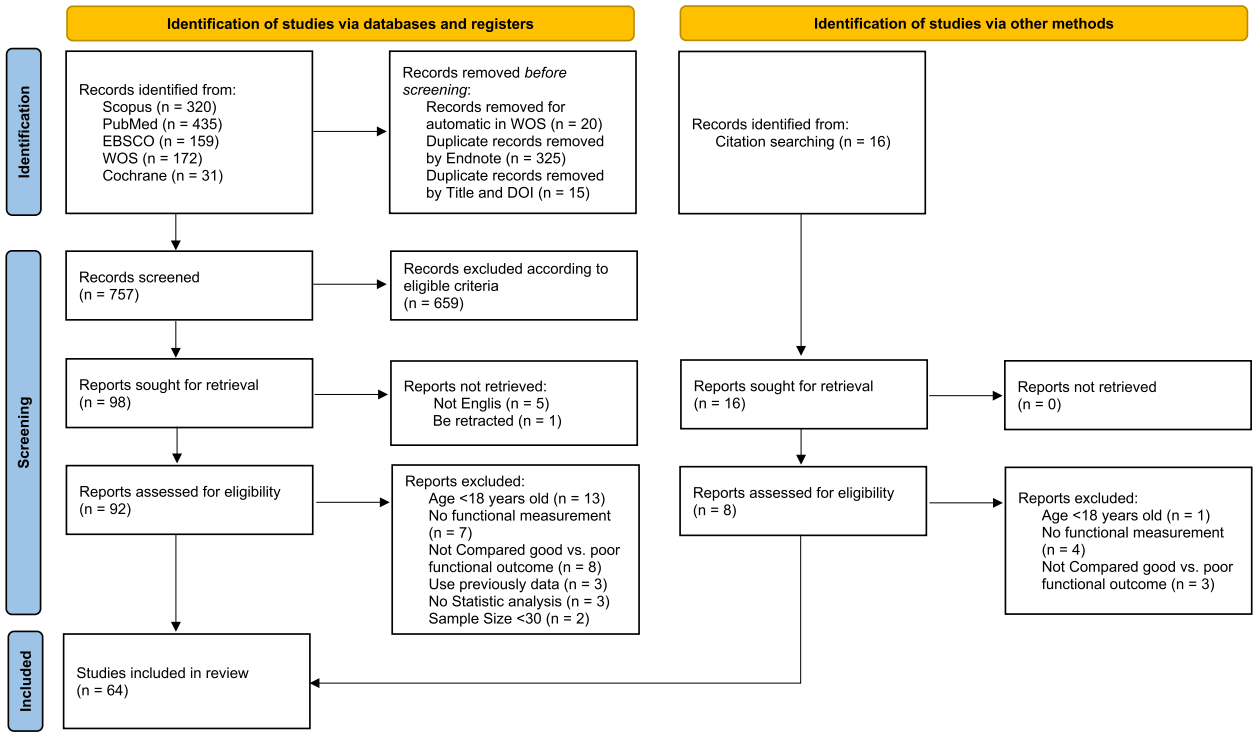


Fig. 1 PRISMA flow diagram

(MRI), MR angiography (MRA), MR venography (MRV), computed tomography venography (CTV), or CT angiography (CTA)). (3) functional outcome measurements should be reported in the research either in different assessment tools (for example, NIHSS, mRS, and ADL), which could reflect physical function in different aspects. (4) Cross-sectional studies, cohort studies, and case–control studies will be involved in the review. (5) Papers concerning the epidemiology, clinical manifestations, treatment, or prognosis, especially with either logistic regression, Cox regression, or any inferential-statistical analysis, were eligible. (6) All publications were written in English from the initial day to June 1, 2024.

Exclusion criteria

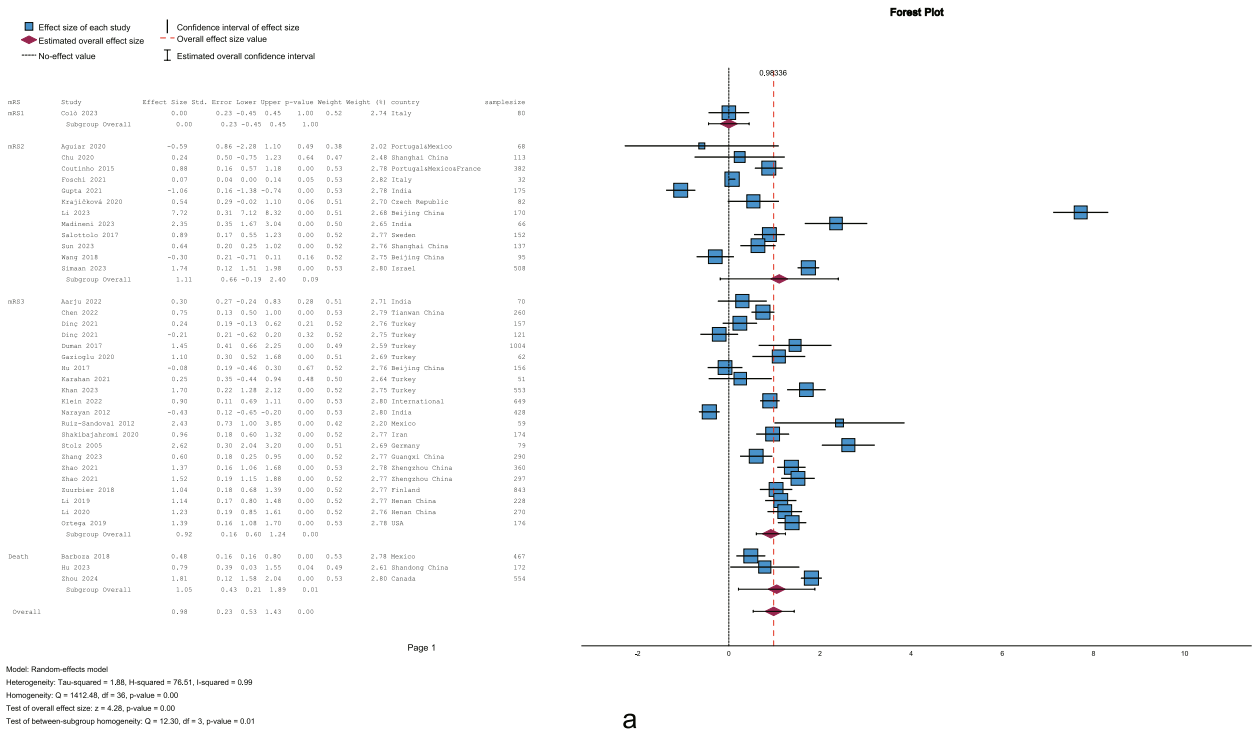
We excluded studies with the following criteria: (1) studies that did not provide empirical data (e.g., reviews, commentaries, opinions, case reports, interviews, theoretical papers, conference abstracts, letters, and gray literature). (2) studies with retinal vein clotting, subarachnoid hemorrhage, or spontaneous intracerebral hemorrhage were excluded. (3) Other disease-related CVST included traumatic brain injury, COVID-19 vaccination, intracranial meningioma, meningitis, cerebral venous system hypoplasia, or malformation. (4) Other thrombus diseases, such as venous thromboembolism (VTE), include deep venous thrombosis (DVT) and pulmonary embolism (PE). (5) Studies looked at how different clinical treatments (medication, rehabilitation, nursing approaches, etc.) affected disease prognosis and consequences. (6) Studies with smaller sample sizes (e.g., fewer than 30 patients), whereas case reports or series were not considered. (7) The full text was not available.

