frontiers | Research Topics

Reviews in stroke

Edited by
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Reviews in: Stroke

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Editorial: Reviews in: stroke

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stroke, acute, diagnostic, etiology, neuroimaging, intervention, rehabilitation

Editorial on the Research Topic
Reviews in: stroke

Stroke constitutes a significant global health challenge, with 12.2 million new strokes per year worldwide, a mortality of 6.5 million, and a cumulative disability of 143 million disability-adjusted life years [DALYs; (1)]. To confront this challenge, the clinical and scientific community is dedicated to addressing various aspects, including primary and secondary prevention, acute stroke care, biomarkers, patient stratification, and neuroplasticity and rehabilitation. The approaches involved encompass both clinical randomized trials and hypothesis-driven or exploratory research.

The global efforts in stroke research result in a substantial number of publications per year, as evidenced by a swift exploration of the PubMed database using the search term "stroke," which yielded over 34,000 references in the year 2022 only. This deluge of literature highlights the necessity for meta-analyses and systematic reviews, which aggregate and synthesize a large body of evidence from multiple studies using comprehensive and systematic approaches. We, therefore, have collaborated to curate this Research Topic, with the following objectives: (i) increasing the statistical power by combining data from multiple clinical and preclinical studies and thereby helping to estimate the robustness of an effect; (ii) enhancing the generalizability of findings and fostering the application of preclinical research insights into broader clinical applications; and (iii) exploring subgroups or moderating factors for an observed effect and thus help to personalize treatment strategies.

The Research Topic "*Reviews in: stroke*" includes 25 articles that cover a variety of topics around stroke. One of the major emphases is on acute stroke diagnostics and treatment. We capture current topics like the impact of COVID-19 on acute ischemic stroke care (Stuckart et al.) or the use of telemedicine in acute stroke and its diagnostic accuracy (Poongkunran et al.). Several articles provide insight into neuroimaging (Zheng et al.; Huang et al.; Yoshimoto; Cheng et al.) and serum markers (Liu Y. et al.) that might help with patient selection and treatment monitoring in acute stroke. Other articles look at new treatment options for both ischemic and hemorrhagic stroke [(2); Zheng et al.; Fu et al.].

A further focus of this Research Topic is on risk factors and stroke etiology and addresses questions such as: what is the impact of inflammatory processes on the risk for atherosclerosis and stroke (Wang L. et al.; Jia et al.; Xie et al.; Pinzon et al.)?

Can we identify risk factors for in-stent stenosis after intracranial stenting (Wang N. et al.)? And what do we know about perioperative stroke, an entity that is clinically relevant but only marginally addressed in the literature (Ji et al.), and the etiology of cervical artery dissection (Gunduz et al.)?

The third emphasis is on stroke rehabilitation and covers therapeutic interventions such as constrained-induced movement therapy (Cui et al.), balance training (Zhang et al.), and interventions in post-stroke dysphagia (Liu J. et al.). A further article covers the use of AI for the prediction of post-stroke cognitive deficits (Li et al.).

Taken together, this Research Topic provides a variety of topics related to clinical and preclinical stroke research with the common aim of synthesizing the evidence using systematic reviews and meta-analyses. We hope that it will help clinicians and scientists in the field of stroke and foster translational progress.

Author contributions

BS: Writing – original draft. KB: Writing – review & editing. EC-J: Writing – review & editing. KKV: Writing – review & editing. JY: Writing – review & editing. CN: Supervision, Writing – original draft, Writing – review & editing.

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Effects of chin tuck against resistance exercise on post-stroke dysphagia rehabilitation: A systematic review and meta-analysis

Jing Liu[1†], Qiuyi Wang[1†], Jing Tian[1], Wanqiong Zhou[1], Yitian Gao[1], Xuemei Chen[1], Wei Zhang[1], Yajing Gao[2] and Lanshu Zhou[1*]

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Background: Chin tuck against resistance (CTAR) exercise was introduced to substitute for the commonly used Shaker exercise for dysphagia rehabilitation. The effects of CTAR exercise in stroke survivors needs to be validated.

Objective: To investigate the effects of Chin tuck against resistance (CTAR) exercise on the swallowing function and psychological condition in stroke survivors compared to no exercise intervention and the Shaker exercise.

Materials and methods: The Cochrane Library, PubMed, Web of Science, EMBASE, CINAHL and four Chinese databases were searched for randomized controlled trails (RCTs) and quasi-RCTs from inception to February 2022.

Results: After screened and assessed the methodological quality of the studies, nine studies with 548 stroke survivors were included in the systematic review. 8 studies were included in the meta-analysis using RevMan 5.4 software. The mean difference (MD) or standardized mean difference (SMD) with 95% confidence intervals (CIs) were calculated. The results revealed that CTAR exercise is effective in improving swallowing safety (MD, −1.43; 95% CI, −1.81 to −1.06; $P < 0.0001$) and oral intake ability (SMD, −1.82; 95% CI, −3.28 to −0.35; $P = 0.01$) compared with no exercise intervention, CTAR exercise is superior to Shaker exercise in improving swallowing safety (MD, −0.49; 95% CI, −0.83 to −0.16; $P = 0.004$). The psychological condition in CTAR group is significant better than the control group (MD, −5.72; 95% CI, −7.39 to −4.05; $P < 0.00001$) and Shaker group (MD, −2.20; 95% CI, −3.77 to −0.64; $P = 0.006$).

Conclusions: Our findings support CTAR exercise as a superior therapeutic exercise for post-stroke dysphagia rehabilitation than Shaker exercise. More high-qualities RCTs from larger multicenter are needed to analysis the effects of CTAR exercise in patients with different type and phase of stroke and explore the optimal training dose.

KEYWORDS

chin tuck against resistance exercise, stroke, rehabilitation, dysphagia, systematic review

Introduction

Dysphagia is any difficulty during bolus transport from the oral cavity to the stomach in the swallowing process (1). It is one of the most common complications that affecting 37–78% stroke survivors (2, 3) and is strongly associated with a high risk of aspiration pneumonia, malnutrition, and increased mortality (4–6). For many patients, dysphagia resolves spontaneously within 14 days, but 50.9% of dysphagia persist at discharge, and 15% of patients still have dysphagia at 1 month of the onset of stroke, 11–50% still have dysphagia at 6 months (6–8). The residual functional deficits not only seriously affect the quality of life of stroke survivors, but also is a major cause of post-stroke depression and social isolation (9). Thus, exploring effective dysphagia rehabilitation methods is an essential concern of post-stroke care.

Therapeutic exercises that stimulating and strengthening the swallow-related muscles are strongly recommended for dysphagia rehabilitation (10). The suprahyoid muscle complex (SHM) is critical during the pharyngeal phase of swallowing as it controls the movement of the larynx, hyoid bone, and epiglottis to protect the airway, and the opening of upper esophageal sphincter to allow bolus transfer into the esophageal (11). For stroke survivors, based on the neuroplasticity principle, regular and repetitive resistance training can lead to the strength of swallowing muscles and may be effective on the recovery of sensorimotor control system of swallowing (12). Thus, SHM strengthening exercise has been a focus of research and practice in post-stroke dysphagia rehabilitation. The head-lift exercise (HLE), also called Shaker exercise, is the most commonly used SHM strengthening exercise that has been demonstrated to be effective in strengthen the SHM, reduce pyfiform sinus residue and increase upper esophageal sphincter opening in dysphagia (13, 14). It requires patients to lift their heads against gravity to look at their toes in a supine position (15). But Shaker exercise has some drawbacks. When patients raise their heads, the sternocleidomastoid muscle are inevitably activated, causing unnecessary muscle fatigue and physical effort (16). For elderly patients who are physically frail, repeated lifting of and holding their heads up is challenging. Several studies reported that participants showed a low compliance and felt frustrated (16–18). Therefore, chin tuck against resistance (CTAR) exercise was introduced as a new rehabilitative exercise that could substitute for Shaker exercise by Yoon et al. (19). For CTAR exercise, the patient is instructed by speech and language therapists to tuck their chin toward their manubrium sterni to squeeze an inflatable rubber ball that placed between their chin and chest while seated. Similar to Shaker exercise, CTAR exercise includes isometric and isokinetic tasks. The isokinetic task is the squeezing of the ball as hard as possible for successive repetitions, while the isometric task is the squeezing of the ball and sustaining the squeeze for a period of time (19). People can choose the appropriate resistance according to their physical condition. Several studies have been conducted to validate the biomechanics effects of CTAR exercise and compared with Shaker exercise using surface electromyography (sEMG), which demonstrate CTAR is effective in stimulating the SHM but there are inconsistent conclusions in the comparison of CTAR and Shaker exercise (20, 21). To our knowledge, a previous systematic review (22) summarized the applications of CTAR exercise, in which both healthy participants and patients with dysphagia were included. Due to the high heterogeneity and limit number of studies, they only performed a descriptive qualitative analysis that CTAR is more selective in the activation of the SHM than Shaker exercise. But whether the strength of SHM can elicit the improvement of swallowing function still needs to be verified, as post-stroke dysphagia is functional dysphagia caused by hemisphere damage rather than organic disorder. Additionally, we noticed that a series of RCTs that explore the effects of CTAR exercise in stroke survivors were reported recently. Therefore, the objective of this study was to included the newly published studies and performed a meta-analysis of the results on the effects of CTAR exercise in stroke survivors to provide a reliable evidence for the policy and practice development of post-stroke dysphagia rehabilitation.

Abbreviations: CTAR, chin tuck against resistance; HLE, head lift exercise; SHM, suprahyoid muscle complex; VFSS, video fluoroscopic swallowing study; TDT, traditional dysphagia treatment; PAS, penetration-aspiration scale; FOIS, functional oral intake scale; FILS, Fujishima Ichiro food intake level scale; GUSS, Gugging Swallowing Screen; WST, water swallow test; SSA, standardized swallowing assessment; SDS, self-rating depression scale.

Materials and methods

This systematic review and meta-analysis was conducted based on the Cochrane Handbook for Systematic Reviews of Interventions (https://training.cochrane.org/handbook), and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) (23, 24). This review was previously registered on PROSPERO (CRD42021265975).

Search strategy

We systematically searched the following electronic databases from inception to February 2022: Cochrane Library Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, Web of Science (WOS), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) for studies published in English, China Biology Medicine disc (CBM),

China National Knowledge Infrastructure (CNKI), WanFang, and VIP database for studies published in Chinese. The following search terms were used: "chin tuck OR chin down OR CTAR" AND "stroke OR apoplexy OR cerebrovascular accident OR CVA OR brain vascular accident OR brain infarction OR cerebral infarction OR ischemic stroke OR hemorrhagic stroke" AND "dysphagia OR deglutition disorder OR swallowing disorder OR swallowing dysfunction OR impaired swallowing." We also searched the reference lists of the included studies and Google Scholar to identify relevant studies.

Eligibility criteria

Studies were included if they met the following criteria: (1) study design: a randomized controlled trial (RCT) or a quasi-RCT; (2) participants: adults diagnosed with post-stroke dysphagia that confirmed by a videofluoroscopy swallowing study (VFSS) or fiberoptic endoscopic evaluation of swallowing (FESS) or standardized dysphagia assessment instrument; (3) intervention and comparison: a comparison of CTAR exercise with no exercise intervention or with Shaker exercise; and (4) outcome measures: the primary outcome are the swallowing safety and oral intake ability as measured by standardized dysphagia assessment scale; the second outcome is psychological condition as measured by Self-Rating Depression Scale (SDS). There was no restriction on the language of publication.

Studies were excluded if they (1) were reviews, case reports, conference abstracts, expert opinion articles or peer-review publications or if (2) their full texts were not available or valid outcome data could not be extracted.

Study selection and quality assessment

First, all searched studies were imported to NoteExpress 3.2.0 to delete duplicates. Then, two reviewers (L.J. and W.Q.Y.) independently completed the title and abstract screening to exclude irrelevant studies, followed by full-text screening according to the eligibility criteria. All reviewers were familiar with stroke rehabilitation and had taken an evidence-based training course.

The methodological quality of the included studies was assessed by two reviews (T.J. and Z.W. Q) independently. The Cochrane risk of bias tool for randomized controlled trials was used for 8 RCTs, in which 5 domains were examined: (a) selection bias, (b) performance bias, (c) detection bias, (d) attrition bias, and (e) reporting bias (25, 26). The risk of bias for each domain was reported as low, high, or unclear. The Joanna Briggs Institute (JBI) critical appraisal checklist was used for 1 quasi-experimental study (27). Discrepancies were resolved by discussion.

Data extraction

Two reviewers (L.J. and W.Q.Y.) independently extracted the data using a predefined form, and the following data were collected: first author's name, publication year, sample size, participants' characteristics (age, type and phase of stroke), protocols for the intervention and control groups (device, frequency, repetition, and duration), outcome measures and results. The authors were contacted *via* email if incomplete data were provided for analysis.

Statistical analysis

According to our objective, two comparisons were performed: CTAR exercise vs. no exercise intervention and CTAR exercise vs. Shaker exercise. Based on the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3, 2022), meta-analysis consists of two stage. First, we calculated the mean change and standard difference from baseline to post-intervention in each group. The formulas were used if the standard difference was not presented (28):

$$Corr_E = \frac{SD^2_{E,baseline} + SD^2_{E,final} - SD^2_{E,change}}{2 * SD_{E,baseline} * SD_{E,final}} \quad (1)$$

$$SD_{E,change} = \sqrt{SD^2_{E,baseline} + SD^2_{E,final} - \left(2 * Corr_E * SD_{E,baseline} * SD_{E,final.}\right)} \quad (2)$$

To ensure that different scales represented the same effect direction for outcome measurement, we chose the most commonly used scale to determine the effect direction, and the mean change in scale scores with different directions was multiplied by −1. Then, the meta-analysis was conducted using Review Manager software (RevMan, version 5.4). Mean difference (MD) (when all studies measure the outcome using the same scale) or standardized mean difference (SMD) (when studies measure the outcome using different scales) was calculated for each study and synthesized into a pooled effect size with 95% confidence interval (CI).

The heterogeneity across the studies was analyzed by statistical testing with I^2. I^2 values <40, 40–75%, and >75% were considered low, moderate, and high heterogeneity, respectively. Random effects models were used to perform meta-analyses. In this study, a P-value < 0.05 was considered statistically significant.

Results

Study selection

A total of 154 articles were identified from databases, and 58 duplicates were removed using the duplicate finder tool in

NoteExpress 3.4.0. Seventy-two studies were excluded after title and abstract screening, one study was excluded because full text was not available. Another 17 studies were excluded after reading the full text. One study from USA (29), one from Singapore (20), one from Turkey (30), and one from Netherlands (31) were excluded due to the wrong population. One study (32) from Greece was excluded because its intervention consisted of CTAR exercise and thermal-tactile stimulation so we could not evaluate the effects of CTAR exercise separately. Two ongoing RCTs (33, 34) from the UK and India were excluded. Finally, 9 studies were included in this systematic review, including 8 RCTs and one quasi-RCT. Five studies (35–39) came from China, three studies (40–42) came from South Korea, and one study (43) came from India. 8 studies was included in the meta-analysis as Lai's study (38) used the dysphagia screening tool rather than standardized assessment scale as outcome measures, which may limit the accuracy of the results. The PRISMA flow diagram shows the study selection process (see Figure 1).

The risk of bias

Figure 2 displays a summary of the risk of bias assessment for the 8 RCTs. Two studies provided insufficient details about their methods of randomization (35, 37). Only two studies reported the process of allocation concealment (36, 41). None of the 8 RCTs reported the blinding of participants and outcome assessments, but considering that participant blinding was impossible in exercise-based intervention, six studies were determined to have a low risk of performance bias (36–42), and the other two studies were considered to have a high risk of between-group sample contamination because of their unclear randomization and allocation (35, 37). For detection bias, six studies measured swallowing function using a standard evaluation scale based on VFSS (35, 36, 39–42); thus, they were considered to have a low risk of detection bias. No selective reporting and other bias were identified. The overall appraisal of one quasi-experimental study was "include."

Characteristics of the included studies

The characteristics of participants in the 9 included studies are shown in Table 1. A total of 548 participants were included, with sample sizes of each study ranging from 22 to 120. Five studies included both hemorrhagic and ischemic stroke patients (37, 40–43), and four studies included only ischemic stroke patients (35, 36, 38, 39). The post-stroke time varied from 4 days to 63 weeks.

The characteristics of the intervention are shown in Table 2. Of the included 9 studies, 3 studies were three-arm trials (35, 39, 42). Thus, a total of 12 datasets were analyzed. Eight of the datasets (411 patients) compared CTAR exercise combined with traditional dysphagia treatments (TDT) vs. only TDT (e.g., oral facial massage, thermal-tactile stimulation, and transcranial direct current stimulation). The other four datasets (137 patients) compared the effects of CTAR exercise vs. Shaker exercise.

Regarding CTAR intervention, six studies used an inflatable rubber ball placed between the chin and the sternum (35–39, 43), 1 study used a hand-held flexible resistance bar (42), 1 study used a modified hand-free resistance bar secured to a desk surface (40), and 1 study used a hand-held resistance bar connected to a game-based PC tablet screen (41). Only the game-based device could adjust the intensity of training resistance. For the training protocols, 3 studies involved only isokinetic tasks (35, 37, 39), 2 studies involved only isometric tasks (38, 43), and the other 4 studies involved both (36, 40–42). The isokinetic task was 1 set of 30 consecutive squeezes, while the isometric task was the holding of the squeeze from 10 to 60 s for 3 to 10 repetitions. The training frequency varied from 1×/day for 5 days/weeks to 3×/day for 7 days/weeks. The duration of treatment varied from 8 days to 6 weeks.

For outcome measures, swallowing function and psychological condition were primary outcomes. A total of 11 different scales were used to measure swallowing function: (1) Swallowing safety: Six studies used the Penetration-Aspiration Scale (PAS) based on VFSS (35, 36, 39–42). The PAS is a widely used standard assessment scale to evaluate swallowing safety, which includes 8 points to reflect the depth of bolus penetration into the airway and the airway response to invasion. Higher scores indicate higher levels of airway aspiration and greater aspiration severity (44). (2) Oral intake ability: Three studies used the Functional Oral Intake Scale (FOIS) (40, 41, 43), and 1 study used the Fujishima Ichiro Food Intake Level Scale (FILS) (37). The FOIS is a 7-point scale that describes the feeding performance of oral intake (45), while the FILS is a 10-point scale. For both scales, a score of 1 indicates total nasogastric (NG) feeding, and higher scores represent better oral intake ability. (3) dysphagia screening tool: Two studies used the Water Swallow Test (WST) (37, 38), 1 study used the Gugging Swallowing Screen (GUSS) (43), and 1 study used the Standardized Swallowing Assessment (SSA) (38). The WST, GUSS and SSA are all simple bedside tools for dysphagia screening that are commonly used to identify high-risk populations with dysphagia and estimate the severity of dysphagia (46). Regarding psychological condition, 3 studies used the Self-depression scale (35, 36, 39).

Other outcomes included the compliance of patients (41), the score on a self-reporting questionnaire of enjoyment and physical fatigue (41), the NG tube removal rate (40, 41) and the physiological changes during the detailed phases of the swallowing process (41, 42).

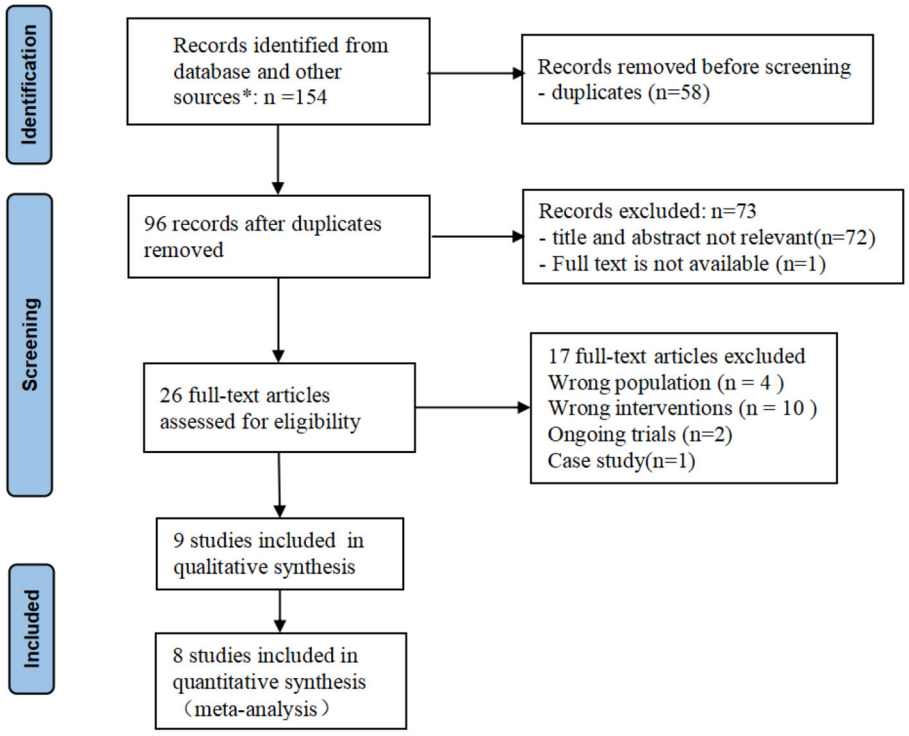

FIGURE 1
PRISMA flow diagram of study selection. *The number of records identified from each database searched: Cochrane Library: $n = 11$; Pubmed: $n = 11$; Web of science: $n = 37$; EMBASE: $n = 27$; CINAHL: $n = 12$; CBM: $n = 2$; CNKI: $n = 35$; WanFang: $n = 13$; VIP: $n = 6$.

Data synthesis

CTAR exercise vs. no exercise intervention

Swallowing safety as measured by PAS scores

The aggregated results of 5 studies (123 patients in CTAR group and 124 in the control group) showed that CTAR group had a significantly lower PAS score than the no exercise intervention group (MD, −1.43; 95% CI, −1.81 to −1.06; $P < 0.00001$; I^2, 0%) (see Figure 3), which suggested that patients in CTAR group had better swallowing safety and a lower risk of aspiration. The studies were homogenous.

Oral intake ability as measured by FOIS or FILS scores

The aggregated results of 3 studies (54 patients in CTAR group and 53 in the control group) showed a greater intervention-induced effect of oral intake ability in the CTAR group than that of the control group (SMD, −1.82; 95% CI, −3.28 to −0.35; $P = 0.01$; I^2, 89%) (see Figure 4). The heterogeneity between studies was high.

Psychological condition as measured by SDS scores

Three studies measured psychological condition using the SDS. The meta-analysis showed that the SDS scores in CTAR group were significantly lower than those in the control group (MD, −5.72; 95% CI, −7.39 to −4.05; $P < 0.00001$; $I^2 = 0\%$) (see Figure 5), which supported that the psychological condition of patients in CTAR group was significantly better than that in the control group. The studies were considered homogenous.

Other outcomes

Park et al. (42) evaluated the detailed phases of the complete swallowing process during a VFSS and found that CTAR group showed significantly better scores in the oral cavity and laryngeal elevation/epiglottic closure and less residue in the valleculae and pyriform sinuses. Kim et al. (40) reported that the rates of NG tube removal in CTAR and control groups were 25 and 15%, respectively.

CTAR exercise vs. Shaker exercise

Swallowing safety as measured by PAS scores

Four studies (119 patients in CTAR group and 118 in Shaker group) used the PAS to assess swallowing safety and compared the effects of CTAR and shaker exercises. The aggregated results showed that the change scores of CTAR group was significantly greater than that of Shaker group (MD, −0.49; 95% CI, −0.83 to −0.16; $P = 0.004$; I^2, 0%) (see Figure 6), which suggested that CTAR exercise was more effective in improving

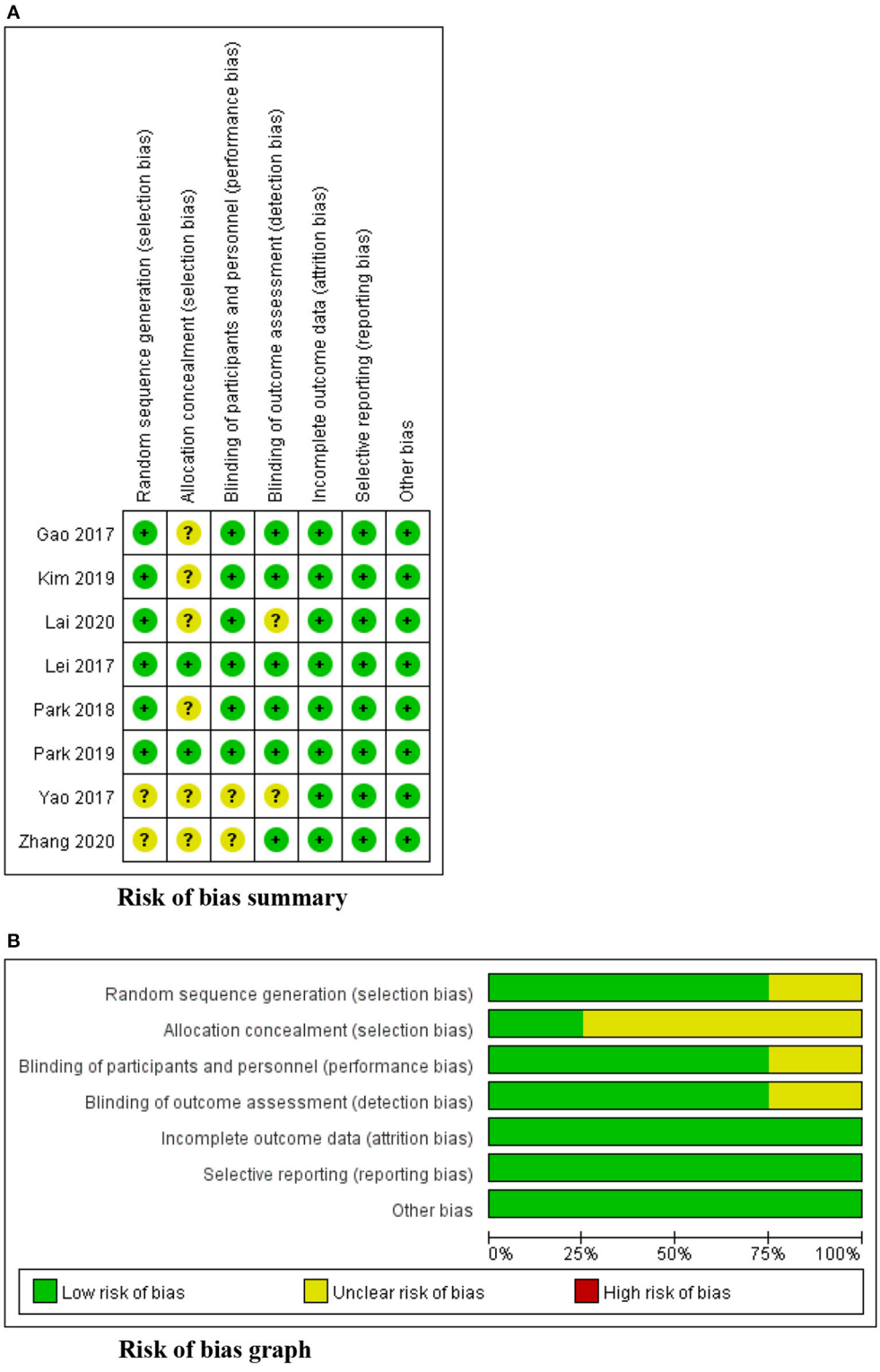

FIGURE 2
Risk of bias **(A)** summary **(B)** graph.