Table 1 Demographics and publication status

Title	Total
Total number of participants	18,958
Mean age (year)	38.46
Female (%)	63.03%
Functional measurement (mRS) (%)	
mRS 1	3.33%
mRS 2	35.00%
mRS 3	60.00%
mRS 6	8.33%
Publication Year	2005–2024
Countries	Number of publications / Sample size
China	23 / 4453
International	9 / 6525
Turkey	6 / 1948
India	6 / 889
Developing countries	41 / 8262
Developed countries	23 / 10,696

Search strategy

The search strategy was designed in accordance with the "Cochrane Guidelines for Systematic Reviews of Health Promotion and Public Health Interventions." There are 5 electronic databases, including PubMed / Medline, Scopus, EBSCOhost, Web of Science, and Cochran Library, were used to search for articles. The selected keywords were based on the PICO strategy. Using Scopus as an example, the search strategy was as follows: ((TITLE-ABS-KEY(("cerebral" OR "intracranial") AND ("venous" OR "vein*" OR "sinus*") AND ("thrombosis" OR "thrombus")) AND TITLE-ABS-KEY("prognosis" OR "prognostic" OR "risk factors" OR "predictive factors") AND TITLE-ABS-KEY("National Institutes of Health Stroke



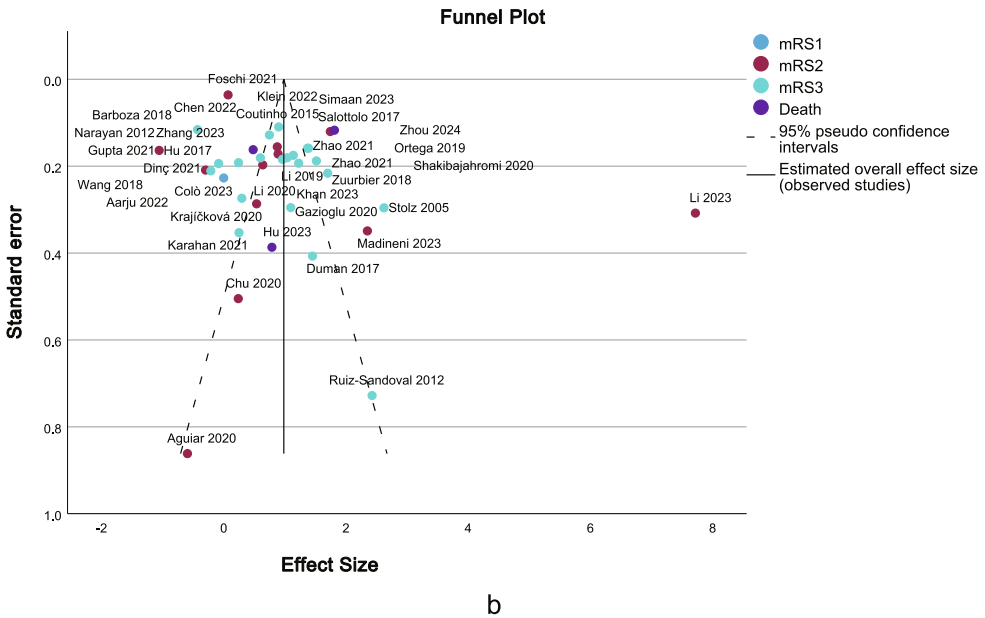


Fig. 2 Meta-analysis with forest plot (**a**) and funnel plot (**b**) of pooled effect size on age

Scale" OR "NIHSS" OR "mRS" OR "Modified Rankin Scale" OR "ADL" or "activities of daily living" OR "Barthel index" OR "functional" OR "function" OR "scale") AND ALL("odds ratio" OR "risk ratio" OR "hazard ratio" OR "logistic regression" or "Cox" OR "regression")) AND (LIMIT-TO (DOCTYPE,"ar")) AND (LIMIT-TO (LANGUAGE, "English"). The search strategies were adjusted according to the different databases.

Study selection

All studies from the selected databases were imported into EndNote 20 for duplication checking. Title/abstract screening was independently performed by two authors (LL and SF). Any discrepancies were resolved by a consultant with the corresponding author as a third party. To ensure accuracy and consistency, Cohen's kappa was reported as agreement for the full text involved in data extraction and quality evaluation before the consensus meeting.

Data extraction and synthesis

A data extraction form was designed in the EXCEL, including Country, Study ID, Author/Year, Subtype of Participants, Sample Size, Functional Outcome Measurement, Level of Cutoff Points between Good and Poor, and prognostic risk factors. Data from full-text articles were extracted by three authors independently (LL, SF, and WW). LL for double checking and reassuring the data.

The prognostic risk factors associated with poor functional outcomes were determined in patients undergoing CVST. All factors were calculated and reported as a percentage of studies in which each risk factor appeared, which hierarchically mapped prognostic risk factors across the included studies.

Statistical analysis

The data extracted from each study were analyzed using SPSS version 29.0. (IBM). More than three studies that

Table 2 Prognostic risk factors associated with poor functional outcomes

Factors	N	Output	Effect size	95% CI	I2	*P* value	*P* value for Meta-regression
Demographic							
Age	37	lnOR	0.98	0.53–1.43	0.987	0.000*	
Gender (Male)	6	OR	2.14	0.52–8.77	0.922	0.290	0.243
Type of stroke							
Intracranial hemorrhage	25	OR	3.79	2.77–5.20	0.761	0.000*	0.214
Ischemic infarction	8	OR fix	3.18	2.40–4.23	0.200	0.000*	0.032*
Clinical manifestation (general)							
Headache	8	OR fix	0.22	0.17–0.29	0.000	0.000*	0.175
Seizure	14	OR	2.74	1.76–4.27	0.796	0.000*	
Clinical manifestation (neurological specific)							
Focal deficit	13	OR fix	4.72	3.86–5.78	0.388	0.000*	0.526
Coma	12	OR	11.60	6.12–21.98	0.854	0.000*	
Consciousness disorder	7	OR	7.07	4.15–12.04	0.740	0.000*	< 0.001*
NIHSS	4	lnOR	1.69	(-)0.09–3.47	0.987	0.060	
Blood Biomarkers							
NLR	7	lnOR	1.72	0.96–2.47	0.963	0.000*	0.015*
Lymphocyte	5	cohens'd fix	−0.63	(-)0.78-(-)0.47	0.184	0.000*	
D-dimer	4	lnOR	1.34	0.87–1.80	0.778	0.000*	
CRP	3	lnOR	2.99	(-)0.40–6.37	0.991	0.080	
Radiology image							
Parenchymal lesion	5	OR	4.71	1.12–19.84	0.900	0.030*	0.379
Deep cerebral venous thrombosis	8	OR	6.30	2.92–13.63	0.719	0.000*	0.390
Complication							
Cancer	6	OR fix	3.87	2.95–5.07	0.424	0.000*	
Blood glucose level	5	OR	3.52	1.61–7.68	0.937	0.000*	
Hemoglobin/anemia	5	OR	1.61	0.96–2.69	0.988	0.070	
Blood pressure	5	OR	7.53	0.55–103.77	0.984	0.130	0.051

*Statistical significant

reported the same outcome measures were included in the quantitative analysis; otherwise, a narrative approach was adopted.

Continuous variables were extracted as mean and standard deviation (SD). Any articles with data not reported as mean and SD but as median and IQR will be converted into mean and SD following the guidelines by Wan et al. [20].

Twelve statistics were used to determine the heterogeneity of the studies, and a threshold of 50% was applied to distinguish between homogeneity and heterogeneity. The fixed-effects model was used for $I2 \leq 50$, and the random-effects model was used for $I2 > 50$ [21]. To visualize the pooled effect size, forest plots were generated. The quality of the bias is presented in the Funnel Plot. The Bubble Plot displays the meta-regression between particular prognostic risk factors and subtype analysis in functional outcome measurement. The effect sizes were indicated as minor (d = 0.2), medium (d = 0.5), and large (d = 0.8) based on hierarchical pooling. The output of $P < 0.05$ as statistically significant.

Quality analysis

LL and SF evaluated the quality of the included studies using the Newcastle–Ottawa scale as a guideline. The cohort, case–control, and cross-sectional studies were all included in the Newcastle–Ottawa scale. Stars were assigned to each observational category. All included studies were independently assessed by LL and SF, and any disagreements were discussed with the corresponding author as a third-party. The categories of quality in evidence were reported as very good (9–10 points), good (7–8 points), satisfactory (5–6 points), and unsatisfactory (0–4 points).

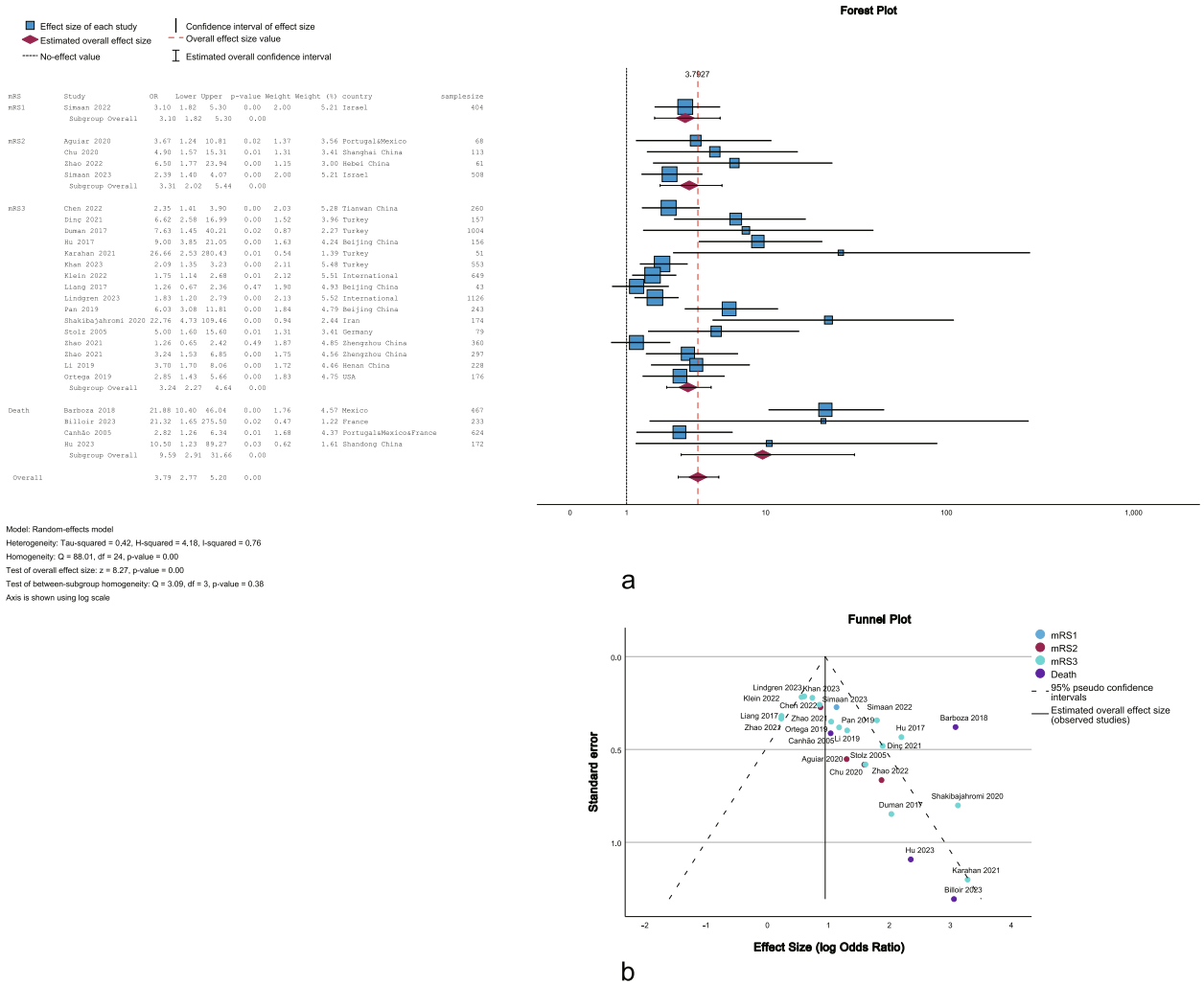


Fig. 3 Meta-analysis with forest plot (**a**) and funnel plot (**b**) of pooled effect size on intracranial hemorrhage

Results

Study selection

The five databases yielded 1117 studies, with an additional 16 discovered through citation searches. After EndNote duplication verification and manual double-checking, the 757 studies were left for title or abstract screening. Following full text reading, 64 publications met the eligibility criteria and were selected for final quantitative analysis in this systematic review (Fig. 1). The PRISMA flow diagram was based on the guideline [22]. The consistency between the two assessors was evaluated, and Cohen's kappa was 0.929 ($P < 0.001$).

Study characteristics

Among the 64 included studies [4, 23–85], 12 were cross-sectional studies, 51 were cohort studies, and one was a case–control study. All studies had sample sizes ranging from 30 to 1,281 participants (a total of 18,957). The publication dates are from 2005 to 2024. The countries that implemented the research included 23 studies in China, 9 studies involving more than two countries for collaboration, 6 studies in India, and 6 studies in Turkey. Among the included studies, 41 were conducted in developing countries, and 23 were conducted in developed countries. No randomization method was used in any study (Table 1).

Study population

Among the 64 included studies, 52 reported the mean age of the patient population [23, 24, 26, 28–30, 32–38, 41–47, 49–56, 59–66, 68, 70–79, 81–85], and 37 studies reported on the age difference between good and poor functional outcomes [23, 24, 28, 32–37, 39, 41–46, 49, 50, 52, 54, 59, 61, 64–66, 70–72, 75–77, 79, 80, 82–85]. The pooled mean age was 38.46 years (range 18–87), and the pooled effect size of age was 0.98 (95% CI: 0.53–1.43, I2 = 0.987, $P = 0.00$) (Fig. 2).

Of the 57 studies reporting data on sex distribution, females accounted for 63.03%, and 6 studies reported males with pooled effect size in Odds Ratio (OR) of 2.14 (95% CI: 0.52–8.77, I2 = 0.922, $P = 0.290$) as a specific risk factor for poor functional outcomes but without statistical significant [28, 33, 52, 56, 65, 78].

Functional outcome measurements

All studies reported functional outcome measurements of patients using the mRS at discharge or short-term