TABLE 1 Characteristics of participants in the included studies.

Author	Country	Study design	Sample size (IG/CG)	Mean age (year) IG/CG	Phase of stroke	Type of stroke
Santhosh Priya (43)	India	Quasi-RCT	A:16/16	35–85	Acute	Hemorrhage, infarction
Gao and Zhang (39)	China	RCT	A:30/30	70.88/71.14	Acute	Hemorrhage, infarction
			B:30/30	70.88/71.12	Acute	
Yao et al. (37)	China	RCT	A:26/24	64.2/63.0	Acute	Hemorrhage, infarction
Lei and Guo (36)	China	RCT	A:30/30	70.8/71.14	Acute	Only infarction
			B:30/30	70.8/71.12	Acute	
Park et al. (42)	Korea	RCT	A:11/11	62.16/58.43	Chronic	Hemorrhage, infarction
Park et al. (41)	Korea	RCT	B:19/18	60.9/59.45	Chronic	Hemorrhage, infarction
Kim and Park (40)	Korea	RCT	A:12/13	63.5/65.2	Unclear	Hemorrhage, infarction
Zhang et al. (35)	China	RCT	A:40/40	72.46/73.36	Acute	Only infarction
			B:40/40	72.46/74.11	Acute	
Lai (38)	China	RCT	A:41/41	72.41/73.02	Both	Only infarction

swallowing safety than Shaker exercise. The studies were considered homogenous.

Oral intake ability

One study measured oral intake ability using the FOIS, and the results showed no significant difference in FOIS scores between CTAR and shaker group.

Psychological condition as measured by SDS scores

Three studies compared the SDS scores of CTAR and shaker groups. The aggregated results showed that the psychological condition of patients in CTAR group was significantly better than that of patients in Shaker group (MD, −2.20; 95% CI, −3.77 to −0.64 $P = 0.006$; $I^2 = 0\%$) (see Figure 7). The studies were considered homogenous.

Other outcomes

Park et al. (41) reported that CTAR group showed a significantly lower drop-out rate, better feedback in terms of motivation and interest/enjoyment, and lower physical fatigue than Shaker group.

Discussion

The purpose of this systematic review was to investigate the effects of CTAR exercise on swallowing function and psychological condition of stroke survivors. Overall, the results showed a positive effect of CTAR exercise on improving swallowing safety, oral intake ability, and psychological condition compared with no exercise intervention. Compared with Shaker exercise, the results of the meta-analyses suggested that CTAR exercise was more effective in improving swallowing safety and psychological condition.

To our knowledge, this is the first systematic review and meta-analysis to examine the clinical effects of CTAR exercise in stroke survivors and confirm that CTAR exercise has superior effects than Shaker exercise in post-stroke dysphagia rehabilitation. The main results are consistent with a previous systematic review, which compared the effects of CTAR exercise in improving swallowing safety compared with no exercise intervention (47). But they did not compare oral intake ability and the effect of CTAR with Shaker exercise. Our findings demonstrated that strengthening exercise of SHM is not only fit for dysphagia that resulting from upper esophageal sphincter dysfunction, but also effective for rehabilitation of post-stroke dysphagia due to hemisphere damage. Previous studies that evaluated the biochemical changes of CTAR exercise reported that for instant muscle performance, CTAR exercise could exhibit significantly higher instant mean and max muscle fatigue of the SHM, with less stimulation of the sternocleidomastoid muscle than performing Shaker exercise (20). And after 8-week training, a significant greater anterior tongue pressure, and maximum mouth opening were observed in participants performing CTAR exercise compared to Shaker exercise (30,

TABLE 2 Characteristics of intervention and control group in the included studies.

Author	CTAR device	IG	CG	Training parameters	Frequency	Follow up	Outcome measures
Santhosh Priya (43)	Inflatable rubber ball	CTAR + TDT	A: TDT	Only isometric tasks: 10 s × 10	3 times/days, everyday	8 consecutive days	GUSS, FOIS
Gao and Zhang (39)	Inflatable rubber ball	CTAR + TDT	A: TDT	Only isokinetic tasks: 30 times × 3 (3 times/days)	Everyday	6 weeks	VFSS-PAS, SDS
			B: Shaker +TDT				
Yao et al. (37)	Inflatable rubber ball	CTAR + TDT	A: TDT	Only isokinetic tasks: 15 times × 3 (2 times/days)	5 days/weeks	4 weeks	FILS, WST
Lei and Guo (36)	Inflatable rubber ball	CTAR + TDT	A: TDT	Isokinetic tasks: 30 times × 3	Everyday	6 weeks	VFSS-PAS, SDS
			B: Shaker + TDT	Isometric tasks: 60 s × 3 (3 times/days)			
Park et al. (42)	Hand-held device	CTAR + TDT	A: TDT	Isokinetic tasks: 30 times	5 days/weeks	4 weeks	VFSS-PAS
				Isometric tasks: 60 s × 3			
Park et al. (41)	Game-based device	CTAR + TDT	B: Shaker + TDT	Isokinetic tasks: 30 times	5 days/weeks	4 weeks	VFSS-PAS, FOIS, patient feedback, drop-out rate
				Isometric tasks: 60 s × 3			
Kim and Park (40)	Hand-free device	CTAR + TDT	A: TDT	Isokinetic tasks: 30 times	5 days/weeks	6 weeks	VFSS-PAS, FOIS, NG tube removal
				Isometric tasks: 10 s × 3			
Zhang et al. (35)	Inflatable rubber ball	CTAR + TDT	A: TDT	Isokinetic tasks: 30 times × 3 (3 times/days)	Everyday	6 weeks	VFSS-PAS, SDS
			B: Shaker +TDT				
Lai (38)	Inflatable rubber ball	CTAR + TDT	A: TDT	Isometric tasks: 60 s × 30 (3 times/days)	Everyday	20 days	Water swallow test, SSA

IG, intervention group; CG, control group; TDT, traditional dysphagia treatment; A-CTAR + TDT vs. TDT, B-CTAR vs. Shaker; PAS, penetration-aspiration scale; FOIS, functional oral intake scale; FILS, Fujishima Ichiro food intake level scale; GUSS, Gugging and swallowing screen; WST, water swallow test; SSA, standardized swallowing assessment; SDS, self-rating depression scale.

31). Our findings, focus on the clinical effects of CTAR exercise in stroke survivors, supported that performing CTAR exercise to repetitive stimulating the SHM could translate into the biomechanics changes during the swallowing process and subsequently lead to increased swallowing safety and better recovery of oral intake ability, which is meaningful to avoid the risk of penetration-aspiration and improve the quality of life of stroke survivors. Additionally, another strength of our study is that we verify patients performing CTAR exercise have better psychological condition compared with no exercise intervention and Shaker exercise, which can be explained by two aspects. First, studies have shown that post-stroke depression is strongly associated with the severity of functional impairment, so better improvements in swallowing function can induce a positive effect on the patients' psychological condition (48). Second, in contrast to a considerable number of patients feeling frustrated with their failure to perform Shaker exercise, patients provided positive subjective feedback about CTAR exercise, as they could complete the exercise with suitable training intensity based on their physical condition, and CTAR exercise was more interesting and motivating, especially when the exercise was combined with computer games (19, 41). Therefore, we

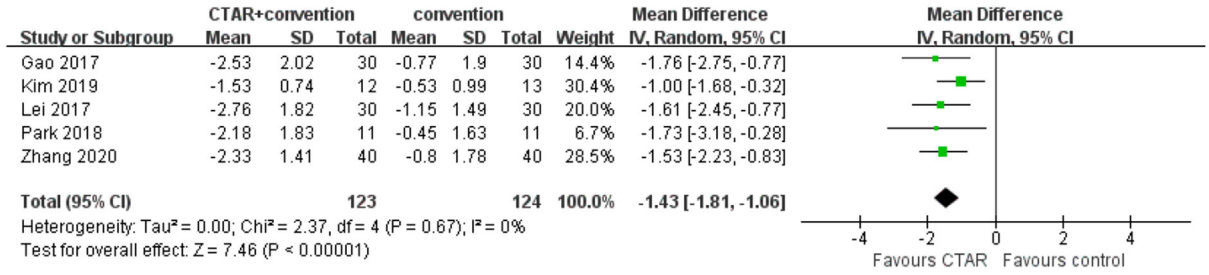

FIGURE 3
Pooled changes of swallowing safety in CTAR exercise vs. no exercise intervention.

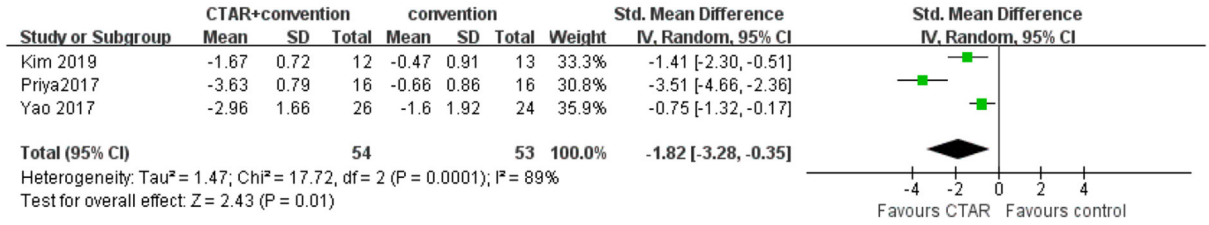

FIGURE 4
Pooled changes of oral intake ability in CTAR exercise vs. no exercise intervention.

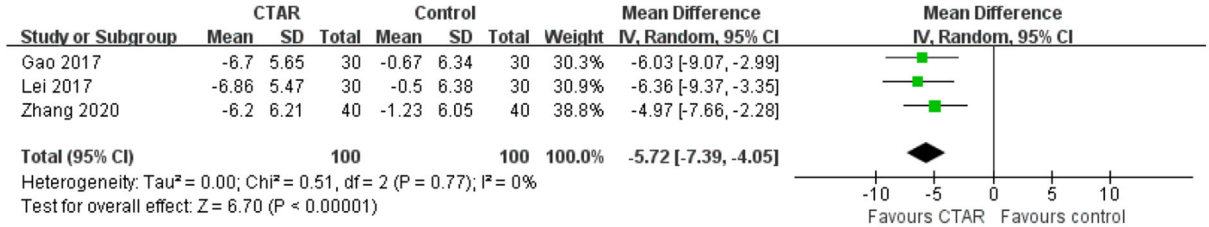

FIGURE 5
Pooled changes of psychological condition in CTAR exercise vs. no exercise intervention.

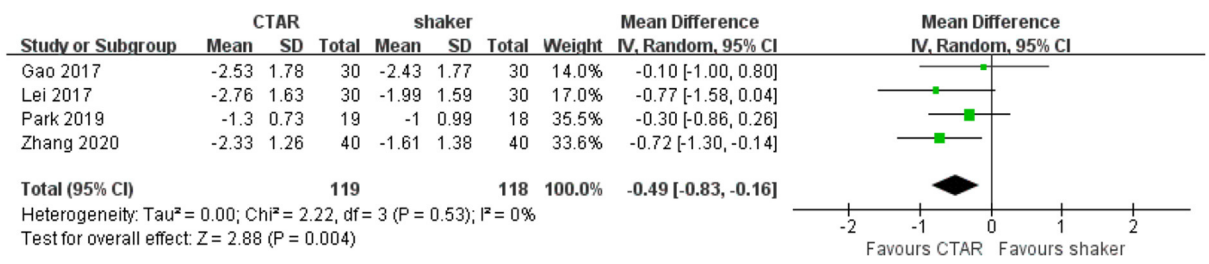

FIGURE 6
Pooled changes of swallowing safety in CTAR exercise vs. Shaker exercise.

recommend CTAR exercise as the first choice rehabilitative exercise for stroke survivors with dysphagia. For patients who cannot sit, Shaker exercise can be used as an alternative.

However, we also found that the training protocol varied greatly in previous CTAR studies. Exercised-based therapy utilizes the neuroplasticity principle that repetition, intensity,

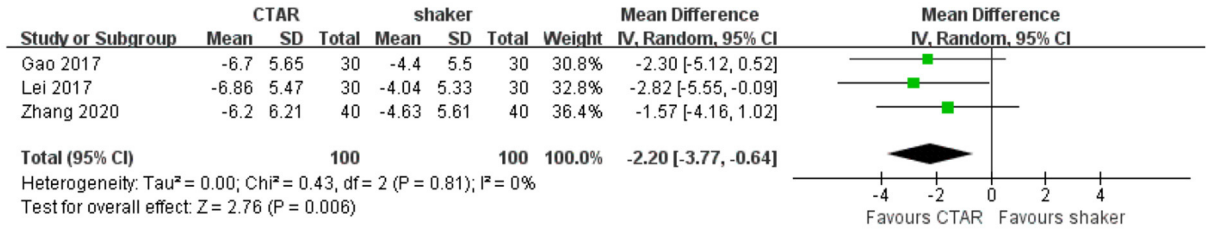

FIGURE 7
Pooled changes of psychological condition in CTAR exercise vs. Shaker exercise.

frequency and duration are especially important to achieve muscular hypertrophy (12, 49). Incorrect dose prescription may cause insufficient or negative effects. Blair et al. (50) considered it is unlikely to establish an optimal dosing for a training exercise, the dosing should be determined by the patient's age, primary dysphagia etiology, comorbidities, and physical fitness level. But several studies have demonstrated that it takes at least 4 weeks of resistance training to induce physiological changes in stroke patients (13, 51, 52). Most studies included in this review conducted a 4- or 6-week intervention (35–37, 39–42), and the other 2 studies conducted interventions for only 8 and 20 days (38, 43). For the repetitions, 30 consecutive repetitions for the isokinetic exercise and 3 sustained 60-s squeezes for the isometric exercise were adopted by most studies, which was consistent with the recommended dose for Shaker exercise (49). However, 2 studies performed only isometric tasks (38, 43), while the other 3 studies performed only isokinetic tasks (35, 37, 39). The training frequency also varied from 1×/day for 5 days/weeks to 3×/day for 7 days/weeks. Therefore, future research should continue to explore the relationship between the training dose and the training efficacy and establish universal standard parameters for CTAR exercise to maximize patient benefits.

This study has several limitations. First, there were heterogeneity between the included studies in terms of the patient conditions, type of stroke, and time post-stroke. The meta-analysis of oral intake ability and the overall severity of dysphagia showed substantial statistical heterogeneity, which may be due to the different measurement scales used in the studies. As Egger's publication bias test is known to have limit efficiency for meta-analysis that involving <10 studies, we did not conduct the test. Second, some studies had a high risk of bias in terms of randomization and allocation, which may limit the quality of the evidence. Third, most studies included in this review were from South Korea and China, which may limit the generalization of our findings. But this does not mean that no CTAR studies were performed in other countries. As CTAR exercise was proposed in 2014, most studies were conducted in healthy adults. We excluded these studies during study selection. Two CTAR trials from the UK and India were registered in the International Clinical Trials Registry Platform of the World Health Organization (WHO) recently. Thus, research on the effects of CTAR exercise on post-stroke dysphagia is continuously increasing, and more high-quality RCTs from different countries are warranted to enrich our findings.

Conclusion

In conclusion, the findings of this study suggest that CTAR exercise is an effective therapeutic method for post-stroke dysphagia rehabilitation and is superior to Shaker exercise in improving swallowing safety with positive effect to patients' psychological condition. Larger multicenter RCTs are needed to verify the effects of CTAR exercise in patients with different conditions, types of stroke, and times post stroke. It could also be worth to explore the optimal training dose of CTAR exercise to establish effective treatment protocols.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

JL and QW: screened the title, abstract, full-text of the identified studies, and drafted the manuscript. JT: performed the data extraction. WaZ and YiG: evaluated the risk bias of included studies. XC, WeZ, and YaG: performed the data verification. LZ: conceptualization, supervision, and funding acquisition. All authors reviewed and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Research progress of endogenous hematoma absorption after intracerebral hemorrhage

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Non-traumatic intraparenchymal brain hemorrhage is referred to as intracerebral hemorrhage (ICH). Although ICH is associated with a high rate of disability and case fatality, active intervention can significantly lower the rate of severe disability. Studies have shown that the speed of hematoma clearance after ICH determines the patient's prognosis. Following ICH, depending on the hematoma volume and mass effect, either surgical- or medication-only conservative treatment is chosen. The goal of promoting endogenous hematoma absorption is more relevant because surgery is only appropriate for a small percentage of patients, and open surgery can cause additional trauma to patients. The primary method of removing hematoma after ICH in the future will involve understanding how to produce and manage macrophage/microglial endogenous phagocytic hematomas. Therefore, it is necessary to elucidate the regulatory mechanisms and key targets for clinical purposes.

KEYWORDS

phagocytosis, microglia, scavenger receptor, intracerebral hemorrhage, haematoma absorption

1. Introduction

Intracerebral hemorrhage (ICH) refers to non-traumatic intraparenchymal brain hemorrhage, which is generally caused by long-term hypertension and arteriosclerosis. A sudden rise in blood pressure can result in vascular rupture and bleeding, and the blood can enter the brain parenchyma, where it solidifies and causes a mass effect. Subsequently, cells with phagocytic function engulf these blood clots. Blood clots are chemical accumulations of red blood cells (RBCs) and their lysis products such as hemoglobin (Hb), heme, iron, and globin. The pathological mechanisms of brain injury caused by these clots in the brain parenchyma include the inhibition of cell metabolism, inflammatory response, iron overload, oxidative stress, and tissue edema. Currently, hematoma-scavenging craniectomy or minimally invasive hematoma removal is the primary treatment approach for rapid hematoma clearance. However, the surgical approach has not yet been able to dramatically improve the long-term neurological prognoses in such cases. There are strict surgical guidelines, for example, hematoma-scavenging craniectomy requires craniotomy and can result in additional secondary injury. It is frequently used for patients with significant cerebral bleeding. Although minimally invasive hematoma removal can prevent craniotomy, it may result in incomplete removal of the hematoma, particularly when there is active bleeding. Accelerating the absorption of endogenous hematomas is another crucial strategy to inhibit nerve damage secondary to hematomas and for their complete removal.

It has been discovered that peroxisome proliferator-activated receptor (PPAR) and nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathways can control the expression of scavenger receptor genes and activate microglia to promote endogenous hematoma absorption (1, 2). Promoting the expression of CD36 and CD163 on microglia/macrophages can enhance the phagocytosis of Hb, whereas blocking CD47 on red blood cells can promote the phagocytosis of RBCs. In addition, endogenous hematoma absorption can be facilitated by several mechanisms that increase the phagocytic capability of macrophages and microglia. Based on the current status of ICH research and treatment, this review intends to identify specific targets, explain the relevant mechanisms of endogenous hematoma absorption, and propose novel ideas for the treatment of endogenous hematoma resorption.

2. Cells involved in phagocytosis after ICH

In a mouse model of ICH with autologous blood injection, macrophages and dendritic cells were found to be congregated within hours of ICH (3). There is a slight increase in the percentage of dendritic cells in the hematoma compared to that in the peripheral blood of patients with ICH (4). Among the various types of phagocytic cells, macrophages/microglia remain primarily researched for phagocytosis of hematoma components following ICH (5, 6). Essentially, there are two types of macrophages. Tissue-resident macrophages are highly specialized cells that perform specific functions in the tissues where they settle, such as microglia in the central nervous system, perivascular macrophages, osteoclasts in bones, and intestinal macrophages in the gastrointestinal tract. The other type, the monocyte-derived macrophages (MDMs), can infiltrate tissues because of inflammation and chemokines. However, tissue-settled macrophages and MDMs have also been studied as a class. In 2018, Chang proposed that MDMs are essential for hematoma clearance and functional recovery after ICH (7). Subsequently, in 2021, marked differences were observed in the transcriptional states of MDMs and tissue-resident macrophages (microglia) in ICH, suggesting that the two have different functions. MDMs have a better phagocytic ability, as evidenced by the fact that they phagocytize RBCs around the hematoma in the majority of cases (8). The discovery of unique markers of tissue-resident macrophages and MDMs will aid in future research to determine their roles separately. To clarify whether endogenous hematoma absorption after ICH is required to target tissue-resident macrophages and MDMs, additional experimental data are necessary.

Abbreviations: ICH, intracerebral hemorrhage; Hb, hemoglobin; PPAR-γ, peroxisome proliferator-activated receptor-γ; Nrf2, nuclear factor erythroid 2-related factor 2; MDMs, monocyte-derived macrophages; RBCs, red blood cells; SRs, scavenger receptors; Hb–Hp, hemoglobin–haptoglobin; SIRPα, signal-regulating protein α; HO-1, heme oxygenase 1; H_2S, hydrogen sulfide; UCP2, uncoupling protein 2; RIC, remote ischemic conditioning; STAT6, signal transducer and activator of transcription 6; IL-4, interleukin 4; DUSP8, dual-specificity phosphatase 8; DFX, deferoxamine.

3. Scavenger receptors associated with endogenous hematoma phagocytosis

Scavenger receptors (SRs) are a class of architecturally varied proteins capable of recognizing a multitude of ligands on the cell surface, including pathogens and endogenous and modified host-derived molecules. In addition to serving as phagocytes and innate immune recognition receptors, SRs play a significant role in several physiological and pathological processes as inflammatory signal regulators. At least six distinct molecular types have been reported in the literature, among which CD36, CD163, CD91, SR-A (also known as CD204), and Lox-1 are connected to hematoma absorption after ICH.

3.1. CD36

CD36 belongs to the class B scavenger receptor family and is widely expressed in a variety of cells, such as microvascular endothelium cells, adipocytes, skeletal muscle cells, dendritic cells, smooth muscle cells, and hematopoietic cells. CD36 features as an SR involved in cell adhesion, antigen presentation, and identification and internalization of apoptotic cells (9). The majority of CD36 is expressed on microglia and mostly on Iba1+ cells with microglial morphology around the core area of the hematoma, as observed in a rat collagenase-induced ICH model (6). However, the expression of CD36 does not have an impact on hemoglobin levels within 24 h of ICH (6), and the volume of hematoma that is absorbed in the middle and late stages is much lower in CD36 gene-deficient rats than in normal rats, indicating that CD36 expression can influence the absorption rate of hematoma in these stages (6, 10). Mouse RBCs purified by density gradient centrifugation were diluted to 10^8 cells/ml and added to cultured microglia at a ratio of 10:1 to establish an *in vitro* ICH model. Deletion of the CD36 gene led to a reduction in microglial phagocytosis of RBC (10), indicating that CD36 on microglia plays a role in promoting phagocytosis of RBC and hematoma absorption. However, it is still uncertain how CD36 expression in macrophages/microglia can influence erythrocyte phagocytosis. Notably, studies have shown that increasing CD36 expression can influence microglia to induce the M2 phenotype surrounding hematoma, which enhances their phagocytosis and anti-inflammatory effects (11). In addition, microglia are the only cells specifically identified in ICH for the CD36-mediated clearance of hematoma components. Therefore, we believe that upregulating CD36 after ICH can increase endogenous hematoma absorption; however, the precise mechanism and cell types involved remain to be investigated.

3.2. CD163

The hemoglobin SR CD163 is expressed on cells of the monocyte–macrophage lineage and participates in the uptake of hemoglobin–haptoglobin (Hb–Hp) complexes and promotes free Hb uptake (12, 13). Hb produced by erythrolysis in hematomas attaches to Hp once it is free, and the Hp–Hb complex can then

be endocytosed by CD163-mediated phagocytes (14). In addition, increased Hb levels have been found to upregulate neuronal CD163 expression (15), although a significant association between neuronal CD163 and endogenous hematoma absorption was not confirmed in the current investigation. Leclerc et al. discovered that although there is a significant correlation between phagocyte CD163 and Hb clearance, hematoma volume in mice with CD163 gene deletion 3 days after ICH was 43.4±5.0% less than that in the wild-type mice. However, the mortality of ICH mice with CD163 $^{-/-}$ in 4–10 days was 66.7%, which was significantly higher than that of WT mice (33.3%), and the residual hematoma after 10 days was also higher than that of WT mice. Subsequent research has shown that CD163 is a scavenger receptor for Hp-Hb complexes and clears uncomplexed Hb under severe hemolytic conditions associated with Hp depletion. The authors believe that it plays a more important role in secondary brain injury after ICH (16). In previous studies, the time windows for CD163 to function were disregarded after ICH. Future studies can evaluate these time windows to efficiently connect the various hematoma absorption mechanisms. Future studies should focus on CD163, which has clinically meaningful therapeutic potential in post-ICH phagocytes.

3.3. Other related SRs

To absorb heme after erythrocytolysis, cells that express low-density lipoprotein receptor-related protein-1 (LRP1, also known as CD91) engulf the heme–hemopexin (heme–Hx) complex (17, 18). In addition, Bruton's tyrosine kinase–calreticulin–LRP1–Hx (BTK–CRT–LRP1–Hx) pathway regulated by the Toll-like receptor 7 (TLR7) agonist imiquimod simultaneously increases heme-Hx clearance (19). Toll-like receptor 9 (TLR9) promotes the clearance of hematoma and iron by activating macrophages/microglia after ICH, and the Nrf2/CD204/HO-1 pathway is involved in TLR9-induced macrophage/microglial phagocytosis (20). However, more studies are required to demonstrate that the CD91–heme–Hx pathway facilitates the absorption of endogenous hematomas because investigations on the aforementioned pathways have not been conducted at sufficient depth. The role of CD 204 and other SR after ICH must also be explored, as well as their potential involvement in the phagocytosis of hematoma components by macrophages/microglia.

4. Substances and methods for regulating phagocyte function

4.1. CD47

CD47 is a transmembrane protein that is a ligand for signal-regulating protein α (SIRPα) expressed in phagocytes, including macrophages and dendritic cells. When SIRP is activated, a signal transduction cascade that inhibits phagocytosis is activated (21). RBCs express the "don't eat me" signal through CD47, and this signal can interact with the macrophage inhibitory receptor SIRP to prevent phagocytosis (22). CD47 inhibiting antibodies can facilitate hematoma removal and alleviate brain damage in mice (23). Another study on ICH elderly rat model showed similar results. CD47 blocking antibody can promote hematoma clearance, reduce secondary injuries, and increase the number of macrophages/microglia in a hematoma (5). Furthermore, it has been proposed that the depletion of M2 microglia with clodronate liposomes can aggravate brain damage caused by ICH; thus, it was discovered that RBC CD47 expression inhibits microglial polarization to the M2 phenotype and phagocytic RBC, thereby inhibiting hematoma clearance, as these changes enhance brain damage after ICH (24). The inhibition of CD47 expression on RBC can improve hematoma absorption by phagocytes. Targeting the inhibition of CD47 expression on RBC is necessary because it can stop phagocytes from devouring other intraparenchymal cells that are not part of a hematoma.

4.2. Phosphatidylserine

Phosphatidylserine is a ubiquitous phospholipid located at the entrance of the plasma membrane. During apoptosis, phosphatidylserine is exposed to the outer surface of the plasma membrane, which is called phosphatidylserine eversion. It serves as a signal for the phagocyte to "eat me" and promotes phagocytosis (25). Macrophages phagocytose RBC, which are largely dependent on phosphatidylserine, and this has been observed in both patients with ICH and mouse ICH models. In addition, engulfing RBCs with phosphatidylserine eversion regulates the MDMs phenotype in humans and mice, as well as hematoma absorption and patient rehabilitation (7). In fact, many phosphatidylserine receptors are also categorized as SR, such as CD91, T-cell immunoglobulin and mucin receptor 4 (TIM 4), stabilin-1, and others (26). Furthermore, phosphatidylserine has been proposed to identify and attach to the extracellular domain of CD36, recognizing and phagocytizing senescent cells through phosphatidylserine-CD36 interaction (27). As a result, we believe that it will be particularly interesting to investigate the relationship between erythrocyte phosphatidylserine eversion and SR in ICH.