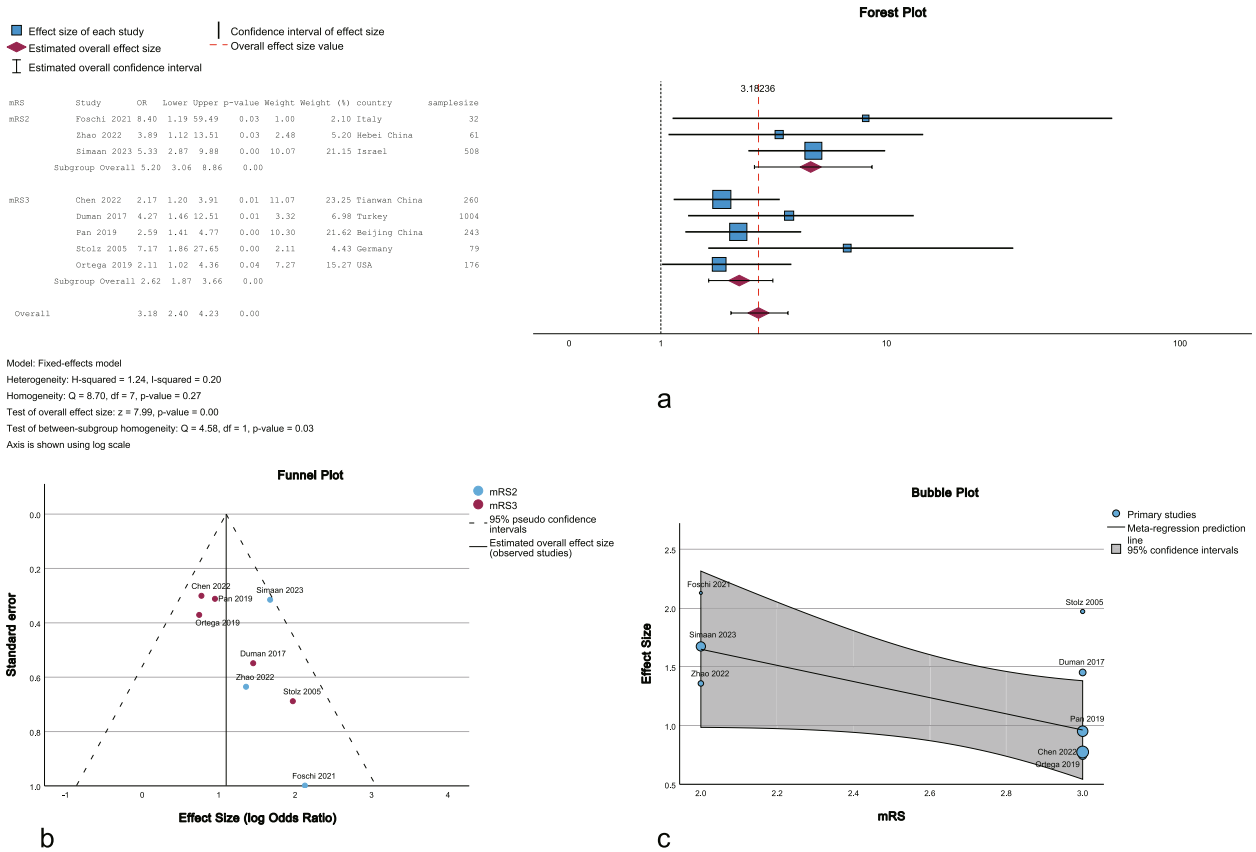


Fig. 4 Meta-analysis with forest plot (**a**), funnel plot (**b**) and bubble plot (**c**) of pooled effect size on ischemic infarction

(e.g., 3 months) or long-term (12 months) follow-up, and dichotomized as good (favorable) or poor (unfavorable) according to the study design. The mRS was classified into 7 levels representing different severe neurological deficits in patients from different settings. Patients with mRS scores of 0 as no symptoms; 1 as mild symptoms but no disability (0–1 also considered as independent); 2 as minimal disability; 3 as moderate disability and could walk without help but required daily assistance; 4 as moderately severe disability and could not walk without help as well as need daily assistance; 5 as severe disability with bedridden and continuous nursing care (3–5 as dependent); and 6 as dead [39, 43]. Different studies have categorized the mRS measurement of functional outcomes into binary variables based on different score levels. The percentage of studies reporting an mRS score of ≥ 1, 2, 3, or 6 as the division of poor clinical outcomes was in 3.33%, 35.00%, 60.00%, and 8.33%, respectively (Table 1).

Prognostic risk factors

The prognostic risk factors associated with poor functional outcomes were extracted from all included studies and are presented as percentages. The categories were organized by demographic setting, stroke type, clinical manifestation (general & neurological specific), examination of blood biomarkers, radiological images foreseen, and complications (Table 2).

Intracranial hemorrhage and ischemic attack

There were 25 studies reported intracranial hemorrhage as a prognostic risk factor for poor function [24, 28, 30–33, 36, 39, 44–46, 49, 50, 55, 56, 62, 66, 68, 70, 76–78, 83–85], and 8 studies about the ischemic infarction [32, 39, 41, 62, 70, 78, 84, 85]. The pooled data show that the effect size (OR) of intracranial hemorrhage was 3.79 (95% CI: 2.77–5.20, I2 = 0.761, P = 0.00) and 3.18 (95% CI:2.40–4.23, I2 = 0.200, P = 0.00) in ischemic infarction for effect size, which was represented in the fix-effects model (Fig. 3) (Fig. 4a and b).

Geneal vs. neurologically specific manifestations

Seizure and headache are the two most frequently reported clinical manifestations in patients undergoing CVST. The proportions were 21.88% (14/64) and 12.50% (8/64), respectively. The pooled effect size (OR) was 2.74 (95% CI: 1.76–4.27, I2 = 0.796, P = 0.00) in seizure [31, 33, 34, 38, 42, 44, 51, 54, 55, 57, 60–62, 70] (Fig. 5). The homogeneity test for headache was not statistically

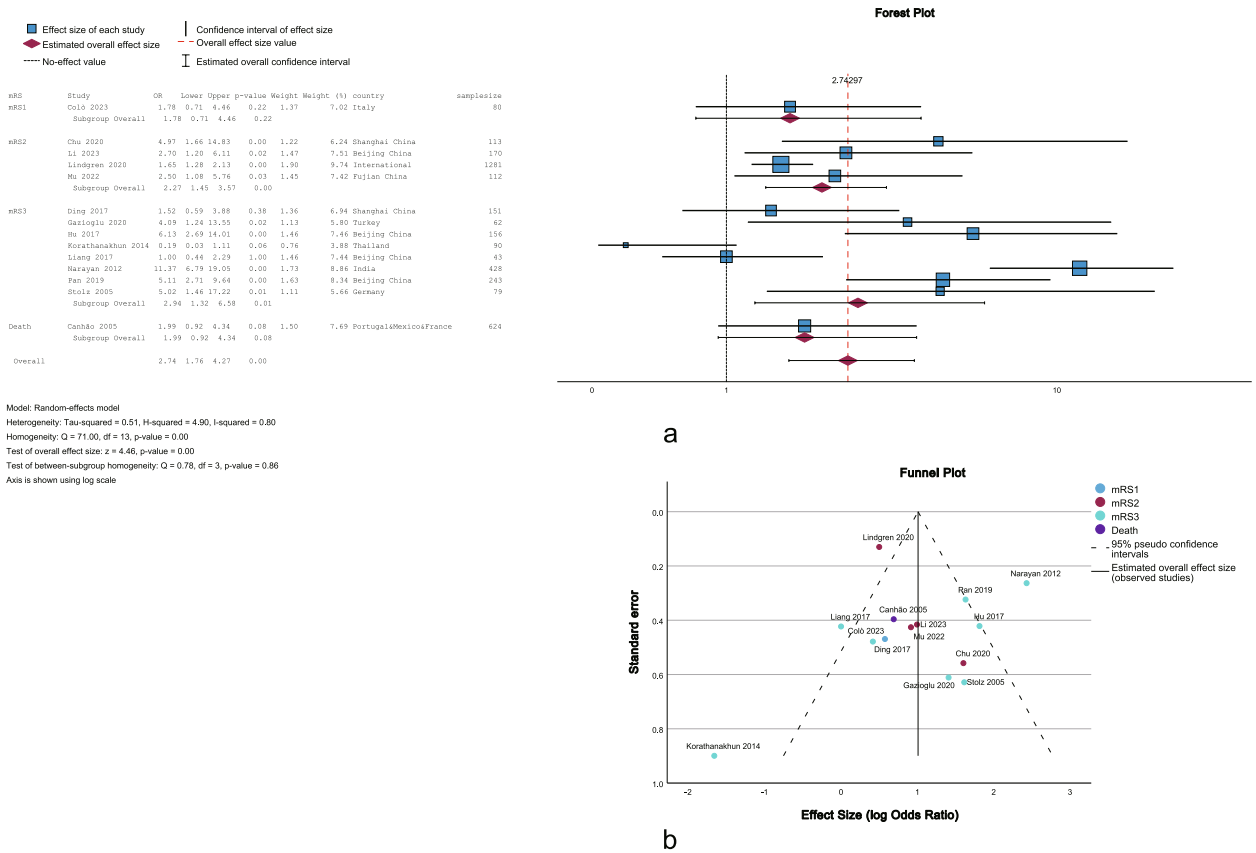


Fig. 5 Meta-analysis with forest plot (**a**) and funnel plot (**b**) of pooled effect size on seizure

significant ($P=0.000$), and the fix-effects model was used with a pooled effect size (OR) of 0.22 (95% CI: 0.17–0.29, I2 = 0.00, $P=0.00$) [23, 32, 35, 65, 66, 75, 84, 85] (Appendix 1).