4.3. Heme oxygenase 1

Heme oxygenase 1 (HO-1) can catalyze heme to produce carbon monoxide, iron, and biliverdin. Zhang et al. investigated the function of HO-1 in 12-month-old mice (28) and found that intraperitoneal injection of the HO-1 inducer cobalt protoporphyrin IX in a collagenase-induced mouse ICH model can promote hematoma clearance, while the HO-1 inhibitor zinc protoporphyrin IX inhibits hematoma clearance in the later stages of ICH (7–28 days). In contrast, cobalt protoporphyrin IX-induced HO-1 expression can exacerbate secondary brain injury and neurological defects in the early stages of ICH (1–3 days). Consistent with the results of our research group, we believe that the neuroprotective effect of HO-1 begins early (12 h to 7 days), as observed in a rat autologous blood ICH model. In addition, HO-1 controls the Nrf2-ARE pathway in the ICH model by preventing Nrf2 from accessing the nucleus and stimulating the production of NF-κB and TNF-α, and the early neuroprotection of HO-1 is related to the nuclear translocation of Nrf2 and NF-κB (29). The

ICH modeling techniques and the selection of HO-1 inducers could be responsible for the variations in HO-1 expression levels and physiological consequences in different phases in the ICH model. Notably, Nrf2-ARE transcription can enhance CD36 expression to encourage macrophage/microglial hematoma phagocytosis (2). Although there is no logical connection between this and the findings of our research team, the significance between them necessitates further consideration. Similarly, the PPAR-γ pathway can enhance the expression of microglia CD163 and HO-1 as well as promote hematoma absorption (30); therefore, targeting HO-1 to promote hematoma absorption after ICH requires a combination of other molecules and multiple signaling pathways. In addition, further investigation is required into the therapeutic window of targeted HO-1, ideally in conjunction with its clinical application.

4.4. Complement component C1q

Complement mediates the phagocytosis of apoptotic cells and cell debris (31). C1q is the serum complement component, which initiates the conventional complement activation pathway and is mainly involved in immunological and inflammatory responses. Some researchers have examined plasma C1q levels in patients with ICH and discovered that these levels were significantly higher than those in healthy individuals. Moreover, poor prognosis at 3 months can be independently predicted by plasma C1q, indicating that C1q may be a potential prognostic biomarker for ICH (32). Further research is needed to determine whether slow hematoma absorption or associated inflammatory responses are responsible for poor prognosis. Interestingly, there may be an interaction between C1q and CD91 (33) because CD91 functions as a heme receptor in the phagocytosis of heme, a component of hematoma after ICH (17). It cannot be denied that complement receptors play a role in the phagocytosis of RBCs by macrophages, which simultaneously release proinflammatory factors (34). In addition, these receptors are easily associated with secondary brain injuries. Further research is required to determine specific steps required to balance the complement-mediating phagocytosis and inflammation.

4.5. Hydrogen sulfide

Hydrogen sulfide (H_2S) is a novel gas-signaling molecule. The primary enzyme in the brain that produces H_2S is cystathionine β-synthase (CBS), and a decrease in CBS during ICH causes the downregulation of endogenous H_2S synthesis (35). H_2S has been studied for its ability to reduce inflammation after ICH (36) and provide neuroprotective benefits (35). In a recent study, H_2S was found to be an endogenous regulator that mediates the sustained phagocytosis of microglia after ICH. Sulfide-quinone oxidoreductase (SQR) can oxidize CBS-derived endogenous H_2S, which results in the reverse electron transport of mitochondrial complex I, leading to the production of superoxide, which conversely activates uncoupling protein 2 (UCP2) to promote microglial phagocytosis of RBC. In summary, the microglial CBS–H_2S–complex I axis is essential for sustained phagocytosis following ICH (37). This study implies that starting from a redox approach, we can conduct research by concentrating on H_2S to encourage hematoma absorption, offering a novel approach for future studies.

4.6. Remote ischemic conditioning

Remote ischemic conditioning (RIC) is a physical therapy method in which the limb is pressurized using a compression cuff. Usually, RIC is performed at 200 mmHg for four cycles of 5 min each, with a reperfusion break of 5 min (38–40). Research has shown that AMPK, which acts as a switch to control cellular metabolism, is essential for RIC to promote hematoma absorption (40). In an isolated perfused rat heart model, the number of delayed remote ischemic preconditioning stimuli was positively correlated with HO-1, and HO-1 was involved in cardioprotection (41). As mentioned earlier, HO-1 levels are closely associated with hematoma clearance (28–30). Although the pathological mechanisms of ICH and cardiovascular disease are different, the relationship between RIC and HO-1 indicates interesting possibilities for future research. In the latest clinical trial study, the safety of RIC in clinical patients with ICH was shown by comparing drug therapy alone and drug plus RIC for 7 consecutive days in patients with ICH. The hematoma-scavenging rate of the drug plus RIC was significantly higher than that of drug treatment alone. While this cannot directly explain the effect of RIC on absolute hematoma scavenging in patients with ICH, the higher scavenging rate of combination therapy is sufficient to show that RIC can promote hematoma clearance (42). Although it has been demonstrated that four cycles of RIC at 200 mmHg are clinically safe and successful in eliminating hematoma, it is still important to determine whether this is the optimal pressure.

4.7. Cerebral white matter fiber

Other studies have identified strategies to influence endogenous hematoma absorption after ICH. White matter fibers, for instance, are present in the core of the hematoma after ICH, and those that survive enhance the quantity of microglia/macrophages that remain there, which facilitates RBC phagocytosis and increases hematoma absorption (43). White matter fibers in the hematoma area either aid microglia/macrophages in entering the hematoma area by reducing phagocyte death or by acting as scaffolding to allow phagocytes to penetrate the hematoma area. Currently, studies on the white matter after ICH have mainly focused on white matter injury (44–47). However, the connection between white matter and endogenous hematoma absorption after ICH has not been well researched. Notably, the white matter of rodents accounts for 10–20% of brain volume, while in humans it accounts for 50% of brain volume (48), indicating that white matter plays a major role in our brain and has great research prospects in endogenous hematoma absorption after ICH. These contents are shown in Figure 1.

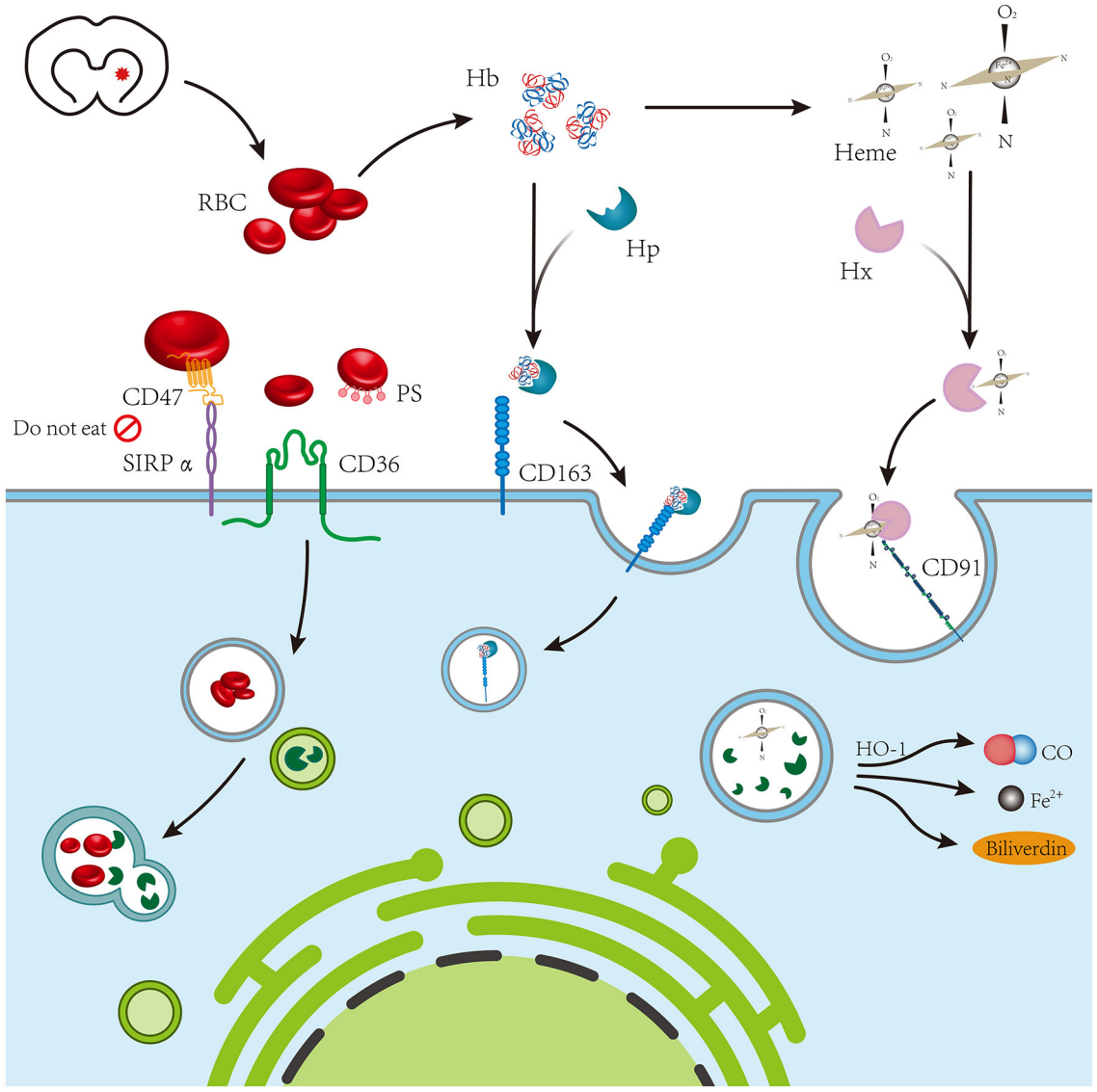

FIGURE 1
The blood chemical components of coagulation following intracerebral hemorrhage mainly include red blood cells, hemoglobin, and heme, which are mediated by CD36, CD163, and CD91 expressed on phagocytes, respectively.

5. Signal regulation of endogenous hematoma absorption

5.1. PPAR-γ signaling pathway

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated receptors of the nuclear hormone receptor family. There are three subtypes of ligand-induced nuclear receptors that control intracellular metabolism: PPAR-α, PPAR-β/δ, and PPAR-γ. PPAR-γ has received considerable attention in ICH research. In *in vivo* and *in vitro* ICH models, fractalkine located in neuronal cells can interact with the unique fractalkine receptor CX3CR1 and promote hematoma absorption through the PPAR-γ/CD163/HO-1 signaling pathway. Meanwhile, a study on 30 patients with ICH reported that patients with reduced hematoma had higher serum fractalkine and modified Rankin scores (mRS scores) than patients with enlarged hematoma (30). In the autologous blood injection ICH model, the PPAR-γ agonist ISO-alpha-acids (IAAs) can activate PPAR-γ and increase the expression of CD36 around the hematoma, causing microglia to polarize to the M2 phenotype, increasing endogenous hematoma absorption and decreasing inflammation around the hematoma (49). The expression of CD36 and CD163 scavenger receptors on microglia/macrophages can be simultaneously increased through the PPAR-γ signaling pathway, effectively promoting endogenous hematoma absorption. Consequently, PPAR agonists are a highly promising class of medications that merit in-depth examination.

5.2. Nrf2 signaling pathway

The Nrf2 signaling pathway effectively reduces leukocyte infiltration and ROS production and is essential for preventing secondary brain damage in animal models of ICH (50). In addition, Nrf2 regulates cellular phagocytosis and promotes hematoma clearance by upregulating the expression of CD36 on the surface of microglia/macrophages through ARE transcription (2). Recombinant C-C chemokine ligand17 (CCL17) promotes hematoma clearance and improves nerve injury by activating the C-C chemokine receptor 4 (CCR4)/extracellular regulated protein kinase (ERK)/Nrf2 signaling pathway to increase CD163 expression (51). Numerous mechanisms may be involved in the mutual regulation of Nrf2 and PPAR-γ gene transcription (52). In addition, research has demonstrated that the synergistic effect of PPAR-γ and the Nrf2 pathway prevents ferroptosis-induced neuronal damage in a rat ICH model (53). The effects of the interaction between PPAR-γ and Nrf2 on endogenous hematoma absorption after ICH cannot be clearly explained by the available experimental data. However, this still provides a new direction for future studies that aim to establish a perfect system for endogenous hematoma absorption after ICH by determining the relationship between various signaling pathways and their interactions.

5.3. Signal transducer and activator of transcription 6 signaling pathway

The signal transducer and activator of transcription 6 (STAT6) is an important signaling pathway in macrophage function and is necessary for macrophages to evolve into M2 macrophages through an alternative pathway. Important cytokines for the polarization of macrophages to M2 include interleukin 4 (IL-4) and interleukin 13 (IL-13), which function by causing STAT6 phosphorylation and stimulating the transcription of STAT6 response genes (54). A small number of studies have demonstrated that IL-4 treatment after ICH promotes hematoma absorption, relieves neuroinflammation, and enhances neural functional recovery through the STAT6 signaling pathway (55, 56). According to one study, IL-4 can induce the polarization of M2 macrophage and microglia *via* the Janus kinase 1 (JAK1)/STAT6 pathway (55). Another study revealed that the STAT6 downstream signaling molecule STAT2 mediates the IL-4-provided function of hematoma absorption after ICH, and since STAT6 and ST2 are both necessary, the IL-4/STAT6/ST2 signaling pathway plays a crucial role in hematoma absorption after ICH (56). Nonetheless, the question remains as to whether the two signaling pathways mentioned above, IL-4/JAK1/STAT6 and IL-4/STAT6/ST2, are identical or whether they interact. However, we do not believe these two pathways are independent. In terms of effects, they both support that IL-4 promotes hematoma resolution by targeting microglia. Of course, this is only a hypothesis and needs to be verified by further experiments. The limited available data indicates that IL-4, as an anti-inflammatory factor, may induce the differentiation of anti-inflammatory microglia (also known as M2 microglia) through the STAT6 signaling pathway and mediate the phagocytosis of hematoma components. There is another signaling pathway that targets microglia-mediated hematoma phagocytosis after PPAR-γ and Nrf2, which will provide a novel idea for evaluating endogenous hematoma absorption after ICH. These contents are shown in Figure 2.

5.4. Regulation of microRNAs

MicroRNAs (miRNAs) are a class of small non-coding RNAs that usually target the inhibition of mRNAs to regulate the transcription and protein expression of associated genes. Through the collection of clinical data, some researchers discovered that miR-21-5p was downregulated in peripheral blood and hematoma samples of patients with ICH, with miRNA-21-5p in hematoma samples being more obviously downregulated (57), although the cause remained unknown. Using bioinformatics techniques, we found that dual-specificity phosphatase 8 (DUSP8) is a direct target of miR-21-5p. A study on the collagenase-induced rat ICH model showed inhibition of DUSP8-induced miR-21-5p activation, and involvement of the phospho-extracellular regulated protein kinase (p-ERK)/HO-1 pathway secondary brain injury. In addition, injection of a miR-21-5p antagonist can significantly inhibit ferrugination in tissues and promote hematoma absorption (58). Although some researchers have investigated how miRNAs regulate the polarization of M1 and M2 microglia after ICH (59, 60), there are no studies linking this to endogenous hematoma absorption. With the gradual development of miRNA research and the maturity of related technologies in recent years, the regulation of miRNAs to promote endogenous hematoma absorption requires more attention. Related research has accelerated new miRNA-based therapeutic strategies to promote endogenous hematoma absorption following ICH.

6. Drugs for promoting hematoma absorption after intracerebral hemorrhage

6.1. Simvastatin

Statins are a class of lipid-lowering medications. Based on recent research involving both *in vivo* and *in vitro* phagocytic models, simvastatin can upregulate CD36 and increase the polarization of M2 microglia through the PPAR-γ pathway, thereby promoting hematoma absorption after ICH (11). Simvastatin shows neuroprotective effects in ICH, and simvastatin–ezetimibe combination therapy after ICH can repair impaired nerve function and reduce inflammation (61). Simvastatin reduces the infiltration of post-ICH neutrophils into the brain parenchyma by regulating peripheral blood neutrophil apoptosis to relieve neuroinflammation (62). These may be potentially linked to endogenous hematoma absorption after ICH. The impact of simvastatin on endogenous hematoma absorption has not been studied in any relevant clinical trial, and some pertinent animal studies are required to confirm that simvastatin has the potential to be used clinically to increase endogenous hematoma absorption.

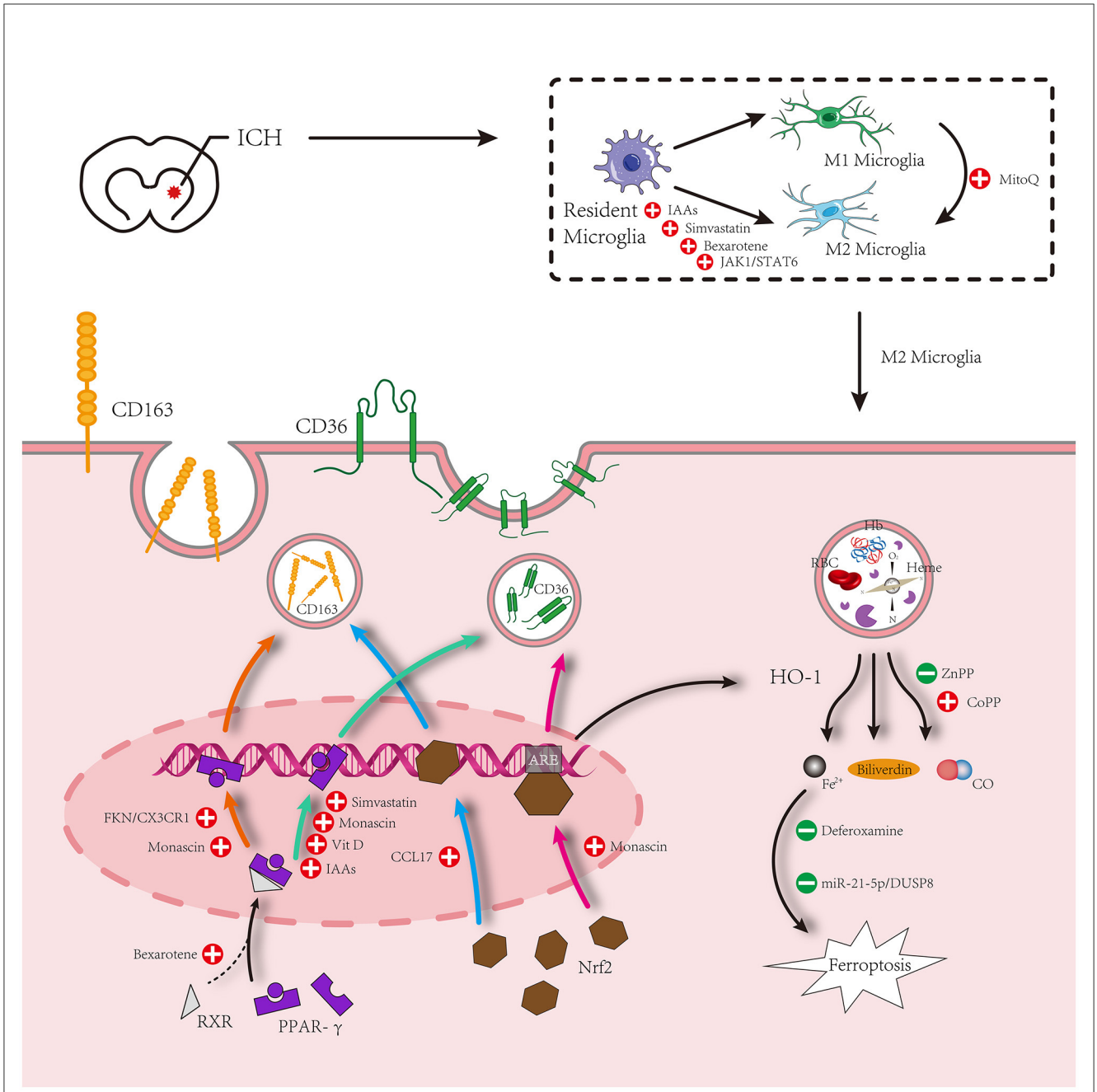

FIGURE 2
Microglia surrounding hematomas after intracerebral hemorrhage are polarized to an M1 or M2 phenotype. M1 phenotype promotes inflammation. M2 inhibits inflammation and promotes phagocytosis. The hematoma component is engulfed by M2 microglia, which mainly increases the expression of proteins related to phagocytosis under the action of PPAR-γ and Nrf2 signaling pathways and relieves the cytotoxicity of metabolites after phagocytosis of hematoma components. Simultaneously, M1 is inhibited by some other drugs to promote the polarization of M2 microglia.

6.2. Deferoxamine (DFX)

Following ICH, RBCs are lysed to release Hb, which decomposes into heme under a series of pathological actions, and heme is further decomposed into iron. Deferoxamine (DFX), an iron chelator, can effectively bind iron and reduce neuroinflammation caused by iron overload (63). According to Hu et al., DFX treatment after ICH enhances heme clearance and reduces heme levels in and around hematomas through the heme–Hx–CD91 pathway (18), which is likely to be a critical step in endogenous hematoma absorption after ICH. However, studies have also demonstrated that DFX reduces erythrolysis and iron overload by inhibiting membrane–attack complexes. In addition, DFX reduces the loss of CD47 in RBC and the invasion of microglia/macrophages after ICH, which weakens RBC phagocytosis (64). Furthermore, Liu et al. revealed that DFX exerts neuroprotective effects by reducing erythrolysis and chelating iron, and inhibits Hb-induced neuronal CD163 upregulation,

which may be related to the inhibition of neuronal death (15). Early clinical trials have shown that DFX mesylate therapy after ICH can inhibit encephaloedema but delay hematoma absorption (65); therefore, we are more inclined to believe that DFX has neuroprotective effects while the promoting effect on hematoma component absorption remains debatable. With the clarification of the ferroptosis mechanism and in-depth study of DFX in neuroprotection, we believe that the link between the neuroprotective effect of DFX after brain injury and the inhibition of endogenous hematoma absorption is worth exploring and has important clinical value. Nonetheless, further animal experiments are needed to provide a basis for clinical trials to verify whether DFX can be used as a drug for clinical endogenous hematoma absorption regulation.

6.3. Monascin

Monascin is a yellow natural pigment formed by the cultivation and fermentation of *Monascus ruber* in cereals under certain conditions, which can reduce blood lipid and blood pressure and has anti-inflammatory and antioxidant effects (66). Monascin has been shown to play a role in endogenous hematoma absorption as a natural dual agonist of Nrf2 and PPAR-γ. A high dose of monascin can promote the reduction of hematoma volume 1–7 days after ICH (67). Long-term investigations showed that Nrf2 and PPAR-γ are crucial for increasing hematoma absorption, which significantly reduces iron overload and brain atrophy after ICH (68). It has also been pointed out that the PPAR-γ agonist monascin increases the levels of haptoglobin (Hp) and CD163 on the surface of phagocytes in plasma, accelerating hematoma absorption through the Hp–Hb–CD163 pathway (1). These animal experiments have found that monascin can promote endogenous hematoma absorption to improve ICH prognosis. However, corresponding clinical data have not been collected to demonstrate the safety of monascin in the treatment of ICH. Phase I clinical studies should be conducted as the next step to verify the security and effectiveness of monascin treatment.

6.4. Other potential drugs

Other potential drugs that promote endogenous hematoma absorption after ICH have also been extensively studied, including wogonin (69), vitamin D (70), and ISO-α-acids (IAAs) (49), which can upregulate surface CD36 of phagocytes *via* the PPAR-γ pathway, promote the polarization of M2 type microglia, and enhance the phagocytosis of M/MΦ to promote endogenous hematoma absorption after ICH. Bexarotene has the ability to pharmacologically activate retinoid X receptor-α (RXRα) and induce nuclear translocation of RXRα and PPAR-γ, which controls the M2 phenotype of microglia, reduces neuroinflammation, and increases hematoma absorption (71). According to a recent study by Chen et al., the mitochondrial reactive oxygen species (ROS)/NLRP-3 pathway, which is also strongly linked to hematoma absorption, may promote the transition of microglia from the M1 to the M2 phenotype under the influence of MitoQ treatment (72). However, the clinical applications of these potential drugs require further research.

7. Prospect

Over the past years, there have been several novel research directions on endogenous hematoma absorption after ICH, such as H_2S-mediated sustained microglial phagocytosis of hematoma, regulation of downstream signaling by miRNAs, the role of cerebral white matter fibers, and even physical therapeutic treatment methods such as remote ischemic conditioning. In conclusion, the core of hematoma absorption after ICH is the ability of phagocytes to engulf RBC. Most existing research is aimed at promoting hematoma absorption by enhancing the M2 shift of microglia and increasing the expression of their surface SRs. However, compared with other factors, PPAR-γ and Nrf2 signaling pathways that regulate leukocyte differentiation antigens on the surface of microglia to promote hematoma absorption have attracted more attention and in-depth research. Some agonists of the PPAR-γ and Nrf2 pathways can be used as clinical drugs for patients with ICH. Therefore, we believe that the regulation of microglia/macrophages will be the "final answer" to endogenous hematoma absorption after ICH. Identifying regulatory mechanisms and significant targets will be a direction for future research.

Author contributions

ZC and CD contributed to the conception and design of the study. ZC and XY provided administrative support. PF and MW provided the study materials. PF and MW collected and assembled the data. PF, MW, and WZ performed data analysis and interpretation. MZ and ZC revised the final version. All authors contributed to the writing of the manuscript and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Twenty-four-hour ambulatory blood pressure variability and association with ischemic stroke subtypes in the subacute stage

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Background and purpose: Blood pressure (BP) variability (BPV) increases the risk of cerebral disease in both hemorrhagic and ischemic strokes. However, whether BPV is associated with different types of ischemic stroke remains unclear. In this study, we explored the relationship between BPV and ischemic stroke subtypes.

Methods: We enrolled consecutive patients aged 47–95 years with ischemic stroke in the subacute stage. We categorized them into four groups based on their artery atherosclerosis severity, brain magnetic resonance imaging markers, and disease history: large-artery atherosclerosis, branch atheromatous disease, small-vessel disease, and cardioembolic stroke. Twenty-four-hour ambulatory blood pressure monitoring was performed, and the mean systolic blood pressure/diastolic blood pressure, standard deviation, and coefficient of variation were calculated. A multiple logistic regression model and random forest were used to test the relationship between BP and BPV in the different types of ischemic stroke.

Results: A total of 286 patients, including 150 men (73.0 ± 12.3 years) and 136 women (77.8 ± 9.6 years) were included in the study. Of these, 86 (30.1%) patients had large-artery atherosclerosis, 76 (26.6%) had branch atheromatous disease, 82 (28.7%) had small-vessel disease, and 42 (14.7%) had cardioembolic stroke. There were statistically significant differences in BPV between subtypes of ischemic stroke in 24-h ambulatory blood pressure monitoring. The random forest model showed that BP and BPV were important features associated with ischemic stroke. Multinomial logistic regression analysis demonstrated that systolic blood pressure levels; systolic blood pressure variability at 24 h, daytime and nighttime; and nighttime diastolic blood pressure were independent risk factors for large-artery atherosclerosis after adjustment for confounders. When compared to branch atheromatous disease and small-vessel disease, nighttime diastolic blood pressure and standard deviation of diastolic blood pressure were significantly associated with patients in the cardioembolic stroke group. However, a similar statistical difference was not seen in patients with large-artery atherosclerosis.

Conclusion: The results of this study indicate a discrepancy in blood pressure variability among different ischemic stroke subtypes during the subacute

stage. Higher systolic blood pressure and systolic blood pressure variability during the 24 h, daytime, and nighttime, and nighttime diastolic blood pressure were independent predictors for large-artery atherosclerosis stroke. Increased nighttime diastolic BPV was an independent risk factor for cardioembolic stroke.

KEYWORDS

ambulatory blood pressure variability, ischemic stroke, large-artery atherosclerosis, branch atheromatous disease, small-vessel disease, cardioembolic stroke

1. Introduction

Hypertension is an important risk factor for cardiovascular and cerebrovascular disease (1, 2). Elevated blood pressure levels, particularly systolic blood pressure (SBP), significantly increase the risk of stroke, poor prognosis, and recurrence in patients with ischemic stroke (3, 4). Blood pressure variability (BPV), an increasing research interest in recent years, mainly reflects continuous fluctuations in blood pressure over hours, days, months, or years, including short-term, medium-term, and long-term blood pressure variability. Reports demonstrate that BPV, independent of the BP level, is strongly associated with heart disease, cognitive impairment, and stroke (5–7).

Twenty-hour ambulatory blood pressure monitoring (ABPM), which documents BP fluctuations during daytime and nighttime, is a more valuable and scientific method for predicting pressure-related brain damage compared to a single blood pressure measurement (8). Previous studies have indicated that BPV positively correlates with ischemic stroke in both large- and small-vessel diseases. For example, a study found that ambulatory blood pressure variability (ABPV) was positively associated with carotid intima-media thickness and prompted the formation of atherosclerotic plaque in hypertensive patients. This suggested that BPV is the strongest predictor of extracranial large-artery disease (9). Meanwhile, higher BPV is linked with early intra-arterial thrombectomy treatment and adverse outcomes in patients with acute ischemic stroke with intracranial large-artery disease (10). Moreover, cerebral small-vessel disease (CSVD) is a common and potentially devastating condition in the elderly. Recent evidence indicated that 24-h ABPV is closely associated with the total CSVD burden as well as with different magnetic resonance imaging (MRI) markers of CSVD, such as white matter hyperintensity (WMH), enlarged perivascular spaces, and lacunar infarction. Together, they gradually aggravate the progression of CSVD (11–14). Simultaneously, nighttime BPV has been confirmed to increase the risk of cardioembolic stroke (CES), which is attributed to the increased risk of cardiovascular disease (15).

These results demonstrate that BPV and ischemic stroke are closely associated and are based on the differences in vascular anatomy, structure, and pathological changes between large and small intracranial vessels in the brain. We hypothesized that there may be differences in clinical characteristics and BPV variability among subtypes of ischemic stroke. However, these differences are poorly understood. Therefore, our novel study investigates the association between BPV and ischemic stroke subtypes. We aim to discover the different effects of BPV across subtypes of ischemic stroke and provide valuable implications for the targeted management of BP in patients with ischemic stroke.

2. Materials and methods

2.1. Ethics approval

This study was approved by the local ethics committee of Zhongguancun Hospital, Beijing, China (20230104). Due to the retrospective and observational design of this study, which posed no potential harm to the enrolled patients, the requirement for informed consent was waived. All medical records and personal information were anonymized and de-identified.

2.2. Study subject

This is a retrospective study that enrolled a consecutive series of patients with acute ischemic stroke within 24 h of admission to the Neurology Department of Beijing Zhongguancun Hospital Affiliated with the Chinese Academy of Sciences between 1 January 2019 and 30 April 2022. Ischemic stroke was defined as the sudden onset of neurologic dysfunction and associated new infarcts on cranial CT or brain MRI (16). All patients included in this study met the following inclusion criteria: (1) Those who were older than 18 years; (2) Had undergone 24-h ambulatory blood pressure monitoring (ABPM) in a subacute stage, defined as the period from 72 h after the onset of symptoms of ischemic stroke until the day of discharge or transfer to a rehabilitation unit (4–21 days) during which the patients were neurologically and medically stable (17); and (3) Had undergone brain magnetic resonance imaging (MRI) and magnetic resonance angiogram (MRA) or computed tomography angiography (CTA). The exclusion criteria were as follows: (1) hospitalization stay of <72 h; (2) Hemorrhagic stroke; and (3) Infarction caused by hematological system diseases, hereditary diseases, artery dissection, intracranial tumor, inflammation, or traumatic brain injury. The early management of ischemic stroke was in accordance with the 2018 American Heart Association/American Stroke of Anesthesiologists (AHA/ASA) guideline criteria (17).

2.3. Clinical information

Clinical data included demographics and stroke risk factors, such as age, sex, hypertension, diabetes mellitus (DM), dyslipidemia, coronary heart disease (CHD), atrial fibrillation, drinking, smoking, and National Institutes of Health Stroke Scale (NIHSS) scores on admission. Laboratory tests included blood urea nitrogen (BUN), creatinine (Cr), fasting glucose (FGB), serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), homocysteine (HCY), hemoglobin, and C-reactive protein (CRP). Antihypertensive drugs used were classified as angiotensin-receptor blockers (ARB), angiotensin-converting enzyme inhibitors (ACEI), calcium-channel blockers (CCB), β-blockers, and diuretics.

2.4. Brain MRI analysis and etiological classification of ischemic stroke

All the patients included in this study underwent brain MRI using a 1.5-Tesla scanner (SIGNA Explore, Erlangen, Germany). The whole MRI sequence had a thickness of 5 mm both in the axial and sagittal planes. The parameters included were as follows: T1-weighted images (repetition time [TR]/echo time [TE] = 1750/29), T2-weighted images (TR/TE = 5485/126), fluid attenuation inversion recovery (FLAIR; TR/TE =8400/150), diffusion-weighted imaging (DWI; TR/TE = 4000/68), and susceptibility-weighted imaging (SWI; TR/TE = 75/47.4, slice thickness = 3mm). Three-dimensional time-of-flight (3D-TOF) magnetic resonance angiogram scans (TR/TE = 23/3.8, slice thickness = 1.4 mm) were obtained in the axial plane.

Vascular imaging, including MRA, CTA, or doppler ultrasonography, was used to assess the stenosis of the intracranial and extracranial arteries. The degree of stenosis was classified according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria as follows: none, 0; mild, 0–49%; and moderate to severe, 50–99% (18, 19).

Acute infarction was defined based on DWI and the apparent diffusion coefficient (ADC) map. The maximum diameter of the infarcts was measured by DWI in axial planes, and the infarct location, size, and extent of vascular stenosis were evaluated by two professional neurologists (LijW and XLiu), who were blinded to the patient's characteristics. Discrepancies were resolved by consensus. The included patients were classified into four etiological subtypes according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria and the definition of related-branch atheromatous (20–22): (1) Large-artery atherosclerosis (LAA): infarct lesions >15 mm in diameter and with significant (>50%) stenosis or occlusion in intracranial or extracranial arteries. (2) Branch atheromatous disease (BAD): infarct lesions in the lenticulostriate arterial (LAS) region with a diameter ≥15 mm, appeared in at least three consecutive axial slices (at a slice thickness of 5 mm) and in the absence of middle cerebral artery stenosis (>50%); or an infarct lesion in the pontine penetrating arterial (PPA) region that extends from the deep pons to the ventral pons unilaterally on the axial DWI in the absence basal artery stenosis (>50%) and potential sources of cardioembolic stroke. (3) Small-vessel disease (SVD): infarct lesion <15 mm in diameter, located in the white matter and the deep gray matter of the brain and brainstem and unaccompanied by ipsilateral large-artery stenosis (>50%). This category also includes infarct lesions in the LSA region with <3 slices or in the pontine region that does not extend to the ventral surface of the pons in order to distinguish them from BAD. (4) Cardioembolism (CE): the presence of at least one risk factor for the cardiac source of embolism (atrial fibrillation/acute myocardial infarction/mechanical prosthetic valve, etc.) and the absence of large-artery atherosclerosis.

2.5. 24-h ABPM and 24-h ABPV

Regular systolic and diastolic blood pressures were recorded using 24-h ABPM with a fully automatic oscillometric device (NC 27560, Sun Tech Medical. Morrisville, U.S.A, 2013). The device was validated according to the protocol of the British Hypertension Society (23). The BP was measured by well-trained research staff after the patient had rested for at least 5 min in a seated position. An appropriately sized BP cuff was fixed to the upper arm of non-hemiplegic patients with a stable clinical conditions. Patients were instructed to perform their usual activities and avoid excessive movement during the measurement. Measurements were taken every 30 min during the day (8 a.m. to 10:59 p.m.) and every 60 min during the night (11 p.m. to 7:59 a.m.). The definition of day and night is based on an automated system with standard time windows. The results were considered usable if more than 80% of the measurements were valid. The 24-h ABPV was represented by several indices: mean systolic blood pressure (SBP)/diastolic blood pressure (DBP), coefficient of variation (CV = SD / mean BP ×100 [%]) (24), and standard deviation (SD) of SBP and DBP in 24 h, daytime, and nighttime. In addition to 24-h ABPV, we calculated the nocturnal dip (%) (25), which represents the percentage of systolic blood pressure drop at night.

$$\frac{mean\ SBP_{daytime} - mean\ SBP_{nightime}}{mean\ SBP_{daytime}} \times 100$$

Dipping category: extreme dipper (> 20%), dipper (≥ 10% and ≤ 20%), non-dipper (0–10%), and reverse-dipper (< 0%). Patients continued to use antihypertensive medication during the study period.

2.6. Statistical analysis

Distributions of continuous variables are presented as mean (SD) for normally distributed variables and medians (interquartile range) for abnormally distributed variables. One-way ANOVA tests or non-parametric tests were used where appropriate. Categorical variables are presented as percentages and chi-squared tests were used. For multiple comparisons between groups, the Bonferroni test and Kruskal–Wallis H-test were used for normally distributed continuous and anomalous continuous

variables, respectively. Multiple logistic regression analysis was performed to identify the association between ABPV and each ischemic stroke subtype. The dependent variable was the subtype of ischemic stroke, and the independent variables were ABPV and positive factors ($p < 0.05$) in univariate analysis, including age, sex, coronary heart disease, NIHSS, smoking, triglyceride, hyperhomocysteinemia, hemoglobin, serum creatinine, fasting blood glucose, and antihypertensive drugs. To reduce collinearity between the data, the blood pressure-dependent variables were not entered into the multivariate logistic regression model simultaneously. Data analysis was performed using IBM SPSS Statistics software version 26.0 (IBM SPSS Inc, Chicago, USA). The effect estimates were determined using 95% confidence intervals (CIs) with statistical significance defined as a p-value of < 0.05.

Random forest is a classic machine learning algorithm that is considered to have a high accuracy in disease risk prediction and diagnosis. The specific model construction process is as follows: (1) The random forest is assumed to have K-trees, and each tree has a certain number of sample sets to train. The sample set is randomly generated in proportion to the original training sample set of N, using the bootstrapping resampling method. (2) M is the number of features. For each tree node, m features are randomly selected, with m being much smaller than M. The Gini coefficient is used to compute the best splitting based on the m features. (3) In this study, 500 decision trees were constructed, and variables were randomly selected at each decision tree node. The optimal feature was selected from the m features, and the decision trees constituted the random forest. R software (version 3.5.1) was used for data analysis.

3. Results

3.1. Patient characteristics

A total of 881 patients with stroke in the subacute stage were admitted to our hospital during the study period. Of these, 106 patients with hemorrhagic stroke were excluded, and an additional 383 patients who did not undergo the 24-h ABPM were also excluded. Ultimately, 286 patients were successfully enrolled in the final analysis after further excluding 106 patients with other determined/undetermined etiology infarcts or other reasons (Figure 1). Baseline characteristics and 24-h ambulatory blood pressure variability were compared across the ischemic stroke subtypes. The average age ranged from 47 to 95 years (mean ± SE: 75.3 ± 11.3), and approximately half of the patients (52.4%) were men. The patients were divided into four groups according to the etiological mechanism of ischemic stroke: 86 patients had large-artery atherosclerosis (30.1%), 76 had branch atheromatous disease (26.6%), 82 had small-vessel disease (28.7%) and 42 had cardioembolic strokes (14.7%).

A comparison of the clinical characteristics and laboratory variables is shown in Table 1. Among the four groups, there were significant differences in age ($p < 0.001$), sex ($p = 0.005$), smoking ($p = 0.004$), NIHSS ($p < 0.001$), TG ($p = 0.005$), FBG ($p = 0.005$), HCY ($p = 0.041$), Cr ($p = 0.002$), CHD ($p = 0.012$), HGB ($p = 0.001$), and β-blocker drugs ($p < 0.001$) among the four groups. No significant differences were found in alcohol intake, history of diabetes,

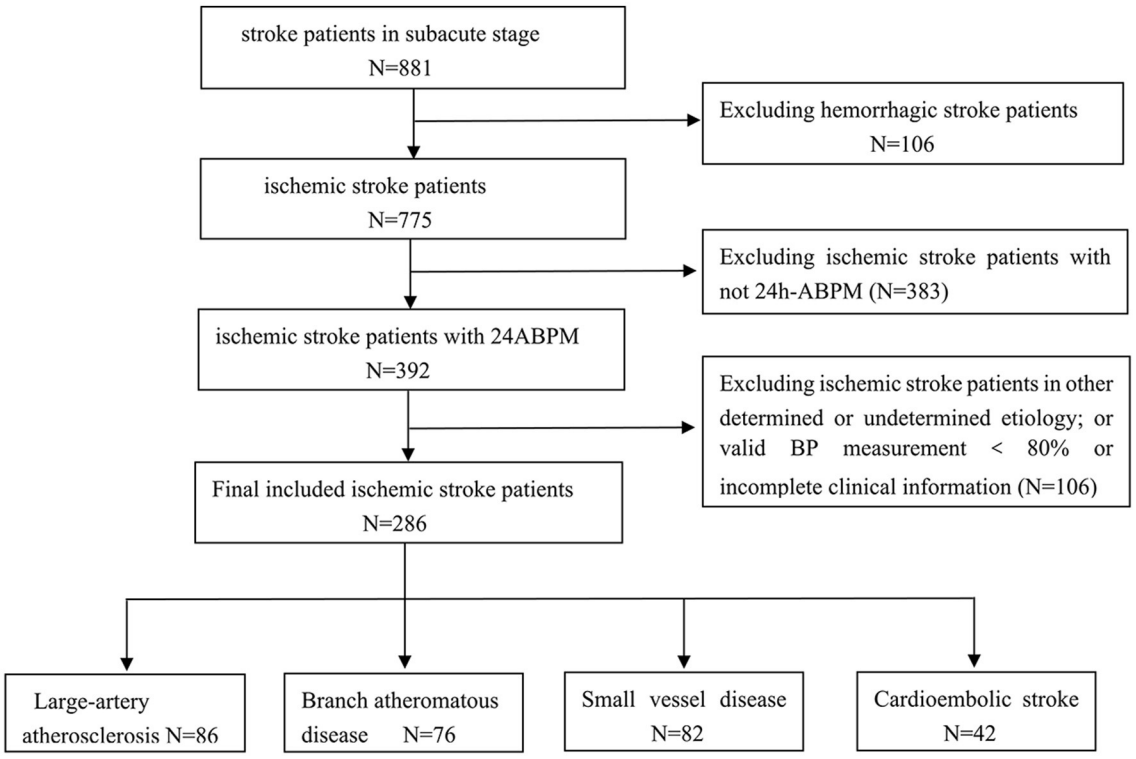

FIGURE 1
Flowchart of patients included in the study. ABPM, ambulatory blood pressure monitoring.

TABLE 1 General characteristics of all subjects in the four ischemic stroke subtypes.

Characteristics	LAA ($n = 86$)	BAD ($n = 76$)	SVD ($n = 82$)	CES ($n = 42$)	F/χ^2/Z	*P*-value
Age, years[a]	74.1 ± 10.6	68.2 ± 11.3	80.5 ± 9.2	80.7 ± 8.8	23.596	<0.001
Sex, male (%)	53 (61.6%)	40 (52.6%)	45 (54.9%)	12 (28.6%)	12.702	0.005
Smoking, yes (%)	27 (31.4%)	29 (38.2%)	13 (15.9%)	7 (16.7%)	13.194	0.004
Drinking, yes (%)	16 (18.6%)	14 (18.4%)	7 (8.5%)	6 (14.3%)	4.269	0.234
History of Diabetes mellitus (%)	41 (47.7%)	44 (57.9%)	38 (46.3%)	18 (42.9%)	3.322	0.345
History of hypertension (%)	69 (80.2%)	64 (84.2%)	65 (79.3%)	36 (85.7%)	1.225	0.747
History of CHD (%)	35 (40.7%)	20 (26.3%)	26 (31.7%)	23 (54.8%)	10.926	0.012
NIHSS[b]	8 (3, 11)	5 (2, 8)	0 (0, 4)	12 (5, 17)	67.110	<0.001
low-density lipoprotein,[a] mmol/L	2.2 ± 0.7	2.4 ± 0.9	2.2 ± 0.6	2.2 ± 0.7	1.561	0.199
high-density lipoprotein,[a,b] mmol/L	0.96 (0.80, 1.14)	1.03 (0.83, 1.18)	1.02 (0.88, 1.25)	1.1 ± 0.4	3.336	0.343
Total cholesterol,[a] mmol/L	3.7 ± 0.9	4.1 ± 1.2	3.9 ± 0.8	3.6 ± 1.0	2.261	0.082
Triglycerides,[b] mmol/L	1.2 (0.9, 1.6)	1.4 (1.0, 1.8)	1.2 (0.9, 1.4)	1.1 (0.9, 1.3)	12.742	0.005
FBG,[b] mmol/L	5.6 (4.8, 6.5)	6.5 (5.3, 9.3)	5.6 (4.9, 7.0)	6.24 (5.0, 7.5)	12.691	0.005
HCY,[b] mmol/L	12.1 (9.4, 15.8)	10.7 (8.6, 12.9)	11.7 (9.8, 15.7)	11.2 (8.6, 14.3)	8.231	0.041
CRP,[b]mg/L	4.1 (1.2, 11.7)	2.3 (1.0, 9.4)	3.1 (1.2, 9.8)	3.7 (1.7, 14.3)	4.209	0.240
Creatinine,[b] umol/L	70.5 (62.7, 87.0)	63.0 (52.3, 77.7)	71.5 (59.7, 90.0)	61.0 (46.7, 82.2)	15.070	0.002
Uric Acid,[a] mmol/L	296.3 ± 82.4	297.1 ± 100.9	304.4 ± 103.4	267.6 ± 106.8	1.377	0.250
HGB,[a] mg/L	127.1 ± 16.9	130.5 ± 16.9	123.1 ± 16.5	119.1 ± 15.5	5.300	0.001
Class of antihypertensive drugs						
Dihydropyridine CCB (%)	52 (60.5%)	44 (57.9%)	44 (53.7%)	20 (47.6%)	2.185	0.535
ARB (%)	35 (40.7%)	33 (43.4%)	30 (36.6%)	14 (33.3%)	1.491	0.684
ACEI (%)	8 (9.3%)	3 (3.9%)	1 (1.2%)	2 (4.8%)	6.116	0.106
β-Blocker (%)	16 (18.6%)	7 (9.2%)	13 (15.9%)	19 (45.2%)	23.826	<0.001
Diuretics (%)	21 (24.4%)	17 (22.4%)	19 (23.2%)	14 (33.3%)	2.003	0.572

[a]Mean ± SD; [b]median (interquartile range). CHD, coronary heart disease; NIHSS, National Institute of Health Stroke Scale; FBG, fasting glucose; HCY, hyperhomocysteinemia; CRP, C-reactive protein; HGB, hemoglobin; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CCB, calcium-channel blocker; LAA: large-artery atherosclerosis; BAD: branch artery disease; SVD, small-vessel disease; CES, cardioembolic stroke.

hypertension, or levels of low-density lipoprotein, high-density lipoprotein, total cholesterol, C-reactive protein, uric acid, and antihypertensive drugs (Dihydropyridine/ARB/ACEI/Diuretics). Furthermore, multiple comparisons showed that there were significant differences in the positive factors in the univariate analysis between the four groups (Supplementary Figure 2).

3.2. Association between 24-h ABP levels and ischemic stroke subtypes

Table 2 presents 24-h ABP levels over the 24 h, daytime, and nighttime, with ischemic stroke subtypes. There were significant differences between mean SBP levels, SBP-SD, SBP-CV, mean DBP level, DBP-SD, and DBP-CV at 24 h, daytime and nighttime ($p < 0.05$). However, the statistically different was not in SBP-CV ($p = 0.051$) and DBP-CV ($p = 0.200$) among the four groups at nighttime. Furthermore, multiple comparisons among the four groups revealed that the BP and BPV during 24 h, daytime, and nighttime with ischemic stroke also have statistical differences (Supplementary Figure 2).

3.3. Feature selection and ranking by random forest

Figure 2 displays the important variables that contribute to the risk of ischemic stroke as identified by random forest: NIHSS, age, GLU, Cr, BP, and BPV (24-h SBP, 24-h SBP-SD, 24-h SBP-CV, 24-h DBP, daytime SBP, daytime DBP, nighttime DBP, and nighttime SBP-SD). These results support the notion that SB and BPV are stronger risk factors for ischemic stroke. To further analyze the difference between BP and BPV in ischemic stroke subtypes, multinomial logistic regression was conducted.

TABLE 2 Ambulatory blood pressure levels and variability in different subgroups.

BP variate	LAA ($n = 86$)	BAD ($n = 76$)	SVD ($n = 82$)	CES ($n = 42$)	F/Z	P -value
24-hour						
SBP[a], mmHg	145.0 ± 16.8	140.5 ± 14.3	138.0 ± 15.9	132.4 ± 16.9	6.473	<0.001
DBP[a],mmHg	78.2 ± 10.7	79.3 ± 10.7	72.5 ± 10.9	73.9 ± 10.5	6.912	<0.001
SBP SD[b], mmHg	15.9 (13.4, 19.4)	13.2 (11.0, 16.3)	14.1 (11.9, 17.5)	16.5 (13.5, 18.2)	6.514	<0.001
DBP SD[a,b], mmHg	10.1 (8.2, 12.1)	9.6 ± 2.7	9.3 (7.6, 11.3)	11.0 (8.9, 13.1)	5.140	0.011
SBP CV[b], %	11.2 (9.3, 13.0)	9.7 (7.7, 11.6)	10.7 ± 2.9	12.6 ± 3.1	8.608	<0.001
DBP CV[a,b], %	12.9 (10.8, 15.3)	12.2 ± 3.6	13.3 (10.7, 15.5)	15.2 (12.0, 18.8)	7.248	0.002
Daytime						
SBP[a], mmHg	144.8 ± 17.7	140.9 ± 14.3	138.0 ± 16.3	131.7 ± 17.6	6.449	<0.001
DBP[a], mmHg	78.0 ± 11.1	79.8 ± 10.8	73.4 ± 12.1	73.5 ± 10.9	5.615	0.001
SBP SD[b], mmHg	15.3 (12.3, 17.9)	13.4 (10.8, 15.9)	14.4 (11.7, 17.6)	15.8 (12.3, 17.6)	4.320	0.003
DBP SD[a,b], mmHg	9.8 (7.7, 11.6)	9.2 ± 2.7	9.1 (7.6, 11.6)	10.3 (8.6, 12.1)	3.678	0.047
SBP CV[a,b], %	10.7 (8.7, 12.0)	9.6 ± 2.6	10.6 (8.8, 12.4)	12.2 ± 2.9	7.363	<0.001
DBP CV[a,b], %	12.6 (10.4, 15.1)	11.7 ± 3.5	13.0 (10.3, 16.0)	14.3 (12.0, 17.0)	7.200	0.001
Nighttime						
SBP[a], mmHg	144.2 ± 18.4	137.3 ± 16.7	138.4 ± 16.8	134.9 ± 17.6	3.530	0.015
DBP[a], mmHg	78.2 ± 11.2	75.8 ± 11.6	70.9 ± 12.2	76.4 ± 11.1	6.068	0.001
SBP SD[a,b], mmHg	14.2 (10.7, 23.0)	11.5 (8.9, 14.4)	12.2 ± 4.9	13.5 (9.6, 16.9)	4.063	0.018
DBP SD[b], mmHg	8.8 (7.1, 11.3)	7.9 (6.1, 10.0)	8.0 (6.1, 9.4)	9.0 (6.8, 11.9)	4.825	0.026
SBP CV[a,b], %	9.8 (7.4, 11.7)	8.3 (6.1, 11.0)	8.8 ± 3.2	10.0 (6.7, 13.2)	2.640	0.051
DBP CV[a,b], %	11.4 (9.2, 15.4)	10.6 (8,2, 13.4)	11.6 ± 4.3	12.5 (9.4, 15.9)	2.398	0.200
Nocturnal dip					19.926	0.018
Reverse dipper (<0%)	38 (44.2%)	26 (34.2%)	47 (57.3%)	27 (64.3%)		
Non-dipper (0–9%)	38 (44.2%)	35 (46.1%)	28 (34.1%)	12 (28.6%)		
Dipper (10–19%)	7 (8.1%)	14 (18.4%)	7 (8.5%)	2 (4.8%)		
Extreme dipper (≥20%)	3 (3.5%)	1 (1.3%)	0 (0)	1 (2.4%)		

[a]Mean ± SD; [b]median (interquartile range). SBP, systolic blood pressure; DBP, diastolic blood pressure; CV, coefficient of variation; SD, standard deviation. LAA, large-artery atherosclerosis; BAD, branch artery disease; SVD, small-vessel disease; CES, cardioembolic stroke.

3.4. The multinomial logistic regression analysis association between 24-h ABP levels and stroke subtypes

Table 3 shows the multinomial logistic regression analysis between 24-h blood pressure variability and stroke subtypes. The results indicated that a higher SBP is an independent risk factor for LAA over 24 h, daytime and nighttime, compared with other stroke subtypes after adjusting for age, sex, CHD , β-blocker drugs, smoking, NIHSS, TG, FBG, HCY, Cr, and HGB ($p < 0.05$). Higher SBP-SD and SBP-CV were also associated with an increased risk of LAA stroke compared to BAD and SVD groups ($p < 0.05$). Meanwhile, when compared with the BAD and SVD groups, the nighttime mean DBP level and DBP-SD were significantly associated with greater risk in the CES group ($p < 0.05$). This indicates that the DBP variability at night was an independent risk factor for CES.