The neurological specific manifestation list below was organized in percentage descent and included focal deficit (13/64) [23, 39, 44, 49, 51, 52, 56, 61, 62, 65, 66, 84, 85], coma, which was measured in the Glasgow Coma Scale (12/64) [31, 40, 43–46, 50, 56, 76, 77, 82, 83], consciousness disorder (change/deterioration) by physician examination (7/60) [28, 32, 39, 54, 61, 62, 66], and NIHSS Assessment (4/60) [33, 44, 50, 70]. The pooled effect size for focal deficit (OR = 4.72, 95% CI: 3.86–5.78, I2 = 0.388, $P=0.00$) was calculated in the fix-effects model with lower heterogeneity (Fig. 6). Coma and consciousness were reported to have pooled effect size (OR) of 11.60 (95% CI: 6.12–21.98; I2 = 0.854, $P=0.00$), and 7.07 (95% CI: 4.15–12.04, I2 = 0.740, $P=0.00$), respectively (Appendix 2). The meta-regression analysis of consciousness disorder revealed that the effect size was increasing among the functional measurements in mRS ($P<0.001$ in Wald Chi-Square) (Fig. 7). The pooled effect size (log OR) in the NIHSS Assessment was not statistically significant, with an output of 1.69 (95% CI: −0.09–3.47, I2 = 0.987, $P=0.060$) in SPSS.

Inflammatory biomarkers of blood

The neutrophil-to-lymphocyte ratio (NLR), absolute lymphocyte count, D-dimer level, and C-reactive protein (CRP)/High-sensitive C-reactive protein level, were four prognostic risk factors reported in more than 3 studies. The statistically significant pooled effect size in NLR (log OR = 1.72, 95% CI: 0.96–2.47, I2 = 0.963, $P=0.00$) [26, 46, 48, 71, 72, 76, 82] (Fig. 8a and b), D-dimer (log OR = 1.34, 95% CI: 0.87–1.80, I2 = 0.778, $P=0.00$) [30, 32, 71, 83], and lymphocyte (Cohen's d = −0.63, 95% CI: −0.78 to −0.47, I2 = 0.184, $P=0.000$) [71, 76, 77, 82, 83] were reported (Appendix 3 and 4). The meta-regression analysis showed that the effect size of NLR increased as mRS score worsened (Wald Chi-Square $P=0.015$) (Fig. 8c).

Radiology image

The position of the thrombus in a specific area of the cerebral venous system was detected during radiological

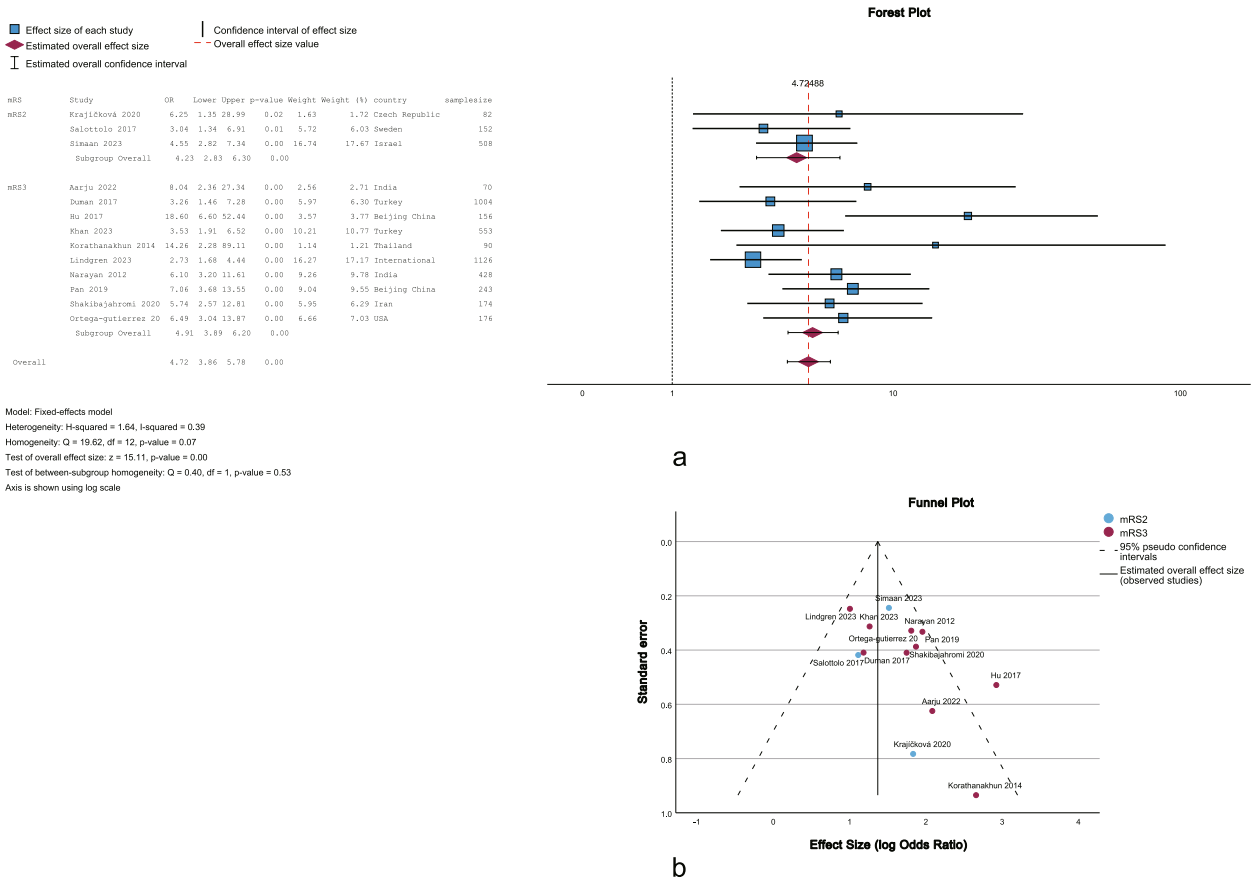


Fig. 6 Meta-analysis with forest plot (**a**) and funnel plot (**b**) of pooled effect size on focal deficit

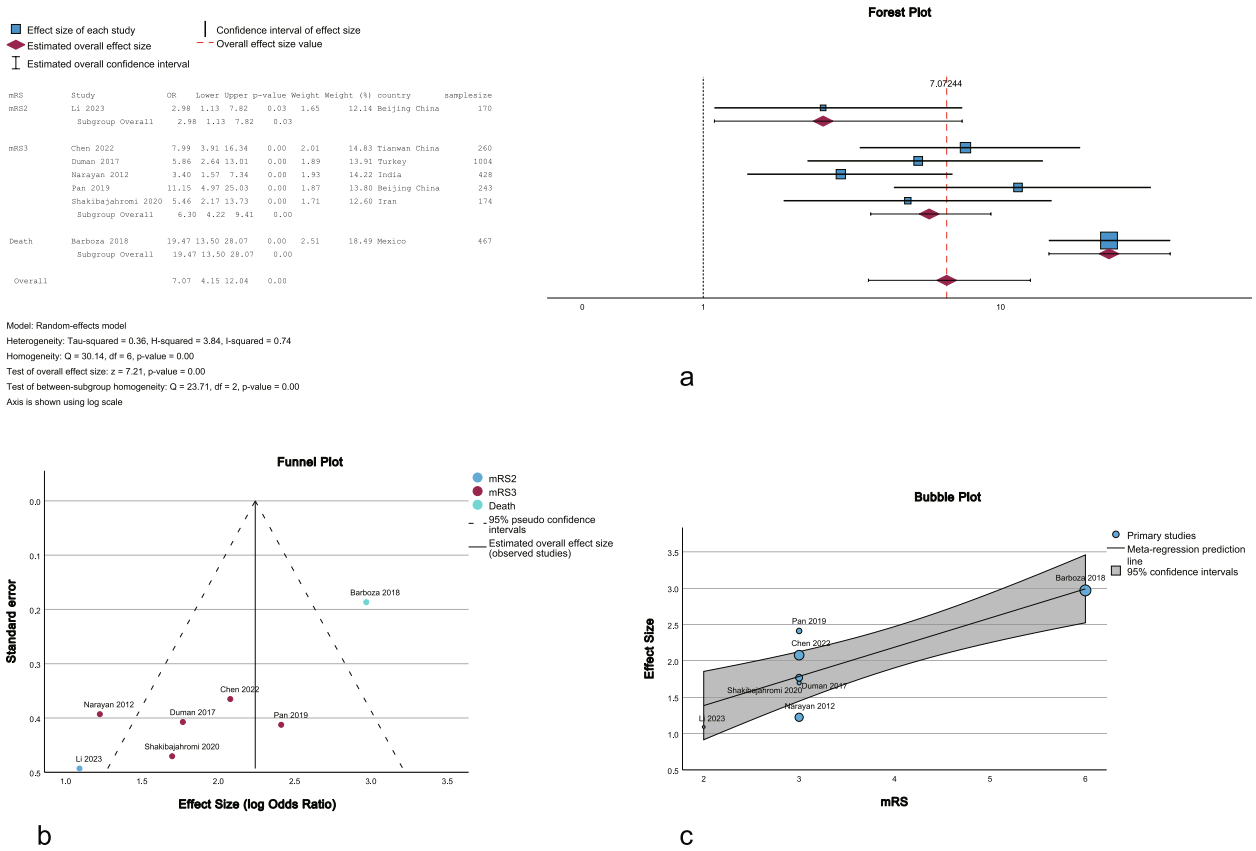


Fig. 7 Meta-analysis with forest plot (**a**), funnel plot (**b**) and bubble plot (**c**) of pooled effect size on consciousness

examination. Deep cerebral vein (venous system) thrombosis has been reported in 8 studies [31, 40, 45, 46, 61–63, 76]. The pooled effect size (OR) was 6.30 (95% CI: 2.92–13.63, I2 = 0.719, *P* = 0.00) (Appendix 5). Parenchymal lesions were reported in 5 studies, and the pooled effect size (OR) was 4.71 (95% CI: 1.12–19.84, I2 = 0.900, *P* = 0.03) [28, 31, 37, 39, 54] (Appendix 6).

Complication

Cancer (6/64) and hyperglycemia (5/64) were statistically significant prognostic risk factors for poor functional outcome. The pooled effect size (OR) was 3.87 (95% CI: 2.95–5.07, I2 = 0.424, *P* = 0.00) for cancer (Fig. 9) [39, 50, 56, 63, 79] and 3.52 (95% CI: 1.61–7.68, I2 = 0.937, *P* = 0.02) for glucose [44, 56, 74, 81] (Appendix 7). The lower hemoglobin level/anemia (5/64), and higher blood pressure/hypertension (5/64) were the other two factors that were mostly reported. However, the pooled effect size was not statistically significant ($P \geq 0.05$) (Table 2).

Quality assessment

Of the 64 studies on CVST patients, 12 were cross-sectional studies, 51 were cohort studies, and 1 was a case–control study. The quality of each study was assessed by accumulating stars based on the description of evidence in each category, with a total score of 10. The percentage of good and satisfactory quality in the cross-sectional studies were 41.67% and 58.33%. In the cohort studies, the qualities of very good, good, and satisfactory were 5.88%, 82.35%, and 11.76%, respectively. There was only one case–control study and the quality was satisfactory (6/10) (Tables 3, 4 and 5).

Discussion

Our study systematically collected prognostic risk factors and quantitatively summarized their effect sizes in on poor functional outcomes in patients undergoing CVST. Following a comprehensive search strategy, we identified 64 studies from the past 20 years that performed statistical analyses of prognostic risk factors to compare good (favorable) and poor (unfavorable) functional outcomes. The quality of each study was assessed using the Newcastle–Ottawa scale for cross-sectional, cohort, and case–control studies. Of these, 50 studies (78.13%) scored more than 7 out of 10 on the Newcastle–Ottawa scale, indicating good evidence of quality. Most studies collected adequate data from

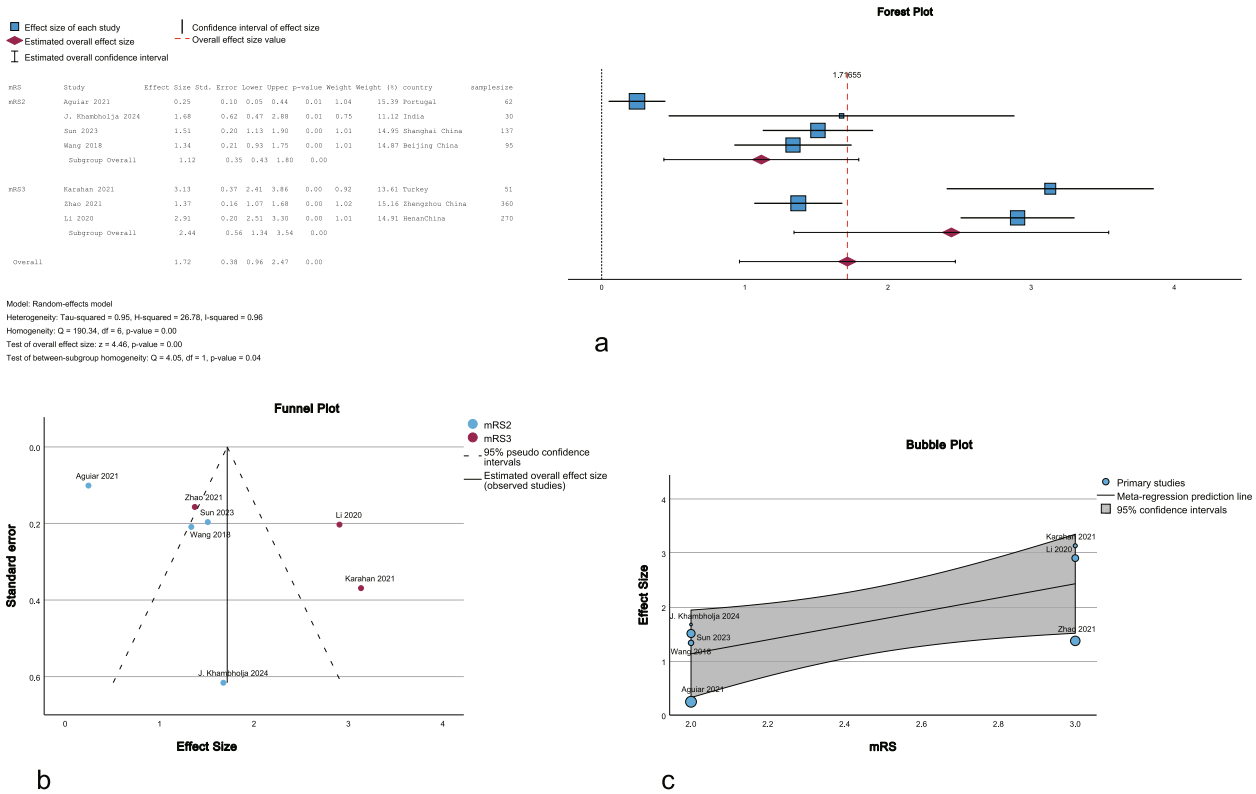


Fig. 8 Meta-analysis with forest plot (**a**), funnel plot (**b**) and bubble plot (**c**) of pooled effect size on nlr

representative settings. In 75% (48/64) of the studies, the sample size exceeded 100, with only one study limited to 30 patients due to COVID-19 restrictions.

The pooled effect size, with low (I2: 0–25%) to moderate (I2: 25–50%) heterogeneity and statistical significance ($P < 0.05$), indicated that ischemic infarction, headache, neurological focal deficit, absolute lymphocyte count, and cancer were significant prognostic risk factors for poor functional outcomes in patients undergoing CVST. Consciousness impairment with substantial heterogeneity emerged, as a more significant risk factor for poor outcomes, a pattern also observed in patients with deep cerebral venous thrombosis.

Age and sex were consistently reported as important variables in many national and population-based epidemiological studies on CVST. Three recent publications since 2023 have highlighted these two variables. A national cohort study from Denmark reported a median age of 41 years for patients with CVST, with 67% being women [10]. A population-based systematic review and meta-analysis from Canada found a mean age of 50.9 years, with 55.4% women [79]. A multicenter multinational prospective observational study in the USA (2000–2018) reported a median age of 46 for men and 37 for women, with women comprising 75.32% of the cohort [13]. CVST is more common than conventional stroke. The global stroke burden study (November 2018 to December 2021) took age ≥ 65 years old as a crucial population as previous [86]. Another retrospective cohort study among 223,358 stroke survivors reported a mean age of 64.8 ± 10.9 years [87]. In our review, age was a statistically significant prognostic risk factor, although high heterogeneity persisted, even in subgroup analyses based on mRS scores. Different studies used different cutoff value to define poor functional outcomes. Younger patients may have better resilience following stroke, which could influence long-term outcomes after endovascular thrombectomy [88]. Although women were reported to be more frequently affected by CVST, gender was not a significant prognostic factor for poor outcomes due to high heterogeneity and limited reporting.