4. Discussion

In this study, we explored the potential association between 24-h ABP levels, 24-h ABPV, and subtypes of ischemic stroke in patients treated at our hospital. We discovered that higher SBP levels significantly increased the risk of large-artery atherosclerosis stroke at 24 h, daytime, and nighttime. Multinomial logistic regression analysis indicated that the SBP level of 24 h was an independent risk factor for large-artery atherosclerosis after adjusting for patient demographics and vascular risk factors. When comparing the risks of SVD and BAD to LAA, SBP-SD, SBP-CV, and DBP levels, these were significantly associated with large-artery atherosclerosis, especially at night. At the same time, nighttime

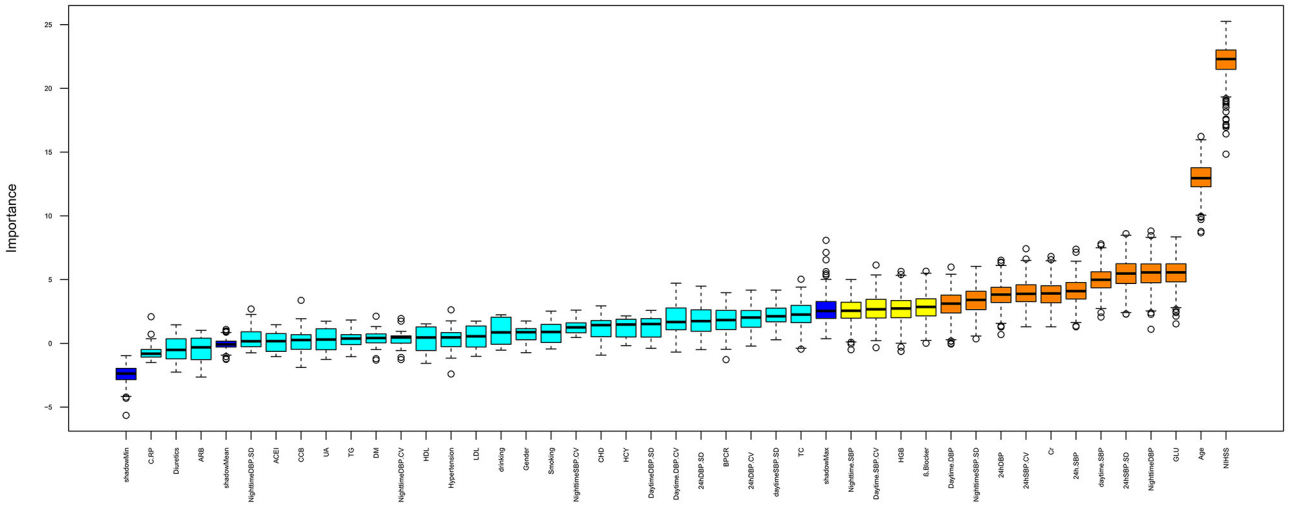

FIGURE 2
Important feature selection by random forest. The plot displays all the features leading up to the stroke. Important variables are in orange boxes, rejected variables are in cyan boxes, and tentative variables are in yellow boxes.

DBP levels and DBP-SD were independent risk factors for CES compared to BAD and SVD, indicating that a higher nighttime diastolic blood pressure variability (DBPV) significantly increased the risk of CES.

We believe that higher SBP levels are strongly associated with ischemic stroke and are a stronger independent risk factor for the strict control and management of hypertension (26). A high mean SBP level and high SBPV were significantly associated with poor functional outcomes of acute ischemic stroke and/or may increase the risk of recurrent stroke during long-term secondary stroke prevention (26–28). This suggests that effective control of the SBPV is important for reducing stroke events. Nonetheless, very few studies have further analyzed the characteristics of blood pressure levels and blood pressure variability in subtypes of ischemic stroke, which may underlie different pathogeneses (29, 30).

The present study showed significant differences in mean BP and BPV between the four ischemic stroke subtypes. First, the SBP in the LAA group was higher than that in the CES, BAD, and SVD groups, similar to previous studies on the contribution of hypertension to atherosclerosis. It has been reported that angiotensin II, a key factor in the pathogenesis of hypertension, and T cells, the main biomarkers of inflammation, simultaneously take part in the unleashing of inflammatory pathways causing elevated blood pressure and atherosclerosis. These pathophysiological changes can lead to an increase in the intima-media thickness of large vessels and the formation of plaque in the artery leading to atherosclerosis; furthermore, the large vessel is gradually stenosed or occluded in the subsequent stages (31, 32).

When compared with BPV among the four groups, we found that SBP-SD (24 h, daytime, and nighttime) was higher in the LAA group compared to the BAD group. Additionally, the SPB-CV at 24 h and the nighttime DBP level showed similar results. Branch atheromatous disease, mainly involving the lenticulostriate arterial and the pontine penetrating arterial, with a smaller blood vessel diameter than the parental artery, was considered to have the same risk factors (hypertension, diabetes mellitus, hyperlipidemia, and hyperhomocysteinemia) as a large atherosclerotic disease. However, the etiology may differ for small and large cerebral arterial diseases. The present study shows that SBPV is higher in LAA than that in BAD, which supports a strong correlation between SBPV with large-artery atherosclerosis stroke (27). Moreover, the clinical characteristics also differed between the LAA and BAD groups. Patients in the LAA group were significantly older than those in the BAD group. Therefore, BAD may be considered an early stage of large-artery atherosclerosis and should be strictly managed with SBP and SBPV. Meanwhile, multinomial logistic regression analysis depicted that the fasting blood glucose (FBG) level was an independent risk factor for BAD. These results are consistent with previous studies showing that DM or HbA1c is associated with BAD, especially paramedian pontine arteries disease (33).

The SBP-SD in the LAA group (24 h, nighttime) was higher than that in the SVD groups, and the same significance was in the mean DBP level and SBP-CV at nighttime. Previous studies have demonstrated that large SBP variability is associated with a higher burden of cerebral small-vessel disease (13, 34). Our research found a difference in SBP variability between LAA and SVD, which may be attributed to their different etiologies. Small-vessel disease, in particular, is caused by a group of pathological processes of the perforating cerebral arterioles, capillaries, and venules of the brain and is considered lipohyalinosis of the penetrating artery. LAA is caused by large-artery atherosclerosis with stenosis or blocking. The apparent differences in anatomy and pathophysiology may explain the differences in the SBP variability.

When comparing BP levels and BPV with BAD and SVD in the CES group, the results demonstrated that nighttime DBP levels and DBP-SD are independent risk factors for CES. In addition, elevated DBP levels and DBPV increase the risk of CES events at night. This is consistent with a multicenter, prospective cohort

TABLE 3 Multinomial logistic regression analysis: association between 24-h ABP levels and stroke subtypes.

	Model 1				Model 2			Model 3	
	CES	LAA	BAD	SVD	SVD	LAA	BAD	BAD	LAA
	ref	OR (95%CI)	OR (95%CI)	OR (95%CI)	ref	OR (95%CI)	OR (95%CI)	ref	OR (95%CI)
24-hour									
SBP, mmHg	1	1.610 (1.192∼2.173)[b]	1.221 (0.880∼1.694)	1.218 (0.892∼1.663)	1	1.321 (1.053∼1.657)[a]	1.002 (0.778∼1.292)	1	1.318 (1.042∼1.688)[a]
DBP, mmHg	1	0.926 (0.600∼1.430)	0.819 (0.502∼1.337)	0.675 (0.420∼1.084)	1	1.372 (0.953∼1.974)	1.214 (0.811∼1.817)	1	1.131 (0.788∼1.622)
SD_{SBP}, mmHg	1	1.166 (0.767∼1.772)	0.709 (0.425∼1.183)	0.779 (0.484∼1.252)	1	1.498 (1.018∼2.203)[a]	0.911 (0.578∼1.436)	1	1.644 (1.086∼2.489)[a]
SD_{DBP}, mmHg	1	0.753 (0.422∼1.343)	0.693 (0.351∼1.366)	0.454 (0.236∼0.873)[a]	1	1.661 (0.973∼2.834)	1.527 (0.832∼2.802)	1	1.087 (1.626∼1.890)
SBP-CV, %	1	1.078 (0.569∼1.075)	0.516 (0.238∼1.116)	0.754 (0.375∼1.514)	1	1.426 (0.814∼2.498)	0.684 (0.349∼1.340)	1	2.085 (1.117∼3.890)[a]
DBP-CV, %	1	0.696 (0.424∼1.142)	0.556 (0.308∼1.002)	0.582 (0.336∼1.008)	1	1.196 (0.758∼1.888)	0.956 (0.565∼1.617)	1	1.252 (0.774∼2.024)
Daytime									
SBP, mmHg	1	1.641 (1.229∼2.191)[b]	1.360 (0.994∼1.863)	1.260 (0.934∼1.700)	1	1.302 (1.045∼1.623)[a]	1.080 (0.846∼1.377)	1	1.206 (0.965∼1.507)
DBP, mmHg	1	0.930 (0.635∼1.362)	0.808 (0.522∼1.252)	0.766 (0.511∼1.147)	1	1.215 (0.877∼1.683)	1.055 (0.728∼1.530)	1	1.151 (0.816∼1.626)
SD_{SBP}, mmHg	1	1.186 (0.745∼1.888)	0.757 (0.433∼1.324)	0.960 (0.575∼1.602)	1	1.236 (0.823∼1.855)	0.789 (0.486∼1.279)	1	1.566 (1.002∼2.447)[a]
SD_{DBP}, mmHg	1	0.739 (0.395∼1.383)	0.692 (0.337∼1.417)	0.541 (0.274∼1.068)	1	1.367 (0.804∼2.323)	1.278 (0.701∼2.331)	1	1.069 (0.613∼1.864)
CV_{SBP}, %	1	0.879 (0.475∼1.628)	0.559 (0.271∼1.153)	0.694 (0.352∼1.370)	1	1.266 (0.728∼2.203)	0.805 (0.428∼1.515)	1	1.573 (0.875∼2.826)
CV_{DBP}, %	1	0.829 (0.519∼1.324)	0.699 (0.401∼1.219)	0.812 (0.488∼1.352)	1	1.020 (0.660∼1.578)	0.861 (0.520∼1.425)	1	1.186 (0.744∼1.889)
Nighttime									
SBP, mmHg	1	1.315 (1.022∼1.692)[a]	1.064 (0.800∼1.416)	1.126 (0.862∼1.470)	1	1.168 (0.954∼1.431)	0.946 (0.748∼1.196)	1	1.235 (0.995 ∼1.534)
DBP, mmHg	1	0.873 (0.596∼1.280)	0.609 (0.393∼0.944)[a]	0.592 (0.394∼0.891)[a]	1	1.475 (1.071∼2.033)[a]	1.029 (0.720∼1.469)	1	1.434 (1.021∼2.015)[a]
SD_{SBP}, mmHg	1	1.202 (0.862∼1.678)	0.838 (0.559∼1.256)	0.864 (0.595∼1.255)	1	1.391 (1.033∼1.874)[a]	0.969 (0.680∼1.381)	1	1.435 (1.049∼1.965)[a]
SD_{DBP}, mmHg	1	0.688 (0.438∼1.079)	0.469 (0.268∼0.821)[b]	0.487 (0.278∼0.852)[a]	1	1.413 (0.886∼2.253)	0.964 (0.569∼1.631)	1	1.466 (0.934∼2.300)
CV_{SBP}, %	1	1.098 (0.711∼1.696)	0.753 (0.452∼1.255)	0.702 (0.428∼1.149)	1	1.565 (1.051∼2.329)[a]	1.073 (0.682∼1.689)	1	1.458 (0.984∼2.160)
CV_{DBP}, %	1	0.974 (0.905∼1.048)	0.929 (0.851∼1.014)	0.929 (0.852∼1.013)	1	1.316 (0.945∼1.833)	1.026 (0.703∼1.498)	1	1.282 (0.917∼1.794)

Model 1: CES is used as a reference; the multinomial logistic regression model was adjusted for age, sex, NIHSS, coronary heart disease, smoking, triglyceride, hyperhomocysteinemia, hemoglobin, serum creatinine, fasting blood glucose, and antihypertensive drugs plus 24-h BP plus BPV. Model 2: SVD is used as a reference, and Model 3 BAD is used as a reference, respectively, and the multivariate regression model includes the same analysis variables as Model 1. The results of the multinomial logistic regression analysis were presented as OR per 10 mmHg increase in BP, 5 mmHg increase in SD, and 5% increase in CV. [a]$p < 0.05$, [b]$p < 0.01$. OR, odds ratio; CI, confidence interval; LAA, large-artery atherosclerosis; BAD, branch artery disease; SVD, small-vessel disease; CES, cardioembolic stroke.

study, which suggested that a higher nighttime BP and a rising pattern of nocturnal BP were significantly associated with the risk of cardiovascular disease in patients who underwent 24-h ambulatory BP monitoring. Furthermore, nighttime BP was more important than daytime BP as a risk factor for total cardiovascular disease burden (15). There are three possible explanations for this finding. First, higher blood pressure variability notably increased the risk of atrial fibrillation (AF) (35). Being an independent risk factor for ischemic stroke, it increased the incidence of stroke four to five times compared to the patients without atrial

fibrillation (36). The second was a heart rate, which was higher in the CES group than in the BAD and SVD groups at night during the 24-h ambulatory BP monitoring period. These are often accompanied by atrial fibrillation or other cardiovascular diseases. Increased and irregular heart rates shorten the duration of diastole in the ventricles, resulting in higher diastolic blood pressure. Third, the changes and characteristics of hypertension in older patients, the reduction in vascular elasticity, and baroreceptor reflex dysfunction increase the fluctuation of blood pressure and the impairment of autoregulation of blood flow in vital organs (37). In the current study, patients in the BAD group were younger than those in the CES group. All of these factors contribute to the development of CES by increasing DBP levels and DBP-SD at night.

The current study had some limitations: First, the classification of subtypes of ischemic stroke based on brain vascular images was not performed with a high-resolution MRI, which is useful in identifying atherosclerotic pathologies in perforated arteries, providing direct evidence to distinguish between LAA and BAD. Second, our study was based on a single-center retrospective analysis, and the limited data may have affected the statistical validity of BP, BPV, and ischemic stroke subtypes. We believe that multicenter, prospective studies are needed to obtain more significant results on this issue. Third, patients underwent a 24-h ABPM while in the hospital, which may have led to some degree of white coat hypertension. A larger and prospective study is needed to further explore the differences in 24-h ABPM measurements between inpatient and outpatient settings for ischemic stroke patients.

5. Conclusion

There were significant differences in BP and BPV among the ischemic stroke subtypes in the subacute stage. Higher systolic blood pressure and systolic blood pressure variability during the 24 h, daytime, and nighttime, and nighttime diastolic blood pressure were independent predictors of large-artery atherosclerosis stroke. Increased nighttime diastolic blood pressure variability was found to be an independent risk factor for cardioembolic stroke.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committe of Beijing Zhongguancun Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

XLi contributed significantly to the conception of the study and modified the manuscript. LijW accumulated clinical data, discussed results, and contributed to the final version of the manuscript. XX, ZC, and PL modified the manuscript. XLiu contributed to the imaging analysis. GW, DY, and YW have provided statistical analysis support. LinW provided constructive and forward-looking advice during the research. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1139816/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Multiple comparisons in demographic information and clinical characteristics. Univariate analysis found that sex, smoking, coronary heart disease, β-blockers, age, hemoglobin, NIHSS, FBG, HCY, TG, and CR have positive differences between groups. Multiple comparison analyses revealed significant differences within groups. *$p < 0.05$, **$p < 0.010$, and ***$p < 0.001$.

SUPPLEMENTARY FIGURE 2
Multiple comparisons in 24-h ambulatory blood pressure. Multiple comparison analyses showed within-group differences in blood pressure levels and blood pressure variability. *$p < 0.05$, **$p < 0.010$, and ***$p < 0.001$.

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Does MRI add value in selecting patients for thrombectomy beyond the 6h window? A matched-control analysis

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Background: Controversy exists regarding the need of advanced imaging for patient selection in the extended window.

Aims: To analyze the effect of initial imaging modalities on clinical outcomes of patients underwent MT in the extended window.

Methods: This was a retrospective analysis of a prospective registry, the Endovascular Treatment Key Technique and Emergency Workflow Improvement of Acute Ischemic Stroke (ANGEL-ACT) registry which was conducted at 111 hospitals between November 2017 and March 2019 in China. Primary study cohort and Guideline like cohort were identified, in each cohort, two imaging modalities for patient selection in 6 to 24h window were defined: (1) NCCT ± CTA, (2) MRI. Guideline-like cohort were further screened based on key features of the DAWN and DEFUSE 3 trials. The primary outcome was 90day mRS. The safety outcomes were sICH, any ICH and 90-day mortality.

Results: After adjusting for covariates, there were no significant differences in 90day mRS or any safety outcomes between two imaging modalities groups in both cohorts. All outcome measures of mixed-effects logistic regression model were consistent with propensity score matching model.

Conclusion: Our results indicate that patients presented with anterior large vessel occlusion in the extended time window can potentially benefit from MT even in the absence of MRI selection. This conclusion needs to be verified by the prospective randomized clinical trials.

KEYWORDS

thrombectomy, stroke, LVO=large vessel occlusion, computed tomography, magnetic resonance imaging

Introduction

The efficacy of endovascular treatment for acute large vessel occlusion (LVO) strokes presenting within the first 6h after symptom onset has been demonstrated in 7 randomized clinical trials (1–7). In addition, the DAWN (DWI or CTP Assessment With Clinical Mismatch

in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) and DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) trials demonstrated robust benefit of mechanical thrombectomy (MT) in the 6 to 24 h window over medical management alone, but with certain imaging criteria of ischemic core (8, 9). Although the stringent imaging criteria of advanced imaging in the extended window are recommended by current guidelines, mandated criteria of ischemic core and penumbra on computed tomography perfusion (CTP) or brain magnetic resonance imaging (MRI) have been criticized for being overly selective and may lead to under-treated (10–13). Recent studies have shown that CTP acquisition did not improve outcomes in patients treated in the extended window (14), and CTP may not be reliable to exclude patients who will not benefit from intra-arterial therapy (10). However, paucity of prospective or retrospective data compared the outcomes of MT in patients selected by non-contrast computed tomography (NCCT) ± CT angiography (CTA) versus those selected by MRI in the extended window. In this study, we sought to compare the effect of NCCT ± CTA with MRI imaging modality on clinical outcomes of MT in patients who presented 6–24 h after symptom onset in a large, prospective, and national endovascular stroke thrombectomy registry in China (15).

Hypothesis

There is no significant difference in terms of primary outcomes and safety outcomes across the MRI and NCCT ± CTA groups.

Methods

Study population

This study is a retrospective sub-analysis of a prospective multicenter registry study, the Endovascular Treatment Key Technique and Emergency Workflow Improvement of Acute Ischemic Stroke (ANGEL-ACT) Registry (Registration-RUL: https://www.clinicaltrials.gov; Unique identifier: NCT03370939). The ANGEL-ACT registry enrolled consecutive patients with acute ischemic stroke attributed to the large-vessel occlusion underwent endovascular therapy within 24 h after symptom onset (or last known well [LKW]) in 111 hospitals of China. Detailed inclusion and exclusion criteria have been reported previously (15). Written informed consent was obtained from all patients or their legally authorized representatives. The original study protocol was approved by a central medical ethics committee and the research board of each participating center.

The Primary study cohort was comprised of all ANGEL-ACT patients presented in the extended time window, with acute large vessel occlusion involving the intracranial carotid artery (ICA), or either the M1 or M2 segments of the middle cerebral artery, premorbid modified Rankin Score (mRS) of 0 to 2, and LKW to arterial puncture time of 6 to 24 h. A homogenous subgroup of these patients was defined as the "Guideline-like cohort" based on the key clinical and demographic features of the DAWN or DEFUSE 3 trials (age ≥ 18 years, baseline National Institutes of Health Stroke [NIHSS] score ≥ 10, ICA or M1 occlusion, and premorbid mRS score 0–1). Patients with missing baseline mRS, NIHSS, core infarct volume in the MRI group and occlusion sites other than ICA, M1 or M2 segments of the middle cerebral artery were excluded from this analysis.

The study cohorts were categorized according to the pretreatment imaging modalities: (1) NCCT ± CTA. (2) brain MRI (T1 + T2 + fluid-attenuated inversion recovery [FLAIR] + diffusion-weighted imaging [DWI] ± magnetic resonance angiography [MRA]). Patients selected by CTP in the ANGEL-ACT registry were excluded, because the small sample size (n = 44) may exclude a large number of patients in the other cohorts after PS matching, which may cause tremendous selection bias.

Imaging analysis and outcomes

All images were independently assessed by core lab staff blinded to clinical and outcome data. Imaging assessment included early ischemic changes on NCCT or DWI using Alberta Stroke Program Early CT Score (ASPECTS) for anterior circulation strokes (ACSs), location of occlusion site, baseline and post-procedural score on the modified Thrombolysis in Cerebral Infarction (mTICI) scale, intracranial hemorrhage (ICH), and symptomatic ICH (sICH). In the MRI group, the ischemic core volume was defined as lesions on DWI or an apparent diffusion coefficient [ADC] threshold of $<620 \times 10^{-3}$ mm/s (16). The assessments were carried out using a fully automated image processing software (RAPID, iSchemaView, Menlo Park, CA, United States) after limited core laboratory reader quality check and standardization of image parameters.

The primary outcome is measured with an ordinal score of mRS at 90 days (shift analysis), mRS scores were evaluated using a standardized telephone interview performed by trained investigators blinded to the baseline and procedural data (17). The secondary outcomes include the proportions of mRS 0 to 1, 0 to 2, and 0 to 3 at 90 days, and dramatic clinical improvement (DCI) which is defined as NIHSS score ≤ 1 at 24 h or ≥ 10 points decrease within 24 h (18). Safety outcomes include any ICH, sICH (according to the Heidelberg Bleeding Classification) (19), and mortality at 90 days.

Statistical analysis

Patients' baseline characteristics and outcome variables were analyzed and presented using percentages, median, and interquartile ranges. Statistical significance for intergroup differences was assessed by the Fisher exact test for categorical variables and by Kruskal-Wallis test for continuous variables. Propensity-matched analysis was performed in order to improve comparability between the two groups. Pre-exposure baseline characters in Table 1 (which include age, gender, baseline mRS, baseline NIHSS, NCCT/DWI ASPECTS score and onset-puncture time) were used to generate the propensity scores. The patients were allocated using a 1:1 matching protocol without replacement (greedy-matching algorithm), with a caliper width ≤ 0.1 of the SD of the logit of the propensity scores. For comparing outcome measures between the cohorts in the prematched and postmatched population, the odds ratios (aOR), along with their 95% confidence intervals (CIs), were calculated using binary or ordinal logistic regression model, and multivariable models were used to adjust for potential confounders. The cofounders include age, ASPECTS, last known well to arterial puncture time, occlusion site, successful reperfusion and centers. All outcome measures between the two groups in the total population

TABLE 1 Baseline and procedural characteristic of the extended time window patients according to imaging selection modality.

Primary study cohort	Before PS matching				After PS matching			
	NCCT+CTA (*n*=196)	MRI (*n*=228)	Standardized difference (%)	*p* value	NCCT+CTA (*n*=102)	MRI (*n*=102)	Standardized difference (%)	*p* value
Age, median (IQR), years	65 (54–72)	63 (54–70)		0.236	66 (54–73)	63 (55–70)	−2.8	0.460
Male sex	133 (67.9)	158 (69.3)		0.754	69 (67.6)	70 (68.6)	−2.1	1.000
Baseline mRS score				0.760			−9.3	0.659
0	173 (88.3)	198 (86.8)			89 (87.3)	92 (90.2)		
1	22 (11.2)	27 (11.8)			13 (12.8)	10 (9.8)		
2	1 (0.5)	3 (1.3)			0 (0.0)	0 (0.0)		
Baseline NIHSS score, median (IQR)	16 (11–20)	14 (10–18)		0.004	14 (12–19)	15 (11–18)	−3.1	0.770
NCCT/DWI ASPECTS, median (IQR)	10 (8–10)	7 (6–8)		<0.001	8 (6–10)	8 (7–9)	−1.6	0.629
Volume, median (IQR), ml	–	17 (9–33)	–	–	–	12 (6–19)		–
Occlusion site				0.835			10.4	0.769
Internal carotid artery	60 (30.6)	63 (27.6)			31 (30.4)	27 (26.5)		
MCA-M1	117 (59.7)	147 (64.5)			61 (59.8)	66 (64.7)		
MCA-M2	19 (9.7)	18 (7.9)			10 (9.8)	9 (8.8)		
Intravenous thrombolysis	47 (24.0)	51 (22.4)		0.730	21 (20.6)	23 (22.6)	4.8	0.865
General anesthesia	126 (64.3)	129 (56.6)		0.112	66 (64.7)	59 (57.8)	14.1	0.389
Successful reperfusion[a]	173 (88.3)	200 (87.7)		0.882	90 (88.2)	95 (93.1)	16.9	0.336
Pass number of thrombectomy, median (IQR)	2 (1–3)	1 (1–3)		0.832	1 (1–2)	1 (1–2)	8.8	0.342
LKW-to-arterial puncture time, median (IQR), min	480 (401–616)	518 (420–747)		0.015	540 (425–698)	485 (410–734)	−4.0	0.388
Puncture-to-reperfusion time, median (IQR), min	88 (55–130)	86 (52–130)		0.708	88 (62–123)	75 (52–120)	−2.2	0.207
Guideline-like cohort	**Before PS matching**				**After PS matching**			
	NCCT+CTA (*n*=157)	MRI (*n*=146)	Standardized difference (%)	*p* value	NCCT+CTA (*n*=73)	MRI (*n*=73)	Standardized difference (%)	*p* value
Age, median (IQR), years	65 (53–71)	63 (51–70)		0.251	65 (54–73)	63 (51–69)	−13.1	0.295
Male sex	106 (67.5)	100 (68.5)		0.902	47 (64.4)	54 (74.0)	−20.9	0.282

(Continued)

TABLE 1 (Continued)

Guideline-like cohort	Before PS matching				After PS matching			
	NCCT±CTA (*n*=157)	MRI (*n*=146)	Standardized difference (%)	*p* value	NCCT±CTA (*n*=73)	MRI (*n*=73)	Standardized difference (%)	*p* value
Baseline mRS score				0.439			−8.3	0.802
0	142 (90.5)	128 (87.7)			63 (86.3)	65 (89.0)		
1	15 (9.6)	18 (12.3)			10 (13.7)	8 (11.0)		
Baseline NIHSS score, median (IQR)	16 (12–21)	14 (11–18)		0.004	15 (12–19)	15 (12–19)	−7.0	0.948
NCCT/DWI ASPECTS, median (IQR)	10 (8–10)	7 (7–9)		<0.001	8 (7–10)	8 (7–9)	0.0	0.975
Volume, median (IQR), ml	–	16 (9–32)		–	–	13 (6–24)		–
Occlusion site				0.406			30.2	0.104
Internal carotid artery	51 (32.5)	41 (28.1)			27 (37.0)	17 (23.3)		
MCA-M1	106 (67.5)	105 (71.9)			46 (63.0)	56 (76.7)		
Intravenous thrombolysis	35 (22.3)	32 (21.9)		1.000	14 (19.2)	13 (17.8)	−3.5	1.000
General anesthesia	99 (63.1)	87 (59.6)		0.557	46 (63.0)	47 (64.4)	−2.9	1.000
Successful reperfusion	139 (88.5)	130 (89.0)		1.000	67 (91.8)	63 (86.3)	−17.6	0.428
Pass number of thrombectomy, median (IQR)	2 (1–3)	1 (1–2)		0.385	1 (1–2)	2 (1–3)	13.4	0.329
LKW-to-arterial puncture time, median (IQR), min	470 (400–600)	521 (420–747)		0.007	498 (415–665)	500 (420–715)	10.9	0.719
Puncture-to-reperfusion time, median (IQR), min	88 (54–130)	79 (53–123)		0.692	90 (54–10)	77 (53–129)	0.9	0.796

ASPECTS, Alberta stroke program early computed tomography score; CTA, computed tomography angiography; DWI, diffusion-weighted imaging; IQR, interquartile range; LKW, last known well; M1, M1 segment; M2, M2 segment; MCA, middle cerebral artery; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NCCT, non-contrast computed tomography; NIHSS, national institutes of health stroke scale; PS, propensity score.[a]Successful reperfusion was defined as a modified Thrombolysis in Cerebral Infarction score of 2b or 3.

using mixed-effects logistic regression models adjusted for the variables with a significant difference of $p < 0.05$ and center as random effect. Patients with missing data were excluded from further analysis. All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC, United States). A probability value of <0.05 was regarded as significant.