The effect size and number of studies were higher for in intracranial hemorrhage than for ischemic infarction. However, homogeneity was better in ischemic infarction. Intracranial hemorrhage was more prevalent among patients with neurological deficits, consistent with the findings of prior reviews and stroke guidelines [89, 90].

Headache and seizure are common initial symptoms of CVST, as reported in many studies, including the 2019 CVT update by Ferro & Susa [3]. In our systematic review,

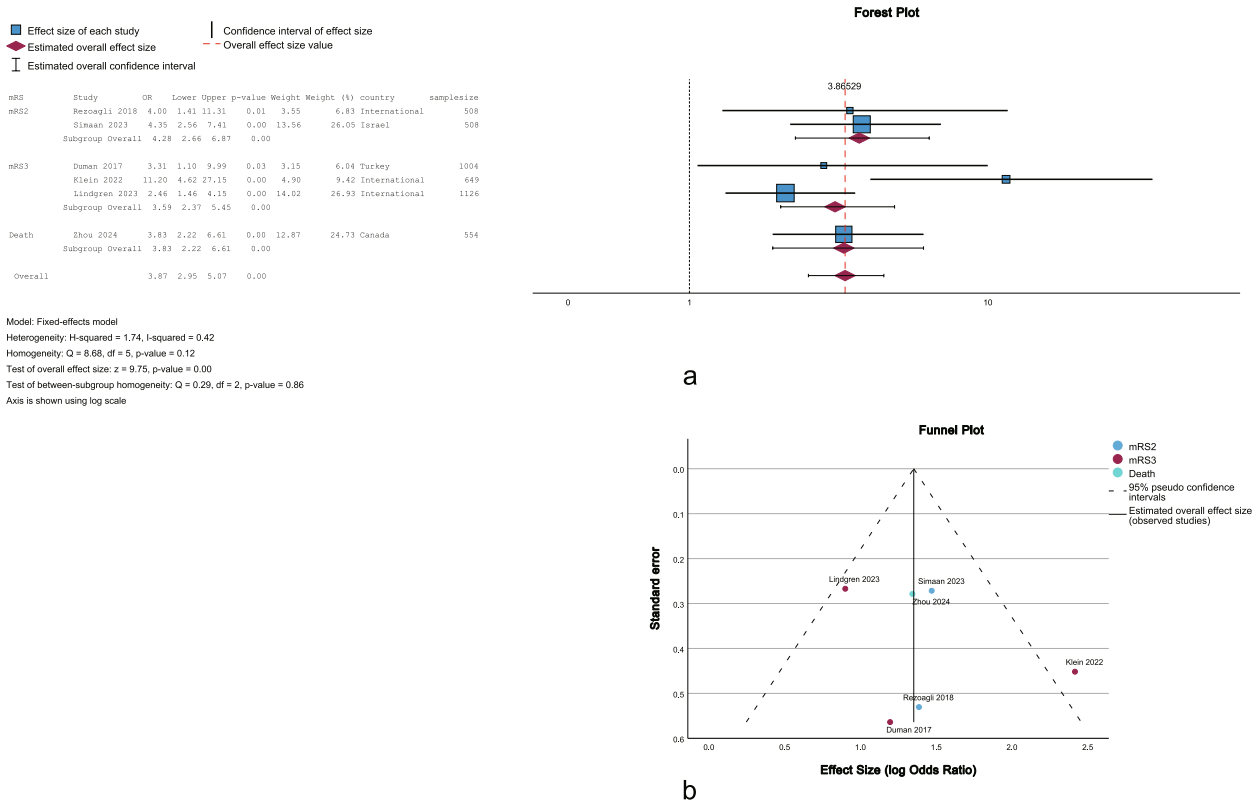


Fig. 9 Meta-analysis with forest plot (**a**) and funnel plot (**b**) of pooled effect size on cancer

the pooled effect size (OR) was less than 1 with moderate heterogeneity (I2 = 0.52). According to the raw data, patients with headache had a statistically better functional outcome. This finding was not previously reported, potentially because of the variability in headache types and severity, which were not standardized across the studies [15]. All studies included in this review were not reported regarding specific degree or properties. In addition, patients without headache were more likely to experience seizure or hemiparalysis. Epileptic seizures after CVST were an independent risk factor, with an OR of 5.66 (95% CI 3.83–8.35) in a meta-analysis [91].

Table 3 Newcastle-Ottawa Scale for cross-sectional studies

First author (year)	Selection				Comparability	Outcome		Total
	Representativeness of the sample	Sample size	Nonrespondents	Ascertainment of exposure	The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled	Assessment of outcome	Statistical test	
Aguiar (2019) [25]	*	118	*	*	**	*	*	8/10
Canhão (2005) [31]	*	624		*	*	*	*	6/10
Chen (2022) [32]	*	260		*	**	*	*	7/10
Coutinho (2015) [35]	*	382			**	*	*	6/10
Ding (2017) [38]	*	151		*	**	*	*	6/10
J.Khambholja (2024) [48]		30		*	*	*	*	5/10
Liang (2017) [55]		43	*	*	**	*	*	7/10
Mu (2022) [60]		112	*	*	**	*	*	7/10
Ortega-gutierrez (2019)	*	176		*	**	*	*	7/10
Shakibajahromi (2020) [66]		174		*	**	*	*	6/10
Sun (2023) [71]		137		*	**	*	*	6/10
Wu (2020) [74]		160		*	**	*	*	6/10

*As stars that given based on the description of evidence in each category

Table 4 Newcastle-Ottawa Scale for cohort studies

First author (year)	Selection				Comparability	Outcome			Total
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study. (yes / no)	Comparability of cohorts based on the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Aarju (2022) [23]	*	*	*		**	*	3 years	62/70	8/10
Aguiar (2020) [24]	*	*	*		**	*	4 years	68/74	8/10
Aguiar (2021) [26]	*	*	*		**	*	90 days	62	8/10
Bakradze (2023) [27]	*	*	*		**	*	90 days	935	8/10
Barboza (2018) [28]	*	*	*		**	*	90 days	*	8/10
Barboza (2015) [29]		*	*		**	*	median 18 months	100/126	7/10
Billoir (2023) [30]	*	*	*		**	*	median 11.9 months	223/231	8/10
Chu (2020) [33]	*	*	*		*	*	6 months	113	7/10
Colò (2023) [34]	*	*	*		**	*	90 days	80	8/10
Dinç (2021) [36, 37]	-	*	*		**	*	3 months	157	7/10
Dinç (2021) [36, 37]		*	*		**	*	3 months	120/121	7/10
Duman (2017) [39]	*	*	*		**	*	12 months	691/1104	8/10
Ferro (2010) [40]	*	*	*		**	*	median 16 months	392	8/10
Foschi (2021) [41]	*	*	*		**	**	90 months	32	9/10
Gazioglu (2020) [42]		*	*		**	*	12 months	37/62	6/10
Gupta (2021) [43]	*	*	*	*	**	*	12 months	175	9/10
Hu (2017)		*	*		**	*	median 24 months (IQR: 18–35)	156	7/10
Hu (2023) [45]	*	*	*		**	*	12 months	172	8/10
Karahan (2021) [46]		*	*		**	*	6 months	51/51	7/10
Karthik (2022) [47]		*	*		*	*	12 months	38/123	5/10
Khan (2023) [49]	*	*	*		**	*	30 days	533 CVT	7/10
Klein (2022) [50]	*	*	*		**	*	90 days	554/801	8/10
Krajíčková (2020) [52]	*	*	*		**	*	3–4 months	82	8/10
Li (2021) [53]		*	*		*	*	6 months	156	6/10
Li (2023) [54]	*	*	*		**	*	6 months	170	8/10
Li (2020) [82]	*	*	*		**	*	22 months (IQR: 6-66)	270/297	8/10
Li (2019) [83]	*	*	*		**	*	22 months (IQR: 6-66)	228/260	8/10
Lindgren (2023) [56]	*	*	*		**	*	365 days (IQR 113–720).	1126/1455	8/10
Lindgren (2020) [57]	*	*	*		**	*	3 months	1106/1374	8/10
Liu (2019) [58]		*	*		**	*	6 months	220/263	7/10
Liu (2018) [4]		*	*		**	*	6 months	238/263	7/10
Madineni (2023) [59]		*	*		**	*	90 days	66	7/10

Table 4 (continued)

First author (year)	Selection				Comparability	Outcome			Total
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study. (yes / no)	Comparability of cohorts based on the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Narayan (2012) [61]	*	*	*		**	*	12 months	373/428	8/10
Pan (2019) [62]		*	*		*	*	median 18 monthe (IQR:12-36)	134/159	6/10
Rezoagli (2018) [63]	*	*	*		**	*	median 6 years	483/508	8/10
Ruiz-Sandoval (2012) [64]	*	*	*		**	*	30 days	59	8/10
Salottolo (2017) [65]	*	*	*		**	*	5 months	149/152	8/10
Silvis (2020) [67]	*	*	*		**	*	median 6 months (IQR:5-13)	874	8/10
Simaan (2023) [85]	*	*	*		**	*	90 days	488/508	8/10
Simaan (2022) [68]	*	*	*		**	*	90 days	404	8/10
Song (2018) [69]		*	*	*	**	*	median 22 months	228/263	8/10
Stolz (2005) [70]		*	*		**	*	12 months	58/79	7/10
Wang (2018) [72]		*	*		**	*	3-12 months	95	7/10
Wei (2023) [73]		*	*		**	*	6 months	306	7/10
Zhang (2023) [75]	*	*	*		**	*	1 month	280/290	8/10
Zhao (2021) [76, 77]		*	*		**	*	median 9 months	360/421	7/10
Zhao (2021) [76, 77]		*	*		**	*	3 months	297/324	7/10
Zhao (2022) [78]		*	*		*	*	Not clearly stated	61	6/10
Zhou (2024) [79]	*	*	*	*	**	*	30 days to 1 year follow up	508/554	9/10
Zuurbier (2018) [80]	*	*			**	*	Not state	571/843	6/10
Zuurbier (2016) [81]	*	*	*		**	*	median 6 months	308/380	8/10

*As stars that given based on the description of evidence in each category

Table 5 Newcastle-Ottawa Scale for case-control studies

First author (year)	Selection				Comparability	Exposure			Total
	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of case and controls based on the design or analysis controlled for confounders	Assessment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Korathanakhun (2014) [51]	*	*			*	*	*	107/107	6/10

*As stars that given based on the description of evidence in each category

Specific neurological symptoms, including focal deficit, coma, and consciousness deterioration. The pooled effect size of focal neurological deficits was a stable prognostic risk factor associated with poor functional. Our systematic review was performed quantitatively in accordance with the updated research in CVT by Ferro et al. in 2019 [3].

Inflammation plays a crucial role in venous infarction, and several inflammatory markers are associated with CVST [92]. Absolute lymphocyte counts lower in patients with poor outcomes, whereas the neutrophil-to-lymphocyte ratio (NLR) is elevated [26, 71]. One study that compared inflammatory markers between CVST patients and CVST mimics (those with anatomical variants in the cerebral sinuses) found that the NLR was lower in CVST mimics [93]. The pooled effect size for CRP was significantly heterogenous and did not significantly differ despite its common use as a marker of systemic inflammation.

Thrombus in the deep cerebral venous system, distinct from the superior/inferior sagittal sinus, straight sinus, transversal sinus, and sigmoid sinus, had a pooled OR of 6.30 with high heterogeneity (I2 = 0.719). Calandrelli et al. [94]established a scoring system to evaluate the deep cerebral venous system (DCVT), involving the veins of Rosenthal, internal cerebral veins, and veins of Galen, as predictors of clinical features.

Malignancy and high blood glucose levels were also associated with poor functional outcomes in patients with CVST. The link between malignancy and mortality is well established. The SI_2NCAL_2C score system was developed [56] and externally validated [95] to predict poor outcomes in CVS, with cancer as a key factor. Cancer-associated thrombosis is common in various malignancies and driven by different coagulation pathways. Patients with active cancer have a higher risk of venous thromboembolism (VTE) than the general population [96]. Hematologic disorders, including hematologic malignancies, have been a commonly unrecognized cause of cerebral sinus venous thrombosis since the 1990s [97]. More studies have highlighted the importance of hematologic disorders as a risk factor for venous thrombosis (and CVST) [7, 47, 59, 75]. Based on the Virchow triad (the role of blood hypercoagulability, blood flow dynamics, and endothelial damage), changes in blood components were reported in many studies, for example, thrombophilia [98, 99], polycythemia [47, 59], and hyperhomocysteinemia [59, 61], which were associated with CVST or a risk factor of CVST, and both of them were subtypes of hematologic disorder. In considering functional outcomes, anemia was reported in 5 studies. However, the pooled effect size showed no significant P-value in the chi-square test between good and poor outcomes. Patients with hematologic disorders present with CVST. In this case, anticoagulation was symptomatic treatment. Guidelines for hematologic malignancy-associated venous thrombosis have been developed [96]. Studies focused on glucose metabolism also demonstrated hypoglycemia as a risk factor for deep vein thrombosis (DVT) based on preclinical mechanism research [100].

Limitations

This systematic review pioneered the exploration and quantitative analysis of prognostic risk factors for short- or long-term poor functional outcomes among patients undergoing CVST and facilitated evidence-based clinical practice and decision making. However, our review has some limitations.

The eligible articles written in English in this study could increase the possibility of losing some studies conducted and published in Non-English countries and journals. Further data collection from a wider range of studies is required.

The heterogeneity of the pooled effect size for some factors was high, even applied with subgroup analysis with different cutoff points in mRS for functional division in binary outcomes between good/favorable and poor/unfavorable. Although a higher I2 value in a meta-analysis should be cautiously accepted, it is important to note that many factors (such as different countries, specific

demographic backgrounds, and lifestyle, et al.) are inherent to the nature of an observational study.

Conclusions

Our systematic review and meta-analysis identified multiple prognostic risk factors associated with poor functional outcomes in CVST. Ischemic infarction, neurological focal deficits, impaired consciousness, absolute lymphocyte count, and cancer were prominent factors related to poor outcomes. Furthermore, intracranial hemorrhage had a larger impact magnitude, and ischemic infarction demonstrated greater homogeneity across studies. inflammatory biomarkers, particularly the neutrophil-to -lymphocyte ratio (NLR), were also associated with poor outcomes; however, certain markers, such as CRP, showed heterogeneity. Headache and seizure, despite being frequent symptoms, had inconsistent relationships with outcomes, possibly due to heterogeneity in clinical presentation and study methodology. Further research is needed to refine prognostic models and tailor treatment strategies for at-risk populations.

Abbreviations

CVST	Cerebral venous sinus thrombosis
NIHSS	Institutes of Health Stroke Scale (NIHSS)
mRS	Modified Rankin Scale
ADL	Activities of Daily Living
GOS	Glasgow Outcome Scale
OR	Odds Ratio
NLR	Neutrophil-to-lymphocyte ratio
CRP	C-reactive protein

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

Supplementary Material 6.

Supplementary Material 7.

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Authors' contributions

The authors' contributions were as follows: LLL: designed the research, screening process, data extraction, quality evaluation, and initial draft of the manuscript; SFL: performed the screening process, data extraction, quality evaluation, and data analysis; As a co-first-author, SFL contribute equally to this study as LLL does. WW: clinical reasoning, data extraction, statistical analysis, result interpretation; XKH: problem solving for any discrepancy in screening process; MHR: critically revised the manuscript; RRD: manuscript polish, and has primary responsibility for final content; and all authors contributed to critically reviewing the manuscript, and read and approved the final manuscript.

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Data availability

Datasets are available through the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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