Results

Of the 1793 patients enrolled in the ANGEL-ACT registry, 468 patients (26.1%) underwent MT in the 6 to 24 h window. In the primary study cohort, 1 patient was excluded due to missing baseline mRS, while 29 patients were excluded due to missing baseline NIHSS score in the guideline-like cohort. 424 patients (23.6%) were included in the Primary study cohort and a total of 303 patients (16.9%) were included in the Guideline like cohort. In the Primary study cohort, 196 (46.2%) patients underwent NCCT ± CTA alone and 228 (67.9%) patients underwent MRI. After PS matching, 228 patients were matched, with 109 patients in each group. In the Guideline-like cohort, 157 patients (51.8%) underwent NCCT ± CTA alone, and 146 (48.2%) underwent MRI, After PS matching, 156 patients were matched, with 78 patients in each group. This process is shown in Figure 1. All patients enrolled in the participating centers were transferred to the emergency room for initial triage and no patients were directly transferred to the angiography suite.

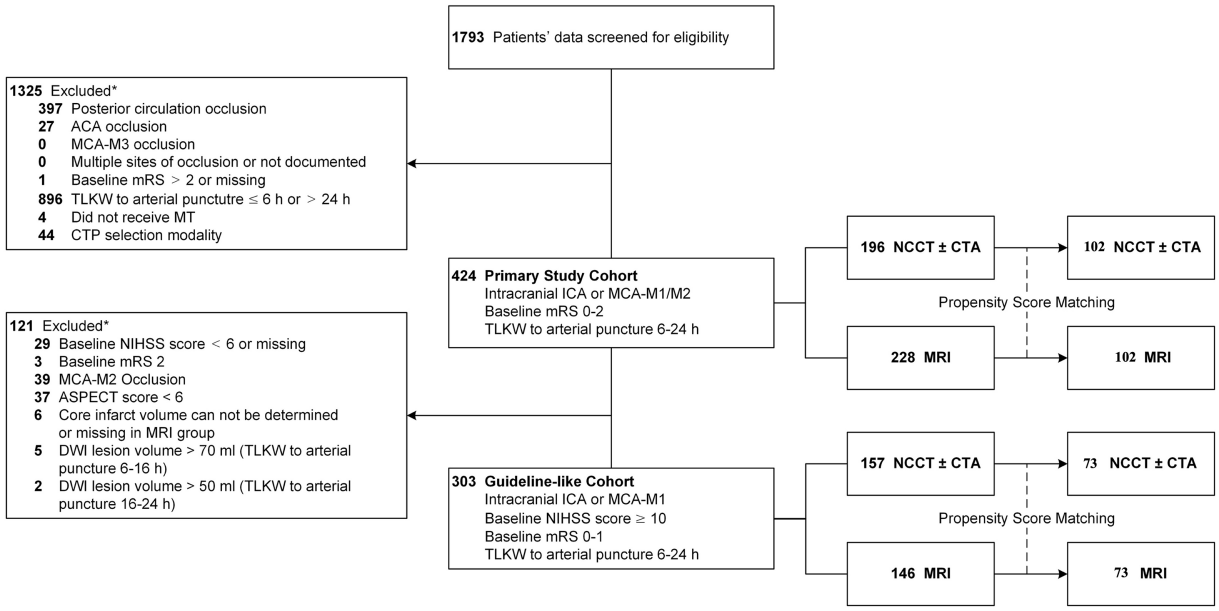

FIGURE 1
Flow diagram showing study population screening, eligibility, and inclusion.

Baseline characteristics

Baseline characteristics are shown in Table 1. Before PS matching, in the primary study cohort, NCCT ± CTA group patients had higher baseline NIHSS scores (16 [11–20] versus 14 [10–18]; $p = 0.004$), higher ASPECTS (10 [8–10] versus 7 [6–8]; P <0.001), and shorter LKW to arterial puncture times (480 [401–616] versus 518 [420–747]; $p = 0.015$). Guideline-like cohort showed similar characteristics with NCCT ± CTA group had higher baseline NIHSS scores (16 [12–21] versus 14 [11–18]; p = 0.004), higher ASPECTS (10 [8–10] versus 7 [7–9]; P < 0.001), and shorter LKW to arterial puncture time (470 [400–600] versus 521 [420–747]; $p = 0.007$). All baseline characteristics are well-balanced after PS matching as is shown in Table 1.

Outcome measures

A comparison of outcome measures is shown in Table 2. The shift on the 90-day mRS score is depicted in Figure 2. In the primary study cohort, after adjusting for covariates before PS matching, there were no significant difference in terms of 90-day functional disability (ordinal mRS shift: aOR 1.01, 95% CI [0.61–1.70], adjusted p value [aP] = 0.956), mRS 0-1(aOR 0.99, 95% CI [0.50–1.95], aP = 0.971), mRS 0–2 (aOR 0.98, 95% CI [0.52–1.88], aP = 0.974), mRS 0–3 (aOR 0.90, 95% CI [0.47–1.71], aP = 0.744), and DCI (aOR 1.22, 95% CI [0.50–2.99], aP = 0.666) across the MRI and the NCCT ± CTA groups. There were no significant difference in rates of ICH (27.2% vs. 23.0%, aP = 0.936), sICH (10.0% vs. 5.9%, aP = 0.889), and 90-day mortality (10.6% vs. 12.1%, aP = 0.724) across MRI versus NCCT ± CTA alone patients neither. The results of Guideline-like cohort were similar with that of the primary study cohort.

All outcome measures of PS matched population were consistent with mixed-effects logistic regression models in the prematched population, which is also presented in Table 2 and Figure 2, with no significant difference in 90-day functional disability (ordinal mRS shift: OR 1.25, 95% CI [0.76–2.04], p value = 0.379), mRS 0-1(OR 1.07, 95% CI [0.61–1.87], $p = 0.813$), mRS 0–2 (OR 1.25, 95% CI [0.72–2.18], $p = 0.436$), mRS 0–3 (OR 1.30, 95% CI [0.73–2.32], $p = 0.370$), DCI (OR 1.38, 95% CI [0.69–2.77], $p = 0.359$), rate of ICH (21.7% vs. 25.3%, $p = 0.552$), sICH (7.2% vs. 5.1%, $p = 0.541$), and rate of mortality at 90 day (13.3% vs. 7.9%, $p = 0.224$) across the MRI and the NCCT ± CTA groups in the primary study cohort, the analysis of the Guideline-like cohort yielded similar results.

Discussion

Analysis of patients in ANGEL-ACT registry showed that patients who suffered ischemic stroke due to large vessel occlusion of intracranial ICA or MCA-M1/M2 underwent MT in the extended window of 6–24 h, selection by NCCT ± CTA leads to no significant difference in clinical outcomes compared with patients selected by advanced imaging of MRI. The result of our study along with others (11, 20, 21) suggests that simplified imaging selection and widen criteria of MT for patients presenting in the extended window might be reasonable. Prospective randomized clinical trials are needed to confirm the results.

The role of CTP in selecting patients who may benefit from MT has been studied in several reports (10, 14, 22), the impact of using MRI to identify those population are not extensively studied. In the United States, CTP is more often used than MRI to select patients in the extended window for MT, because it is more widely available. In the DEFUSE 3 trial (9), 73% of patients underwent CTP compared with and 27%patients underwent MRI. In the Trevo Registry, 34.5%

TABLE 2 Clinical and Radiographic Outcomes of the Cohorts.

Primary study cohort	Before PS matching						After PS matching			
	NCCT±CTA	MRI	Unadjusted analysis		Adjusted analysis[a]		NCCT±CTA	MRI	Unadjusted analysis	
	(*n*=196)	(*n*=228)	OR (95% CI)	*p* value	OR[a] (95% CI)	*p* value	(*n*=102)	(*n*=102)	OR (95% CI)	*p* value
Primary outcome										
mRS at 90 d, median (IQR)	3 (0–4)	3 (0–4)	0.97 (0.69–1.36)	0.845	1.01 (0.61–1.70)	0.956	3 (0–4)	2 (0–4)	1.25 (0.76–2.04)	0.379
Secondary outcomes										
mRS 0–1 at 90 d	85/190 (45.3)	96/226 (42.5)	0.89 (0.61–1.32)	0.568	0.99 (0.50–1.95)	0.971	43/98 (43.9)xxx	46/101 (45.5)	1.07 (0.61–1.87)	0.813
mRS 0–2 at 90 d	94/190 (49.5)	109/226 (48.2)	0.95 (0.65–1.40)	0.801	0.98 (0.52–1.88)	0.974	46/98 (46.9)	53/101 (52.5)	1.25 (0.72–2.18)	0.436
mRS 0–3 at 90 d	115/190 (60.5)	134/226 (59.3)	0.95 (0.64–1.41)	0.798	0.90 (0.47–1.71)	0.744	59/98 (60.2)	67/101 (66.3)	1.30 (0.73–2.32)	0.370
DCI[b]	32/179 (17.9)	36/211 (17.1)	0.95 (0.56–1.60)	0.832	1.22 (0.50–2.99)	0.666	18/96 (18.8)	23/95 (24.2)	1.38 (0.69–2.77)	0.359
Safety outcomes										
Death within 90 d	23/190 (12.1)	24/226 (10.6)	0.86 (0.47–1.58)	0.634	0.89 (0.47–1.70)	0.724	13/98 (13.3)	8/101 (7.9)	0.56 (0.22–1.42)	0.224
Any ICH	43/187 (23.0)	60/221 (27.2)	1.25 (0.80–1.96)	0.336	0.97 (0.42–2.22)	0.936	21/97 (21.7)	25/99 (25.3)	1.22 (0.63–2.37)	0.552
Symptomatic ICH[c]	11/186 (5.9)	22/220 (10.0)	1.77 (0.83–3.75)	0.138	1.07 (0.42–2.69)	0.889	7/97 (7.2)	5/98 (5.1)	0.69 (0.21–2.26)	0.541
Guideline-like cohort	Before PS Matching						After PS Matching			
	NCCT±CTA	MRI	Unadjusted analysis		Adjusted analysis[a]		NCCT±CTA	MRI	Unadjusted analysis	
	(*n* =157)	(*n*=146)	OR (95% CI)	*p* value	OR[a] (95% CI)	*p* value	(*n*=73)	(*n*=73)	OR (95% CI)	*p* value
Primary outcome										
mRS at 90 d, median (IQR)	3 (0–5)	3 (0–4)	1.11 (0.75–1.67)	0.601	1.04 (0.65–1.68)	0.865	3 (0–4)	2 (0–4)	1.17 (0.65–2.08)	0.606
Secondary outcomes										
mRS 0–1 at 90 d	67/151 (44.4)	66/146 (45.2)	1.03 (0.66–1.63)	0.885	0.95 (0.53–1.71)	0.867	33/71 (46.5)	46/73 (49.3)	1.12 (0.58–2.16)	0.734
mRS 0–2 at 90 d	74/151 (49.0)	72/146 (49.3)	1.01 (0.64–1.60)	0.958	0.94 (0.51–1.72)	0.835	35/71 (49.3)	38/73 (52.1)	1.12 (0.58–2.15)	0.741
mRS 0–3 at 90 d	88/151 (58.3)	89/146 (61.0)	1.12 (0.70–1.78)	0.638	0.91 (0.51–1.63)	0.756	43/71 (60.6)	39/73 (53.4)	0.77 (0.39–1.45)	0.388
DCI	27/143 (18.9)	25/136 (18.4)	0.97 (0.53–1.77)	0.915	1.02 (0.41–2.54)	0.967	13/69 (18.8)	15/70 (21.4)	1.18 (0.51–2.70)	0.704
Safety outcomes										
Death within 90 d	20/151 (13.3)	13/146 (8.9)	0.64 (0.31–1.34)	0.237	0.65 (0.25–1.67)	0.370	10/71 (14.1)	4/73 (5.5)	0.35 (0.11–1.19)	0.092
Any ICH	34/149 (22.8)	28/143 (19.6)	0.82 (0.47–1.45)	0.499	0.97 (0.44–2.15)	0.938	11/71 (15.5)	15/73 (20.6)	1.41 (0.60–3.33)	0.432

(Continued)

TABLE 2 (Continued)

Guideline-like cohort	Before PS Matching						After PS Matching			
	NCCT±CTA	MRI	Unadjusted analysis		Adjusted analysis[a]		NCCT±CTA	MRI	Unadjusted analysis	
	(*n* =157)	(*n*=146)	OR (95% CI)	*p* value	OR[a] (95% CI)	*p* value	(*n*=73)	(*n*=73)	OR (95% CI)	*p* value
Symptomatic ICH	8/149 (5.4)	6/142 (4.2)	0.78 (0.26–2.30)	0.649	0.86 (0.31–2.41)	0.771	3/71 (4.2)	2/72 (2.8)	0.65 (0.11–4.00)	0.640

ASPECTS, Alberta stroke program early computed tomography score; AOR, adjusted odds ratio; aP, adjusted P; CI, confidence interval; CTA, computed tomography angiography; DCI, dramatic clinical improvement; ICH, intracranial hemorrhage; IQR, interquartile range; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NCCT, non-contrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

[a]Adjusted for age, baseline NIHSS score, ASPECTS, last known well to arterial puncture time, occlusion site, successful reperfusion and centers.

[b]Defined as NIHSS score ≤ 1 at 24 h or ≥ 10 points drop within 24 h.

[c]According to the heidelberg bleeding classification.

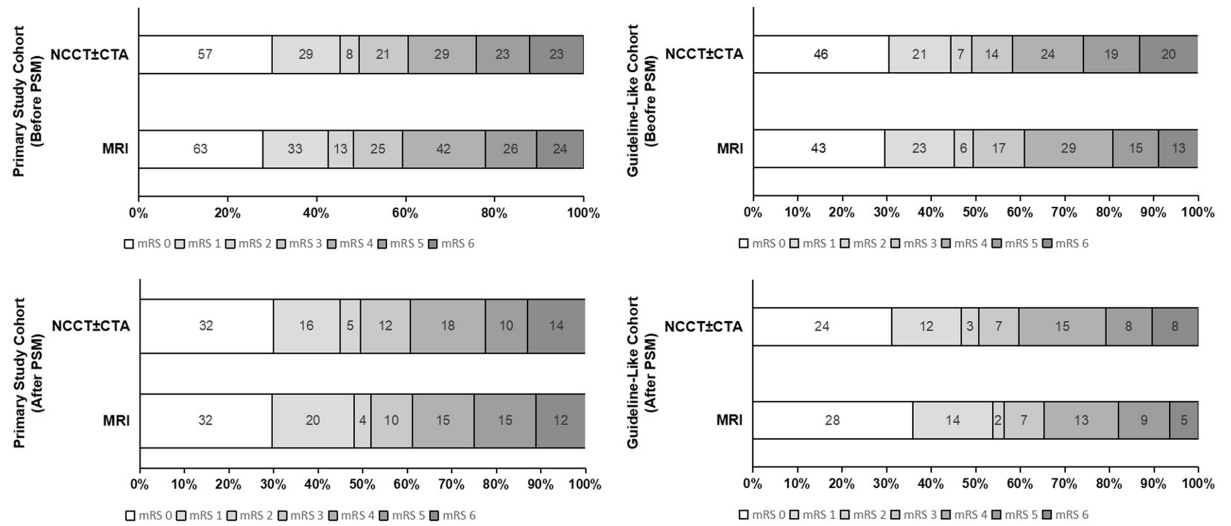

FIGURE 2
Modified Rankin Scale scores at 90 days before and after PSM.

underwent CTP compared with 0.6% patients underwent MRI (14). This does not seem to be the case in China where MRI seems more prevalent. ANGEL-ACT is a prospective multicenter registry conducted at 111 hospitals between November 2017 and March 2019 in China. In the ANGEL-ACT registry, the decision of which imaging modality should be used for selecting patients is made by physicians at each sub site. MRI is more often used in the ANGEL-ACT registry for multiple reasons below: 1) Limited staff availability in the off-hours for CTP contrast injection and image processing. 2) the cost of CT/CTA/CTP is much higher compared with MRI + MRA. 3) Formal written consent is required in China for iodine contrast injection, which is necessary for CTA/CTP but not for MRI. This circumstance provides an opportunity for us to compare the MRI based patient selection and NCCT ± CTA based selection.

There are several advantages of MRI over CTP. Compared with using relative CBF of CTP map to identify ischemic core, MRI seems more accurate, for variability between CBF core volumes and irreversibly injured tissue can occur for a variety of reasons (23). Ischemic core estimates of relative CBF are based on severe reductions in blood flow, when collateral circulation from leptomeningeal anastomosis or capillary starts feeding irreversibly injured tissue, which is more prevalent in the extended window, CTP mapping with relative CBF <30% may not be able to identify irreversible tissue where reperfusion occurred. This could lead to underestimation of the ischemic core. In both SWIFT PRIME and DEFUSE 3 trials, MRI-selected patients had a slightly higher rate of favorable outcomes than CTP-selected patients. Whereas, lesions on DWI or ADC sequence directly reflect the state of the brain tissue and are used as golden standard in CTP studies to decide an optimal threshold for identifying ischemic core (24). Moreover, analysis of the impact of different imaging modalities found there were no significant difference in hospital arrival to femoral puncture times in DAWN, DEFUSE 3 and SWIFT PRIME trials (1, 8, 9).

The aim of additional CTP or MRI criteria in DAWN and DEFUSE 3 is to identify patients with smaller ischemic core, patients with smaller ischemic core and larger ischemic penumbra have more chance to obtain good outcomes. As MT is becoming widely adopted, concerns

on the rationality of the extra imaging criteria raised. Studies on the effect of CTP for patients underwent MT in the extended time window suggest CTP may not improve patients' outcome (11, 20, 21). After balancing baseline characteristics by using PS matching, our study showed no significant difference in any clinical outcome between patients selected by NCCT ± CTA and patients selected by MRI as well. These studies, combined with ours, implicitly suggest that the criteria in the DAWN and DEFUSE 3 might be so stringent that it might exclude patients who can potentially benefit from this therapeutic strategy. The reason underlying such a result worth more exploratory research. On one hand, there are studies suggesting that even patients with large ischemic core can also benefit from MT (10), current ongoing trials (25, 26) investigating the efficiency of MT for large core stroke patients will further clarify this issue, on the other, the histological changes of ischemic stroke in the extended window needs to be further clarified. Moreover, LKW-to-arterial puncture time, which is a crucial workflow metric of stroke care, is significantly shorter in patients selected by NCCT ± CTA alone compared with patients selected by MRI, previous studies on CTP showed similar results (27). This suggests that a pragmatic criterion for selecting patients presenting in the extended window with NCCT ± CTA to receive MT may decrease delays in the stroke care workflow without diminishing the chance of obtaining a good outcome nor increasing risks of post-surgical complications like ICH. This is also meaningful for promoting MT to where advanced imaging modalities are not available.

Our findings should be interpreted based on the following limitations. First, this is a retrospective analysis of a prospective registry, imaging modality (CTP or MRI) that is used to select patients for MT was determined by the physicians at each site, there are no explicit criteria of which imaging modality should be used to select patients. Second, the ANGEL-ACT registry is a real-world multicenter registry that eliminated the potential selection bias imposed by the inclusion criteria in prospective clinical trials. The baseline characteristics are not evenly distributed among the groups, propensity-matched analysis is performed to balance confounding factors between groups in both cohorts to improve comparability, a large number of patients were excluded though. Third, the MRI protocols were not standardized before recruiting subjects, thus varying by sites and equipment manufacturers, which may lead to lack of uniformity on image collection and ischemic core volume assessments. Fourth, there are no data on patients who received medical management alone in the ANGEL-ACT registry, randomized controlled studies comparing two therapy arms are necessary. Fifth, the universality of the conclusion drawn by our analysis is uncertain, which means whether the practice of skipping ischemic core quantification could be universally adopted needs to be further verified.

Conclusion

Our study showed that in patients who suffered ischemic stroke due to large vessel occusion of Intracranial ICA or MCA-M1/M2 underwent MT in the extended window of 6–24 h, selection by NCCT ± CTA leads no significant difference in clinical and radiographic outcomes compared with patients selected by advanced imaging modality of MRI. Simplified imaging selection and widen criteria of MT for patients presenting in the extended window might be reasonable. Prospective randomized clinical trials are needed to confirm the results.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZM designed, led the ANGEL-ACT registry and had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. HC and ZY prepared the first draft of the report. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1135624/full#supplementary-material

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Trimethylamine-N-oxide: a potential biomarker and therapeutic target in ischemic stroke

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Ischemic stroke is by far the most common cerebrovascular disease and a major burden to the global economy and public health. Trimethylamine-N-oxide (TMAO), a small molecule compound produced by the metabolism of intestinal microorganisms, is reportedly associated with the risk of stroke, as well as the severity and prognosis of stroke; however, this conclusion remains contentious. This article reviews the production of TMAO, TMAO's relationship with different etiological types of ischemic stroke, and the possibility of reducing TMAO levels to improve the prognosis of ischemic stroke.

KEYWORDS

ischemic stroke, trimethylamine-N-oxide, gut microbiota, trimethylamine, stroke

1. Introduction

Stroke is the second leading cause of death and the third foremost combined cause of death and disability worldwide; nearly 87% of strokes are ischemic (1). While treatment and secondary prevention of ischemic stroke has reduced ischemic stroke-related burden significantly (2), residual risks remain undiscovered. Therefore, identifying the potential contributing factors to ischemic stroke is critical to improving the management and treatment of ischemic stroke.

Growing evidence suggests that intestinal dysbiosis caused by altered diversity and an abundance in gut microbiota is associated with the pathogenesis, progression, and clinical outcomes of ischemic stroke (3). Trimethylamine-N-oxide (TMAO) is a low-molecular compound produced by gut microbiota via diet metabolization and is thought to be a "counteracting solute" that protects proteins from various destabilizing forces. Multiple studies have shown that changes in TMAO concentration predict the risk of stroke (4), as well as the severity (5) of stroke and its clinical outcome and mortality (6) in patients with ischemic stroke (7). This review examines the latest research progress on the generation of TMAO, TMAO's relationship with different subtypes of ischemic stroke, and TMAO's involvement in new treatment approaches for ischemic stroke.

2. TMAO generation

TMA, a precursor of TMAO, is formed by the intestinal flora through the metabolization of dietary compounds present in a diet. TMA's core nutritional substrates include

phosphatidylcholine/choline, carnitine, betaine, and ergothioneine. Choline, which is derived from foods, such as eggs, milk, and meat (red meat, poultry), is metabolized to Trimethylamine (TMA) by gut microorganisms using choline TMA lyase (e.g., CutC/CutD) (8). L-carnitine is found in high amounts in red meat, poultry, and some dairy products (9, 10) and is catalyzed by carnitine TMA lyase (e.g., CntA/CntB) to produce TMA (11). Betaine exists primarily in plants and is reduced to TMA directly by betaine reductase (8) or is converted indirectly to dimethylglycine, which is then metabolized to TMA via decarboxylation. Dietary sources of ergothioneine, like some soy foods and meat products (liver and kidney), are converted to TMA by ergothionease. Most of the TMA produced by intestinal microbial metabolism is absorbed by the intestinal tract and transported to the liver through the portal circulation, where it is further oxidized to TMAO by flavin monooxygenases (FMO1 and FMO3) and then released into the circulatory system. Eventually, approximately 1/2 of the formed TMAO is excreted, and the other 1/2 is reduced back to TMA via the action of TMAO reductase in the human gut (12) (Figures 1, 2).

3. TMAO and ischemic stroke

3.1. TMAO and the risk of ischemic stroke

There exists a positive correlation between circulating TMAO concentrations and the risk of ischemic stroke (13). Reportedly, the risk of stroke increases with a rise in TMAO levels: the risk of stroke in patients in the group with the highest concentration of TMAO was shown 34–68% higher than that of patients in the group with the lowest concentration (13). Similarly, there is a nonlinear association between elevated TMAO levels and the risk of stroke: the stroke risk correlation curve was shown to increase sharply at TMAO levels between 0 and 10 μmol/L; however, beyond this dose, the risk of stroke decreased slightly. Farhangi et al.'s (13) is also the first meta-analysis to establish a positive dose-dependent relationship between circulating TMAO concentration and the risk of stroke. The etiology of ischemic stroke is categorized according to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) classification (14). One assessment of the relationship between circulating TMAO concentration and the risk of ischemic stroke of different etiologies found that TMAO concentration correlated positively with the risk of aortic atherosclerotic (LAA) ischemic stroke, atrial fibrillation (AF)-caused cardiogenic stroke, and cerebral small vessel disease (CSVD). Chen et al.'s (15) analysis of the first case–control study of LAA stroke patients alongside asymptomatic patients (not at an acute disease state, based on self-report and the physical examination outcome) showed that Plasma TMAO concentrations in LAA stroke patients measured within 72 h of the onset of stroke were significantly higher than those in the normal control group, and this relationship persisted even after adjustments were made for age, sex, smoking, and other factors. Xu et al. (16) also reached a similar conclusion in a cross-sectional study of LAA stroke patients.

As a crucial risk factor for cardioembolic stroke, AF has been scrutinized. According to Liang et al.'s (17) results after evaluating 111 AF patients without ischemic stroke and 68 atrial fibrillation (IS-AF)

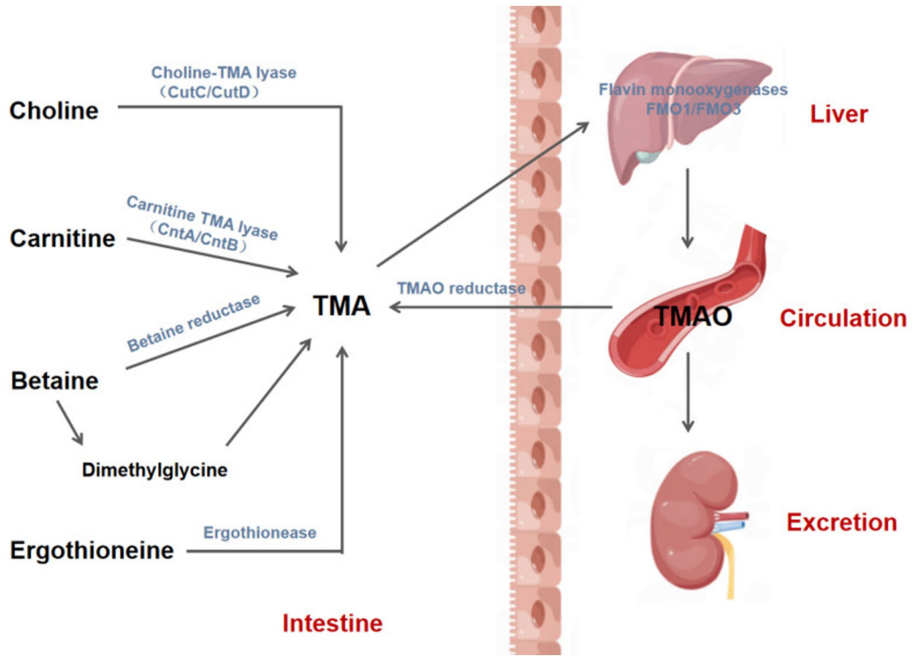

FIGURE 1
Biosynthesis and metabolism of TMAO. TMA is produced by gut mictrobiota through the action of various enzymes to metabolize phosphatidylcholine/choline, carnitine, betaine and ergothionein in the diet, and then absorbed by the intestine and transported to the liver through the portal vein, where TMA is further oxidized to TMAO by flavin monooxygenases 1 and 3 (FMO1/3). Afterwards, TMAO enters the circulatory system and is eventually excreted in the urine or reduced to TMA by TMAO reductase in the intestine. CutC/CutD, Choline trimethylamine-lyase system; CntA, A Rieske-type oxygenase protein; CntB, a predicted reductase with a plant-type ferridoxin domain; TMA, Trimethylamine; TMAO, Trimethylamine-N-oxide.

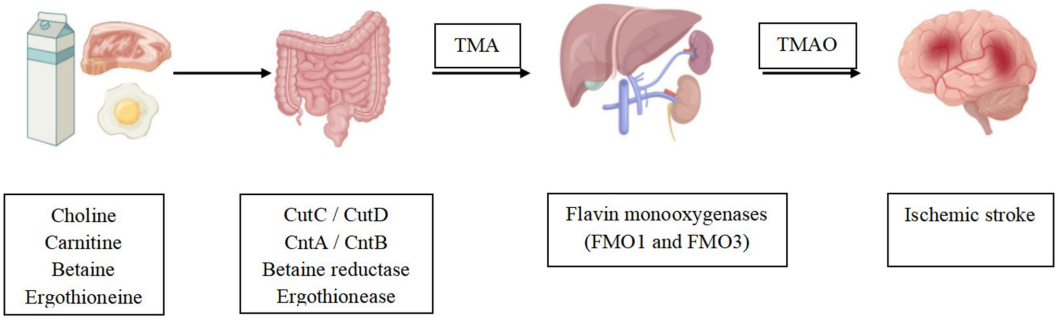

FIGURE 2
TMAO was shown to be associated with ischemic stroke events. Gut microbiota convert dietary nutrients into TMA, which is then oxidized to TMAO by the liver. Altered TMAO concentrations may play a potential role in ischemic stroke.

patients with ischemic stroke, plasma TMAO levels in the IS-AF group were notably higher than those in the AF control group. This finding suggests that TMAO is an independent predictor of IS-AF and could improve ischemic stroke stratification in AF patients. An inquiry on CSVD conducted in 30 hospitals in China (18) found a link between TMAO and an increased risk of periventricular hyperintensity burden.

Although most studies have also established positive correlations between TMAO concentration and ischemic stroke, others have obtained different findings. A 4.8-year follow-up scrutiny of an elderly cohort at high cardiovascular risk in the Mediterranean (19) did not find a positive association between plasma TMAO concentrations and the risk of cardiovascular events (CVE), including stroke, myocardial infarction, and cardiovascular death. Yin et al. scrutinized blood samples from patients with LAA stroke and transient ischemic attack (TIA) within 24 h of their admission and reported drastically lower plasma TMAO levels in patients with LAA stroke and TIA than in the asymptomatic group (20). An analysis (21) of the plasma TMAO samples of 349 stroke patients from the Netherlands within 24 h of admission found that plasma TMAO levels were two times lower in stroke patients than in healthy controls. In Schneider et al.'s (22) research, plasma TMAO levels were markedly higher in patients with ischemic stroke than in the control group at the time of admission but decreased substantially 48 h after the stroke before increasing again in the subsequent 3-month follow-up. In contrast, TMAO levels in the control group did not change between admission and 48 h later. Schneider et al. further emphasized the importance of the time course of circulating TMAO concentrations in ischemic stroke and suggested that TMAO levels are best measured during the acute phase (<24 h), which is consistent with results from Tan et al. (23) on a Chinese acute ischemic stroke population.

Based on the current conflicting data on the specific role of TMAO in ischemic stroke patients, the concentration of TMAO in patients with ischemic stroke is possibly time-dependent. However, an unstandardized TMAO measurement time may provide a partial explanation for the differences in TMAO concentration in patients with ischemic stroke; some studies have not even reported TMAO measurement times. At the same time, a reduction in TMAO levels in patients with an ischemic stroke within 7 days of the onset of the condition could also be caused by treatment, especially treatment with antiplatelet drugs (24). In explaining their results in the follow-up examination of the elderly in the Mediterranean, the authors pointed to the low intake of meat and meat products in the Mediterranean diet and the synergistic effect of nutrient-rich foods, such as vegetables, fruits, legumes, etc., as jointly promoting favorable changes in the intermediate pathways of cardiometabolic risk, including blood lipids, Insulin sensitivity, oxidation, inflammation, and vasoreactivity (23), ultimately leading to a considerably reduced risk of ischemic stroke. Because existing publications have only demonstrated correlations between TMAO levels and the risk of ischemic stroke, the exact causal relationship and the impact of different treatment options for patients with ischemic stroke and previous stroke on TMAO levels must be deciphered further.

3.2. TMAO and the subtypes of ischemic stroke

The relationship between TMAO levels and ischemic strokes of different etiologies (according to the TOAST classification) is currently unclear. In Schneider et al.'s (22) prospective comparison of plasma TMAO levels in 196 patients with ischemic stroke according to the etiology of stroke (according to the TOAST classification), the correlation between TMAO levels and the number of vascular risk factors was weak, and there was no significant association between stroke subtypes. In addition, the difference in median TMAO levels between patients with LAA type and cardioembolic types was not statistically relevant. Another study obtained comparable results (25). The above phenomena are possibly due to overlapping risk factors among patients with ischemic stroke. Patients with cardioembolic stroke also suffer from hypertension (26), diabetes (27, 28), renal insufficiency (29–31), and coronary artery disease (32), disorders that can all lead to elevated plasma TMAO concentrations, resulting in smaller differences in plasma TMAO levels among stroke patients with different etiologies. Xu et al. (33) found drastically higher plasma TMAO levels in stroke patients in the LAA group and CE (Cardioembolic) group than in the control group, speculatively pointing to TMAO as crucial to the pathophysiology of atherosclerosis-related stroke and suggesting that the increase in TMAO levels in the CE group was probably associated with the ability of TMAO to promote platelet hyperresponsiveness and heighten the risk of thrombosis (34). This study partly explained the lack of any significant differences in TMAO concentrations among different subtypes.

Additional research on the causal relationship leading to this phenomenon is required.

3.3. TMAO and the severity of ischemic stroke

Using a rat model of middle cerebral artery occlusion/reperfusion (MCAO/R), Su et al. (35) found TMAO to promote reactive astrogliosis and glial scar formation by inhibiting Smurf2 and upregulating ALK5 to prevent Neurological recovery; neurological recovery was markedly worse in MCAO/R rats treated with TMAO compared to MCAO/R rats. A clinical study on the first acute ischemic stroke (36) diagnosed 97 (26.8%) out of 362 patients with early neurological deterioration (END) and reported higher plasma TMAO levels in END patients, establishing a dose–response relationship between the two. Another case–control study on the first acute ischemic stroke in China (37) reached a similar conclusion and established a positive correlation between serum TMAO level and the NIHSS score. In Li et al.'s (27) cross-sectional study of 108 type 2 diabetes mellitus (DM) patients with ischemic stroke, patients with moderate to severe stroke (NIHSS score > 5) had higher plasma TMAO levels than those with mild stroke (NIHSS score ≤ 5); that is, higher plasma TMAO levels were associated with stroke severity. In these animal experiments (38) and clinical studies (5, 6, 15), elevated circulating TMAO levels upon admission are independent predictors of END and stroke severity in patients with acute ischemic stroke.

3.4. TMAO and the prognosis of ischemic stroke

Little is known about the relationship between TMAO concentrations and ischemic stroke outcomes, including post-stroke infections, cognitive impairment, adverse functional outcomes, and mortality. In an observational case–control study (21), Haak et al. found that stroke and post-stroke infection were associated with severe disturbances in the gut microbiota profile, and this was manifested to a greater degree by the enhanced presence of bacteria linked to TMAO production and the reduction in butyrate-producing bacteria. An animal study on post-stroke cognitive impairment (PSCI) showed that (39) TMAO promotes neuronal aging, damages synapses, and downregulates the expression of synaptic plasticity-related proteins and mTOR signaling pathways, thereby accelerating brain aging and cognitive decline in mice. TMAO has also been revealed to upregulate macrophage scavenging receptors and induce the expression of CD68, a marker with connections to cognitive impairment (40). According to reports from clinical studies, elevated plasma TMAO levels in patients with acute ischemic stroke are linked to PSCI, as determined using MoCA score (41) and MMSE score (42). Tu et al. (7) advanced TMAO as a probable new target for early prediction and treatment of stroke and vascular cognitive impairment. Zhong et al. (43) identified a weak relationship between TMAO levels and MMSE-defined cognitive impairment and no significant association between TMAO and MoCA-established cognitive impairment in patients with acute ischemic stroke at the 3-month post-stroke follow-up mark. Reportedly, higher plasma TMAO concentrations in patients with ischemic stroke predict higher adverse functional outcome events and mortality (6, 44); baseline TMAO levels are considerably more abundant in patients with 90 days or 12 months critical ischemic events and unfavorable functional outcomes (23); and baseline TMAO levels improve the prognostic accuracy of NIHSS scores and conventional risk factors for major ischemic events at 90 days.

Based on the aforementioned studies, aberrations in gut bacteria producing trimethylamine and butyrate are independent predictors of an increased risk of infection after stroke. However, the relationship between TMAO concentration and PSCI remains debatable and could have something to do with the fact that some reported trials have not excluded patients with cognitive decline before stroke. Also, differences in the length of follow-up for stroke patients may lead to false-negative in some patients, thus affecting conclusions. Nevertheless, the finding that elevated early TMAO levels predict poor stroke outcomes broadens the possibility of using TMAO clinically as an independent prognostic marker and therapeutic target.

3.5. TMAO and the recurrence of ischemic stroke

Wu et al.'s (45) analysis of the plasma TMAO levels of 268 patients undergoing carotid artery stenting (CAS) found significant associations between high levels of TMAO and the risk of stroke recurrence. Haghikia et al. (46) reached a similar conclusion in their prospective cohort study: that is, the group with the highest concentration of plasma TMAO was more prone to recurrent stroke within 1 year of follow-up than the group with the lowest concentration. The risk of CVE was dose-dependent. Another investigation demonstrated that the risk of recurrence of major vascular events increased by 2.128 times in ischemic stroke patients with plasma TMAO levels higher than 126.83 pg/mL, (15) a finding consistent with results from a recent observational trial (47), providing a new rationale for the prevention of secondary ischemic strokes.

4. Treatment and intervention

4.1. Diet

Diet is a key factor affecting the concentration of TMAO, with long-term dietary habits having a non-negligible impact on the ability to synthesize TMAO in humans and mice. As has been revealed previously, a high-salt, high-fat, and red-meat-rich diet can amplify circulating TMAO levels (12, 48, 49), omnivores produce more TMAO – through a microbiome-dependent mechanism – than vegans/vegetarians after the ingestion of L-carnitine. Additionally, consuming Mediterranean or vegetarian diets results in the effective reduction of the production of TMAO. As a food ingredient, 3,3-Dimethyl-1-butanol (DMB) (50) diminishes TMAO levels by inhibiting the action of TMAO lyase, which lessens TMA production. Resveratrol (RSV) (51) hinders the production of TMA by reshaping the microbiota; that is, increasing the relative abundance of Bacteroides, Lactobacilli, and Bifidobacteria, thereby reducing TMAO levels. Therefore, a change in dietary habits can result in an decrease in TMAO levels.

4.2. Movement

Allegedly, (52) sedentary and light physical activity have not been found to be associated with TMAO. Meanwhile, moderate to vigorous physical activity (MVPA) correlates negatively with TMAO levels. MVPA can reduce TMAO levels by 0.584 μmol/L for 30 min every day. This result suggests that exercise intensity may also be important. A possible mechanism for this is MVPA's potential help in promoting a healthier gut microbiota environment that is less conducive to TMAO generation (53, 54).

4.3. Probiotics

According to findings from studies with animals, probiotic supplementation can reduce TMAO concentrations; however, the same results have not been obtained in clinical trials (55–58). Enterococcus faecium WEFA23 (59) is a potential probiotic strain in Chinese infants with the ability to decrease TMAO production by downregulating the transcription levels of flavin monooxygenase 3 and remodeling the gut microbiota. *Lactobacillus plantarum* ZDY04 (60) and *Lactobacillus casei* (61) can reshape the composition of intestinal flora by regulating the abundance of Lactobacillus and Bacteroidetes to lessen the concentration of TMAO. However, several other clinical trials have established that probiotic supplementation does not reduce TMAO concentrations. In conclusion, the impact of probiotics on TMAO is inconclusive and more clinical trials are needed to decipher this conundrum.

4.4. Antibiotics

The use of broad-spectrum antibiotics has been shown to reduce the risk of infection in stroke patients, as well as suppress plasma TMAO levels (62), with this inhibitory effect disappearing after the discontinuation of the antibiotics. The adverse consequences of the long-term use of antibiotics, including susceptibility to infection, drug allergy, antibiotic resistance, and the occurrence of antibiotic-related metabolic diseases, also constitute issues that cannot be ignored. Therefore, using antibiotics clinically to suppress plasma TMAO levels is a practice that must yet be scrutinized even further.

4.5. Integrative Chinese and Western medicine

Another mechanism of TMAO presence involved in acute ischemic stroke is inflammatory response. Inflammatory activities after the onset of acute ischemic stroke can further promote brain injury and lead to the poor prognosis of acute ischemic stroke. The Sanhuang Xiexin decoction and Tanhuo decoction have significant anti-inflammatory effects (63). Integrated traditional Chinese and Western medicine treatment [SX (Sanhuang Xiexin decoction + Western medicine), ITCM (Tanhuo decoction + Western medicine), Naochang Tongtiao acupuncture + Western medicine, berberine] have been shown to reduce TMAO levels. SX, ITCM, and Naochang Tongtiao acupuncture + Western Medicine treatment can equally improve the neurological function of patients with acute ischemic stroke (64–68), as demonstrated by the drastically diminished incidence of cerebrovascular events in patients treated with SX and ITCM over 3 and 6 months. In a nutshell, the combination of traditional Chinese medicine with Western medicine can enhance the impact of therapy on ischemic stroke patients to a certain extent, and this sort of impact is that which is a new basis for the treatment of stroke (Figure 3).

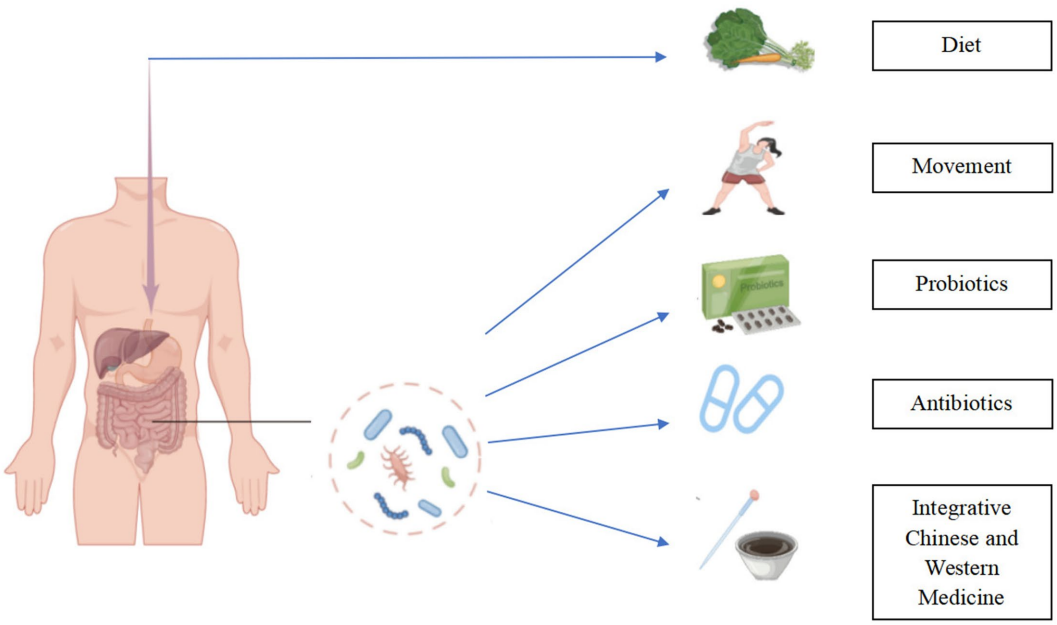

FIGURE 3
Regulating TMAO in the treatment of ischemic stroke. Modification of diet, rigorous exercise, rational use of probiotic supplements and antibiotics, and integration of traditional Chinese and Western medicine can reduce the burden of ischemic stroke by reducing TMAO levels.

5. Summary

This article reviews the relationship between TMAO and stroke of different etiologies, as well as the possible treatment options for reducing circulating the concentration of TMAO. Unfortunately, most available studies are correlational studies, and figuring out whether changes in circulating TMAO levels are a cause or a consequence of ischemic stroke remains a challenge. Moreover, reducing the concentration of TMAO to an appropriate target value to treat stroke is surrounded by controversy (13, 69). Further research is many aspects is, therefore, of significant necessity.

Still, as revealed in this review, TMAO, as a derivative of the gut microbiota, is an important player in ischemic stroke. Investigations have uncovered the marker property of TMAO in predicting the incidence, progression and prognosis of ischemic stroke. Novel treatment approaches to mitigate the burden of ischemic stroke by reducing TMAO levels include adjusting diet, exercising rigorously, using probiotic supplements, and integrating traditional Chinese with western medicine. Antibiotics can inhibit the production of TMAO effectively, but the side effects of their long-term use should be factored into deciding whether to use them or not.

While researchers have proposed a new treatment concept to improve the prognosis of ischemic stroke patients by cutting TMAO levels, there is currently a lack of evidence to support that concept; therefore, the feasibility of bringing this concept to a widely applicable fore rests on additional in-depth experimentations.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Research advances in imaging markers for predicting hematoma expansion in intracerebral hemorrhage: a narrative review

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Introduction: Stroke is a major global health concern and is ranked as the second leading cause of death worldwide, with the third highest incidence of disability. Intracerebral hemorrhage (ICH) is a devastating form of stroke that is responsible for a significant proportion of stroke-related morbidity and mortality worldwide. Hematoma expansion (HE), which occurs in up to one-third of ICH patients, is a strong predictor of poor prognosis and can be potentially preventable if high-risk patients are identified early. In this review, we provide a comprehensive summary of previous research in this area and highlight the potential use of imaging markers for future research studies.

Recent advances: Imaging markers have been developed in recent years to aid in the early detection of HE and guide clinical decision-making. These markers have been found to be effective in predicting HE in ICH patients and include specific manifestations on Computed Tomography (CT) and CT Angiography (CTA), such as the spot sign, leakage sign, spot-tail sign, island sign, satellite sign, iodine sign, blend sign, swirl sign, black hole sign, and hypodensities. The use of imaging markers holds great promise for improving the management and outcomes of ICH patients.

Conclusion: The management of ICH presents a significant challenge, and identifying high-risk patients for HE is crucial to improving outcomes. The use of imaging markers for HE prediction can aid in the rapid identification of such patients and may serve as potential targets for anti-HE therapies in the acute phase of ICH. Therefore, further research is needed to establish the reliability and validity of these markers in identifying high-risk patients and guiding appropriate treatment decisions.

KEYWORDS

imaging markers, hematoma expansion, intracerebral hemorrhage, CT angiography, computed tomography

1. Introduction

Stroke is a major global health concern and is ranked as the second leading cause of death worldwide, with the third highest incidence of disability (1). Intracerebral hemorrhage (ICH) is a type of stroke that occurs when a blood vessel ruptures within the brain, leading to bleeding and damage. It is a devastating condition, and unfortunately, the number of cases continues to rise each year, with an estimated 3.41 million new cases annually (1, 2). Previous studies have reported mortality rates of ICH was 30–50% at 30 days, with nearly 50% of patients dying within 2 weeks of symptom onset (3). The clinical outcome of ICH patients is significantly affected by the initial hematoma volume and location, with hematoma expansion (HE) being present in 33% of cases and serving as an independent predictor of poor clinical prognosis and secondary neurological deterioration (4). Although no unified diagnostic standard currently exists, Computed Tomography (CT) and CT Angiography (CTA) examination are commonly used. Therefore, investigating the baseline CT scan and CTA images of ICH patients is critical for efficient clinical management. In recent years, many studies have identified specific CTA, CT and magnetic resonance imaging (MRI) manifestations that are associated with HE, including the spot sign (SpS) (5), leakage sign (LS) (6), spot-tail sign (STS) (7), iodine sign (IoS) (8), island sign (IS) (9), satellite sign (SaS) (10), blend sign (BS) (11), swirl sign (SwS) (12), black hole sign (BHS) (13), hypodensities (14), fluid-blood level (FBL) (15), subarachnoid extension (SAHE) (16), and MRI SpS (17). These imaging markers provide a more powerful approach for identifying patients at high risk of HE. This review aims to explore the potential correlation between specific hematoma manifestations on CTA and CT and early HE, with the goal of timely and effectively intervening in ICH patients with HE and reducing mortality rates while improving outcomes.

2. The definition of HE

In most studies, HE is defined as an increase in volume of the hematoma greater than 12.5 ml or more than 33% compared to the initial CT scan in follow-up CT scans (2). However, for studies involving CTA contrast agent extravasation, HE is defined as a proportional increase of 33% or an absolute increase in hematoma volume of more than 6 ml (5, 18, 19). Despite the frequent use of the definition of HE as >33% or >12.5 ml in recent studies, a consensus on the definition of clinically significant HE has not yet been reached. It is essential to establish an optimal definition of HE, both mathematically and clinically, to reduce heterogeneity among studies and to better stratify high-risk patients with ICH. Baseline CT scans are typically performed within 6 h of symptom onset, and follow-up CT scans are performed within 24 h after the baseline scan. Methods for calculating hematoma volume include the ABC/2 (Coniglobus formula), area measurement, and three-dimensional drawing. Semi-automatic measurement technology is more accurate than the ABC/2 formula, particularly for irregularly shaped hematomas (20). However, the Coniglobus formula has a maximum error of up to 20% in the calculation of irregular hematomas, which is extremely unfavorable for evaluating the patient's condition with ICH. In recent years, a few studies have utilized medical software to calculate the initial hematoma volume (21, 22). For example, the 3D Slicer software (Version 4.8.0, Harvard University, NY) has a very small error in the calculation of hematoma volume and can detect inapparent HE. Therefore, the use of 3D Slicer for calculating hematoma volume is more accurate and can improve the assessment of patients' condition.

3. Etiology

The main factors that cause HE in patients with ICH include primary hypertension & cerebral amyloid angiopathy (CAA), diabetes, abnormal coagulation and genetic variations (Figure 1).

3.1. Primary hypertension and CAA

Both of them have the potential to cause blood vessel wall thickening, arteriosclerosis, and fragile blood vessels, increasing the risk of HE (23). Early studies showed that anti-hypertensive treatment could efficiently prevent HE, but subsequent studies found that there was no significant correlation between anti-hypertensive treatment and limiting HE and reducing mortality (24). The reason may be that before admission, the HE had already happened or HE may occur a few minutes after the onset of ICH. So anti-hypertensive treatment after admission did not improve the patients' condition.

3.2. Diabetes

Liu et al. (25) found that early HE was associated with high osmotic pressure caused by elevated blood sugar. Elevated blood glucose levels can increase blood–brain barrier (BBB) permeability and lead to its disruption, making it easier for blood components to enter the brain tissue and cause further damage. The disruption of the BBB may also facilitate the infiltration of inflammatory cells into the brain, which can exacerbate the inflammatory response and contribute to HE. Besides, diabetes can impair coagulation function and alter the activity of several coagulation factors, resulting in a procoagulant state that favors the formation of blood clots. When a vessel ruptures in the brain, the formation of blood clots can contribute to the formation of the initial hematoma. Additionally, the procoagulant state may also contribute to the enlargement of the hematoma by promoting the formation of microthrombi that occlude small vessels and lead to ischemic damage in the surrounding tissue. Finally, diabetes can also lead to the activation of various inflammatory pathways, including the nuclear factor-kappa B pathway, which can promote the production of pro-inflammatory cytokines and increase oxidative stress in the brain tissue. These effects can contribute to the progression of the initial injury and exacerbate HE.

3.3. Abnormal coagulation

Abnormal coagulation could significantly increase the risk of HE. Patients with ICH were often accompanied by abnormal blood coagulation, and anticoagulant drugs were used, especially anti-platelet aggregation drugs (26). Restoring coagulation function could strongly reduce the risk of HE and improve the outcome.

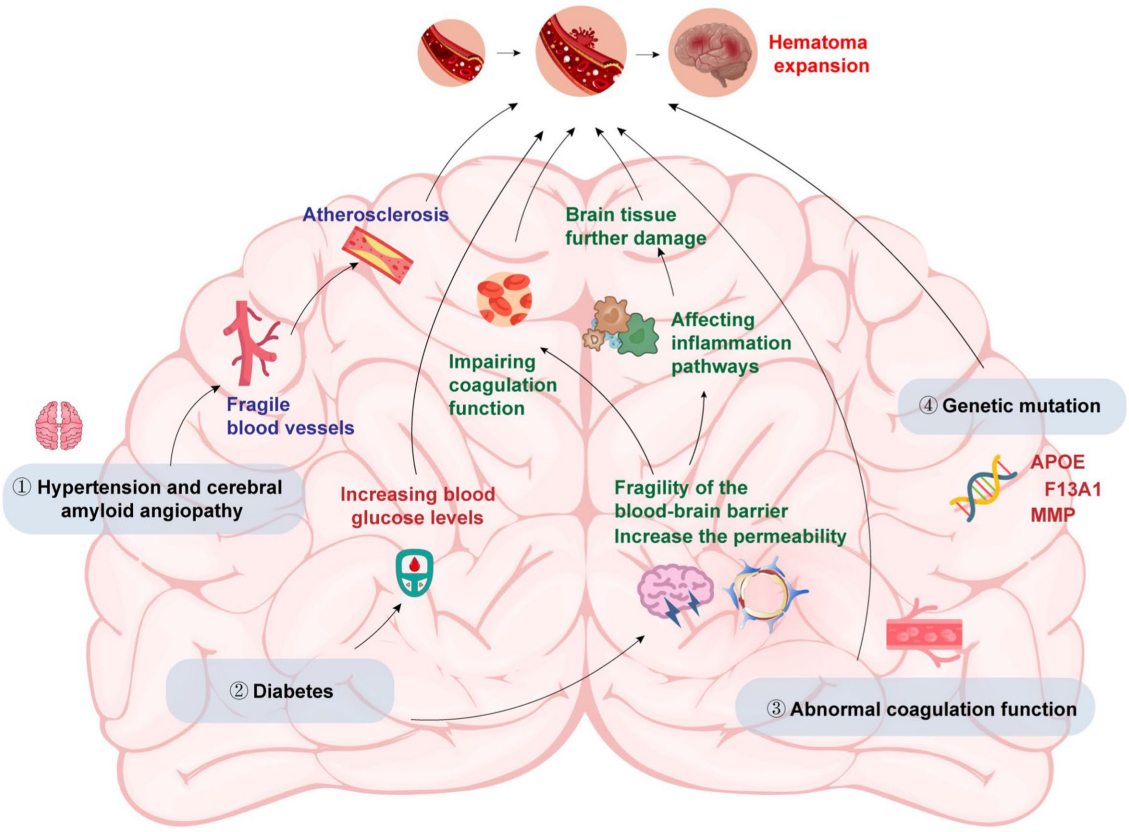

FIGURE 1
The etiology of hematoma expansion in intracerebral hemorrhage (by Figdraw).

3.4. Genetic variations

Studies have shown that genetic variations in certain genes are associated with an increased risk of HE and poor clinical outcomes in patients with ICH. Several single-nucleotide polymorphisms in the apolipoprotein E (APOE) gene have been identified as risk factors for HE and poor outcomes in ICH patients (27). APOE plays a key role in lipid metabolism and transport in the brain. In ICH, the APOE gene may also influence the metabolism and clearance of blood in the brain, leading to an increased risk of HE. Other genes that have been linked to HE in ICH patients include the factor XIII subunit A gene, which is involved in blood coagulation and clot stability, and the matrix metalloproteinase gene family, which is involved in the breakdown of the extracellular matrix and tissue remodeling (28, 29). Variations in these genes may lead to impaired coagulation and clot stability, or increased breakdown of the extracellular matrix, which can promote HE and poor outcomes in ICH. Furthermore, genetic factors may also interact with other clinical and environmental factors to increase the risk of HE. For example, a study found that the combination of certain genetic variants and high blood pressure was associated with an increased risk of HE in ICH patients (30). Another study found that the interaction between genetic variants and smoking was associated with an increased risk of HE and poor outcomes in ICH patients (31).

4. Pathophysiology

According to pathological evidence, the enlargement of hematoma may be attributed to secondary mechanical shearing of the adjacent vessels at the initial site of bleeding. In the 1970s, Fisher et al. (32) proposed the "avalanche" model to explain how primary ICH caused secondary mechanical damage to adjacent vessels. Subsequent studies have revealed that the volume of hematoma in patients with ICH is bimodal, and whether it is a micro-hematoma or a large hematoma is consistent with the "avalanche" injury process (33). According to the "avalanche" model, the enlarged part of the hematoma corresponds to the site of the "SpS" which indicates active bleeding in CTA. Multiple "SpSs" in the same hematoma suggest that multiple blood vessels are bleeding simultaneously (34). Some researchers believed that a single vessel rupture and persistent bleeding caused HE in patients with ICH (35), but so far, there is no direct pathophysiological evidence to support this theory. However, recent studies have shown that vascular abnormalities, including microaneurysms, exist in the brain tissue surrounding the hematoma and are likely to play a role in the pathogenesis of HE (36, 37). Moreover, studies have also suggested that coagulation abnormalities and inflammation may contribute to the development of HE (38, 39). Furthermore, the activation of the inflammatory cascade, generation of coagulation end-products, and hemoglobin degradation products lead to the initiation of a secondary injury cascade, which proceeds *via* diverse molecular pathways,

including but not limited to mitochondrial failure, iron-mediated oxidative stress, and sodium accumulation. Ultimately, these mechanisms result in the generation of proinflammatory mediators that trigger the breakdown of the blood–brain barrier, cerebral edema, and neuronal apoptosis (40). Therefore, it is imperative to conduct further preclinical and clinical research to gain deeper insights into the pathophysiology of both HE and ICH and identify potential therapeutic targets to prevent or minimize its development.

5. Outcome

Recent studies have further confirmed the strong association between HE and secondary neurological deterioration, poor clinical outcomes, and mortality in patients with ICH (4, 41). A dose–response relationship has been observed, indicating that for every 10% increase in hematoma volume, the case fatality rate increases by 5%, and for every 1 ml increase in hematoma volume, the likelihood of ICH patients transition from independent living to being unable to care for themselves increases by 7% based on modified Rankin scale (mRS) evaluations (42). Moreover, the degree of HE expansion has been consistently related to functional prognosis and mortality, regardless of the definition of HE. These findings suggest that identifying patients at high risk of HE and implementing targeted interventions to prevent HE and its sequelae may lead to improved clinical outcomes in patients with ICH.

Moreover, the impact of HE on patient outcomes is not limited to immediate mortality and disability. Studies have shown that HE is also associated with long-term functional and cognitive impairment, reduced quality of life, and increased risk of recurrent ICH (43, 44). The underlying mechanisms of these long-term consequences are not fully understood but may be related to ongoing neuroinflammation and secondary injury to surrounding brain tissue.

To mitigate the impact of HE, early identification of patients at high risk of HE is crucial. In addition to hematoma volume, other imaging markers such as BS, BHS, and IS have also been proposed as predictors of HE (45, 46). However, these markers require specialized training and may not be widely available. Recently, machine learning algorithms have been applied to automatically identify these markers and predict HE, showing promising results (47, 48). Overall, while HE is a common and serious complication in patients with ICH, the development of reliable and accessible imaging markers and targeted interventions may help to improve patient outcomes and reduce the burden of this devastating disease.

6. Characteristic imaging markers of HE

Based on the different imaging technique, we narrate the imaging markers on CTA, CT, and MRI, respectively. A summary of the imaging markers associated with HE in ICH is presented in Table 1.

6.1. Imaging markers on CTA

6.1.1. Spot sign

The SpS presented on the CTA referred to the "enhanced focus in the hematoma" in the original image (5) (Figure 2A). The biological basis of the SpS is not yet fully understood, but recent studies suggest that it may be related to increased permeability of cerebral vessels, indicating a higher risk of HE. According to precious study, the permeability of CT perfusion imaging (CTP) could identify whether there is a SpS. The permeability refers to the rate of contrast agent overflowing from the cerebral vascular, the higher the permeability, the greater the possibility of HE (50). At present, early clinical manifestations, coagulation, APOEε2 alleles, Glasgow Coma Scale at onset, mean arterial pressure > 120 mmHg, and intraventricular hemorrhage (IVH) were associated with the appearance of the SpS (51) have validated the reliability of SpS as an independent predictor of HE in patients with ICH (51, 52). Demchuk et al. (18) have reported that the sensitivity (SEN), specificity (SPE), positive predictive value (PPV) and negative predictive value (NPV) of the SpS for HE were 51.00, 85.00, 61.00, and 78.00%, respectively. Delgado et al. (51) proposed a grading system for quantization of SpS, including number of spot sign, maximum attenuation (H), and maximum size. And studies have shown that the grading system of SpS could not only predict the early incidence of HE in ICH patients, but also accurate classification of HE, in-hospital mortality and clinical outcome (53). This will help to further screen high-risk ICH patients.

Recent research has focused on refining the use of the SpS for clinical decision-making in ICH patients. For example, a recent study found that incorporating the SpS and other clinical factors into a predictive model could accurately identify patients at high risk of HE and guide treatment decisions (54). Other studies have explored the use of machine learning algorithms to automatically detect and quantify the spot sign, which may improve the efficiency and accuracy of diagnosis (55, 56). Overall, the SpS is a promising imaging marker for predicting the risk of HE in ICH patients, and its accurate detection and quantification may help to guide clinical decision-making and improve patient outcomes. However, further research is needed to fully understand the underlying biological mechanisms of the SpS and to refine its use in clinical practice.

6.1.2. Leakage sign

In 2016, Orito et al. (6) proposed the concept of LS based on previous studies on SpS and established a method to determine the positive LS based on the comparison of CTA phase and delayed CTA phase images (Figure 2B). Firstly, each evaluator was asked to set a region of interest (ROI) with a 1 cm margin on the delayed CTA phase image, which was considered the area with the highest HU change between the CTA phase and delayed CTA phase. Secondly, the same ROI was then placed on the CTA image in the same anatomical area. The HU values in the ROI of the CTA phase and delayed CTA phase images are calculated, and an HU increase >10% was considered the positive LS, indicating subtle contrast agent extravasation. Their study found that the LS had a higher SEN (93.30%) and SPE (88.80%) for predicting HE compared to the SpS. Furthermore, patients with positive LS had a significantly worse prognosis than those with negative LS. In fact, the LS may represent a dynamic change of the hematoma and be a more sensitive marker for predicting HE in ICH patients. However, further research is needed to validate these results and establish the clinical utility of the LS. Another potential issue is that this method may result in higher radiation exposure. However, if HE can be diagnosed, the clinical benefits outweigh the additional radiation exposure risk. The presence or absence of the LS does not significantly affect surgical indications. Using the LS to predict

TABLE 1 Summary of imaging markers associated with HE in ICH.

Imaging Markers		Author	Year	Nation	Study Design	Paticipants (*n*)	Male (%)	Age (y)	Positive imaging markers (*n*)	Primary outcome	SEN (%)	SPE (%)	PPV (%)	NPV (%)
CTA	Spot Sign	Wada et al. (5)	2007	Canada	prospective observational multi-center	39	74.29	64 (31–85)	13	HE	91 (62–100)	89 (72–96)	77 (50–92)	96 (81–99)
	Leakage Sign	Orito et al. (6)	2016	Japan	prospective single-center	80	47.5	67.9 (44–93)	35	HE	93.3 (75.7–98.8)	88.9 (81.5–91.2)	—	—
	Spot-Tail Sign	Sorimachi et al. (7)	2013	Japan	retrospective single-center	141	—	64.3 ± 13.1	15	Acute deterioration	—	—	—	—
	Iodine Sign	Fu et al. (8)	2018	China	prospective single-center	91	70.33	53.82 ± 12.83	52	HE	91.5	79.5	82.7	89.7
										Poor outcome	61.5	94.9	94.1	64.9
CT	Island Sign	Li et al. (9)	2017	China	retrospective single-center	252	66.27	IsS (+): 62.3 ± 11.1 IsS (−): 59.2 ± 12.2	41	HE	44.7	98.2	92.7	77.7
	Satellite Sign	Shimoda (10)	2017	Japan	retrospective single-center	241	50.21	70.3 ± 13.0	98	Poor outcome	54	94	95.9	44.1
	Blend Sign	Li et al. (11)	2015	China	retrospective single-center	172	68.02	BS (+): 60.21 ± 12.5 BS (−): 60.45 ± 11.9	29	HE	39.3	95.5	82.7	74.1
	Swirl Sign	Selariu (49)	2012	Sweden	retrospective single-center	203	44.83	73.0 ± 14.0	61	Poor outcome, mortality	—	—	—	—
	Black Hole Sign	Li et al. (13)	2016	China	prospective single-center	206	65.53	60.3 ± 12.2	30	HE	31.9	94.1	73.3	73.2
	Hypodensities	Boulouis et al. (14)	2016	U.S.	prospective cohort single-center	1,029	45.09	71.8 ± 12.7	321	HE	62	77	40	89
	Subarachnoid Extension	Morotti et al. (16)	2020	Italy	retrospective single-center	552	54.71	Development Cohort: 70 (61–77)	147	HE, mortality	83 (71–92)	56 (45–67)	57 (45–67)	83 (70–91)
								Replication Cohort: 77 (66–83)			73 (54–87)	60 (45–73)	52 (37–68)	79 (62–90)
MRI	Spot Sign	Valyraki et al. (17)	2023	France	retrospective single-center	147	65.99	66 (53–80)	91	HE	90 (74–98)	47 (37–58)	94 (83–99)	35 (25–46)

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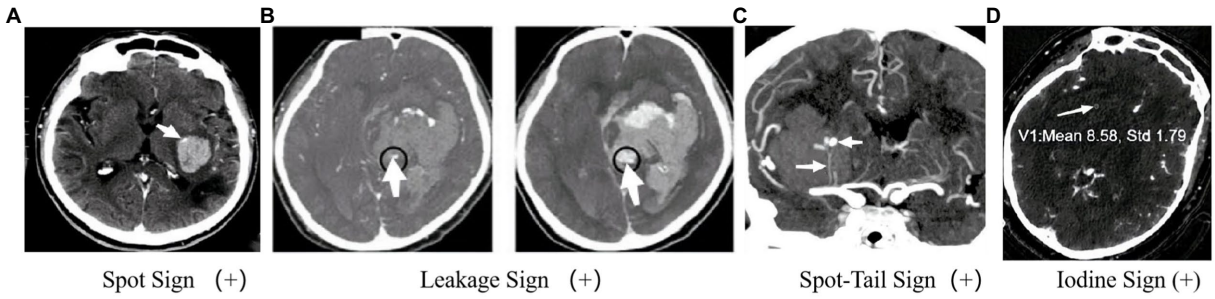

FIGURE 2
Imagination markers on CTA. **(A)** Enhanced focus within a hematoma indicates contrast agent extravasation and reveals the site of vessel rupture (5); **(B)** In the CTA phase, an enhanced focus within the hematoma is observed, and further observation in the delayed CTA phase can identify an increase in CT value within a specific region of interest. A larger enhanced focus may indicate persistent bleeding and HE (6). **(C)** The presence of an intrahematoma striate artery and an enhanced focus within the hematoma may suggest an arterial rupture and pinpoint the location of bleeding (7). **(D)** In GSI, an internal focus with an IC >7.82100μg/ml indicates a positive IoS (8).

HE may help identify patients who need early hematoma evacuation surgery. In addition to surgical indications and aggressive treatment, this method can help understand the dynamic changes in ICH in clinical medicine.

6.1.3. Spot-tail sign

The STS, proposed by Sorimachi et al. (7) in 2013, combines the SpS with the presence of an intrahematoma striate artery on CTA coronal image (Figure 2C), and has shown potential as a more accurate predictor of HE and acute neurological deterioration compared to the SpS alone. Recent studies have further supported the usefulness of the STS. For example, a study by Phan et al. (57) found that the STS was associated with a higher risk of early neurological deterioration, and was an independent predictor of HE, while the SpS alone was not significant in predicting these outcomes. Another study by Li et al. (58) found that the presence of the STS was associated with larger hematoma volume, more frequent IVH, and worse clinical outcome.

One possible explanation for the association between the STS and HE is that the striate artery represents the site of active bleeding, and the sustained blood supply through the striatum to the bleeding site promotes HE. This hypothesis is supported by angiographic images showing contrast agent extravasation from the striate artery. In conclusion, if the hypothesis is valid (i.e., the striate artery is the location of active bleeding), the STS may be a more sensitive predictor of HE and acute neurological deterioration when compared to the SpS. However, more research is needed to confirm this hypothesis and further clarify the mechanism of HE.

6.1.4. Iodine sign

Gemstone spectral imaging (GSI) is a promising scanning mode that enables direct separation of iodine from the blood and subsequent reflection of iodine concentration (IC) by monochromatic imaging. Consequently, a novel method called the IoS has been introduced (Figure 3C), which allows for direct reflection of leaking iodinated contrast and prediction of HE. A positive IoS was defined as: (1) ≥1 enhanced foci on the iodine-based decomposition image within the hematoma of any size and morphology, assessed by visual inspection (conducted by nonradiologists); (2) an internal focus IC >7.82100 μg/ml, measured by reviewers using a region of interest that covered most of the focus area (magnified from ×3 to ×5); (3) discontinuity from adjacent normal or abnormal vasculature. A study conducted by Fu et al. (8) demonstrated that the IoS was a reliable and sensitive marker for predicting HE and poor functional outcomes in ICH patients. Another comparative study of BHS, SaS, and IoS in predict HE in patients with spontaneous ICH demonstrated that the presence of GSI-based IoS had a better predictive value for HE with higher sensitivity and accuracy (60). Despite the usefulness of spectral imaging, its availability and application may not be feasible in various medical institutions, thereby potentially limiting the prevalence of the IoS. Further large-sample and multi-center studies were still urgently needed to identify whether the IoS is a reliable and sensitive marker for predicting HE and poor functional outcomes or not.

6.2. Imaging markers on CT

6.2.1. Shape-related imaging markers

6.2.1.1. Island sign

In 2017, Li et al. (9) proposed the IS as an independent predictor of HE and poor functional outcome in patients with ICH (Figure 3A). The sign is defined as the presence of three or more small hematomas scattered and separated from the main hematoma or four or more small hematomas, some of which are separated from the main hematoma. The island hematoma is round or oval and separate from the main hematoma, and the small hematoma associated with the main hematoma should be vesicular or budlike but not lobulated. The IS represents extreme margin irregularities and is a refinement of the shape irregularity scale. Huang et al. (21) further suggested that the IS is a strong predictor of HE and is useful for scoring the prediction of HE in ICH. In comparison, Zheng et al. (61) showed that although the accuracy of the IS for predicting HE is lower than the SpS, it can be an alternative predictor if CTA cannot be performed. Moreover, Zhang et al. (62, 63) validated Li et al.'s findings and showed that the IS predicts both early HE and long-term poor clinical prognosis, and admission serum glucose is associated with HE and IS. Huang et al. (22) also observed that the incidence of the IS was higher in patients with larger hematomas, implying that "worse hematomas get worse." However, further research is required to explore the pathogenesis of the IS in larger hematomas. Nonetheless, the IS is a useful imaging

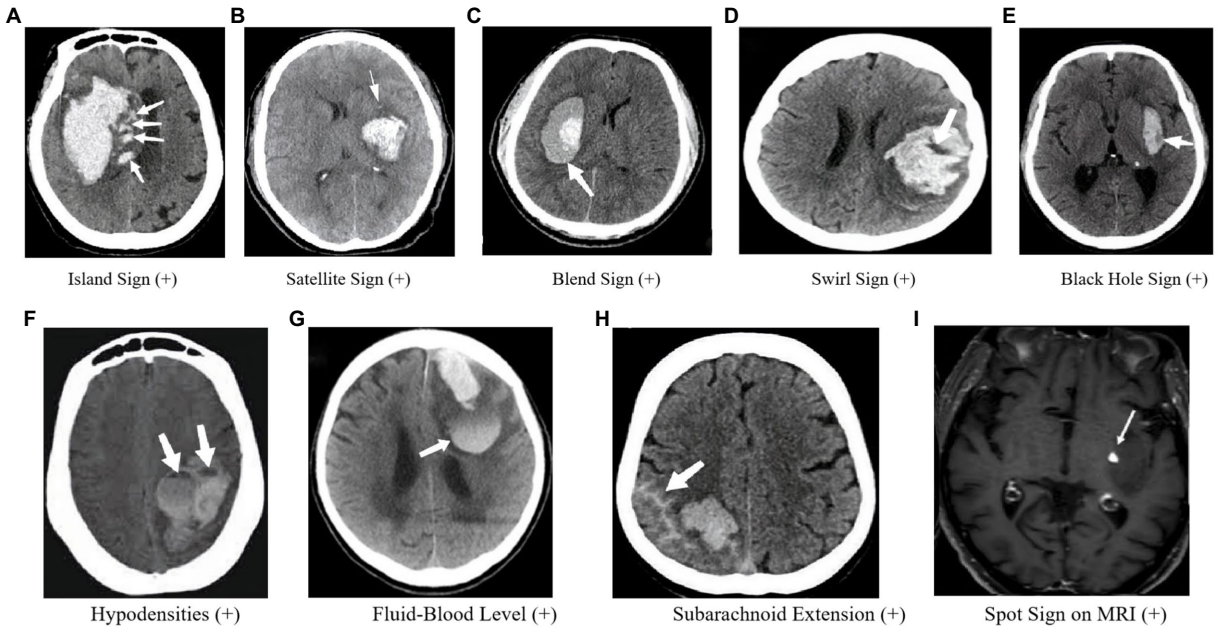

FIGURE 3
Imaging markers on CT and MRI. **(A)** Four or more small hematomas, some of which may be separate from the main hematoma, may indicate persistent bleeding from small vessels in the surrounding area, which could lead to HE. **(B)** A small hematoma located around the main hematoma, referred to as "satellites" (10); If the "satellite" develops further, it may become IS. So the SaS may represent a dynamic change of IS. **(C)** A relatively low-density region with an adjacent high-density region within the hematoma and a well-defined margin between these two regions. **(D)** Low-density region within a high-density hematoma (59). **(E)** Low-density area within the hematoma that is completely surrounded by adjacent high-density hematoma (13). **(F)** Hypoattenuation is associated with the hyperattenuated hematoma with a well-defined density difference between the two attenuation regions (14). **(G)** A horizontal interface between hypodense bloody serum and hyperdense fluid (15). **(H)** SAHE may represent the fragility of vessels as well as the active bleeding in the hematoma surrounding the vessels, lending credence to the "avalanche" hypothesis (16). **(I)** One spot was found on contrastenhanced T1-weighted sequence (17).

marker that can aid in predicting HE and poor clinical outcomes in patients with ICH.

6.2.1.2. Satellite sign

In 2017, Shimoda et al. (10) proposed the definition of the SaS (Figure 3B), which is characterized by a small hematoma completely separated from the main hematoma, with a diameter smaller than 10 mm and a distance between the small and main hematoma ranging from 1 to 20 mm. A study of 257 patients with sICH showed that the presence of at least one SaS in CT images was an independent and serious risk factor for poor prognosis in patients with sICH (10). However, the relationship between SaSs and HE is still unclear. The SaS was found to be strongly associated with increased blood pressure, decreased activated partial thromboplastin time, large hematoma volume, and IVH at admission, which may help predict the prognosis of patients with sICH. The authors suggested that metabolic changes occurring around the hematoma are associated with cytotoxic effects, which may lead to hemorrhagic transformation or reperfusion injury, ultimately resulting in the destruction of the capillary blood–brain barrier and the formation of a SaS as a lesion around the hematoma. However, further research is needed to determine the mechanism of hemorrhage around the hematoma.

It is important to note that some SaSs may actually be part of an irregular hematoma, which is thought to be the result of multiple arteriolar hemorrhage (49, 64–66). Barras et al. (64) identified the SaS as a part of the cut end of a lobulated irregular hemorrhage. Despite this, the SaS can still be used as a predictor for patient outcomes due to its clear definition and easy identification. A comparative study of SaS and SpS in 153 patients with sICH found that the SaS is an independent predictor for HE, with a SEN and SPE of 59.46 and 68.97%, respectively (67). Although the SpS has higher predictive accuracy, the SaS is an acceptable predictor for HE when CTA is unavailable. The incidence of HE in patients with supratentorial hemorrhage is higher in those with positive SaSs compared to irregular hematoma. Therefore, the SaS is a simple image marker that has proven to be of acceptable predictive value for HE. However, further research is needed to verify the underlying mechanisms of the SaS.

6.2.2. Density-related imaging markers

6.2.2.1. Blend sign

In some institutions, the use of CTA examination to assess ICH patients may be limited. As a result, researchers have explored other imaging markers that can predict HE on CT scans. In 2015, Li et al. (11) proposed the BS as a potential marker (Figure 3D). The BS is characterized by a relatively low-density region with an adjacent high-density region within the hematoma, with a well-defined margin between these two regions. The difference in Hounsfield units between these two regions should be at least 18 Hu, and the relatively low-density region should not be completely surrounded by the high-density region.

In a study of 172 ICH patients, the BS was detected in 29 (16.9%) patients on the baseline CT scan. The SEN, SPE, PPV, and NPV of the

BS for predicting HE were 39.30, 95.50, 82.70, and 74.10%, respectively. The specificity of the BS was found to be higher than that of the SpS. The baseline hematoma volume of patients with a positive BS was larger than that of patients with a negative blend sign. Additionally, the hematoma was more likely to expand in patients with a positive BS, suggesting that the BS could be used as an independent predictor of HE.

The BS reflects the attenuation of hematoma density on CT scans in patients with different stages of ICH (68). The density of the hematoma is affected by its composition, with hemoglobin being an important factor in determining its appearance on CT scans. As blood coagulates, the hematoma shows high density on CT scans. On the other hand, when there is active bleeding, the hematoma tends to be lower in density than blood clot condensate. The appearance of the BS is due to the presence of mixed blood at different bleeding times, and hematoma re-bleeding can further lead to HE (11).

6.2.2.2. Swirl sign

The SwS is an imaging finding observed in intracranial hyperattenuated hematomas (Figure 3E), which refers to region(s) of hypoattenuation or isoattenuation within the hyperattenuated ICH that can vary in shape and be rounded, streak-like or irregular (12, 68). Its definition has evolved over time, with Selariu et al. (59) in 2012 defining it as areas of hypoattenuation or isoattenuation compared to brain parenchyma, observed on both axial and coronal planes. The prognostic value of the SwS in spontaneous ICH has been explored in several studies. Kim et al. (69) in 2008 found a univariable association between the SwS and poor clinical outcome, but no association with HE. However, Selariu et al. (59) later reported that SwS were less prevalent in smaller hemorrhages, indirectly suggesting a lower risk of HE. Ng et al. (70) and Huang et al. (21) both found an association between the SwS and HE. In a comparative study of the black hole sign (BHS) and SwS (71), the SEN, SPE, PPV, and NPV of the SwS for predicting HE were 46.50, 71.30, 47.00, and 71.00%, respectively, and multivariate logistic regression showed that the presence of SwS on admission CT does not independently predict HE in patients with ICH. Therefore, further research is necessary to determine the true prognostic value of the SwS in HE.

6.2.2.3. Black hole sign

In recent years, researchers have identified a phenomenon called the BHS on CT scans of patients with ICH (Figure 3F). The BHS is characterized by a low-density area within the hematoma that is completely surrounded by adjacent high-density hematoma. The sign has a clear boundary, is not connected to adjacent brain tissues, and the CT values of the two density regions within the hematoma differ by at least 28 HU. Studies have shown that the BHS is a good predictor of early HE. In a study of 206 ICH patients, 30 (14.6%) were found to have the BHS on their baseline CT scans. The SEN, SPE, PPV, and NPV of predicting early HE were 31.90, 94.10, 73.30, and 73.20%, respectively (13). In a comparative study of the BHS and another sign called the BS both were found to be good predictors of HE, with the BS showing a slightly higher level of accuracy (72). In another investigation of 129 ICH patients, both the SpS and BHS appeared to have good predictive value for HE, but the SpS seemed to be a better predictor (73). Furthermore, the presence of the BHS on initial CT scans independently predicted poor clinical outcomes at 90 days, according to a study of 225 patients (74). The authors found that patients with the BHS were significantly more likely to have a poor clinical outcome (defined as mRS $\geq$ 4) than those without (84.4% vs. 32.1%). Hematoma heterogeneity has also been shown to be associated with HE (52). However, assessing heterogeneity is subjective, and there is no established and reliable imaging standard for its assessment. The appearance of the BHS suggests that there are bleeding episodes at different periods within the heterogeneous hematoma and could be a useful predictor of HE in patients with ICH.

6.2.2.4. Hypodensities

Studies have demonstrated a correlation between hypodensities and HE following ICH (14, 75) (Figure 3G). Moreover, unsatisfactory outcomes at 90 days have been linked to hypodensities. Factors such as a larger hematoma size, prior anticoagulation use, the SpS on CTA, and a shorter time to CT have been associated with hypodensities (76). In one study, the optimal detection time for hypodensities was 1.5–3 h with a cut-off point of 114.5 min. Therefore, vigilance is advised for clinicians when hypodensities are detected between 1.5 and 3 h after ICH onset to prevent secondary neurological deterioration (77).

6.2.2.5. Fluid-blood level

In patients with ICH, baseline CT scans have occasionally revealed FBL (15, 78–81) (Figure 3H), which is defined as a horizontal interface between hypodense bloody serum and hyperdense fluid that has settled dorsally and is visible on CT scans (15, 79). The presence of FBL on Non-Contrast Computed Tomography (NCCT) scans has been linked to anti-coagulation use, a lobar location, and an increased risk of HE (79, 80). As a result of hematoma liquefaction, hemorrhage extravasation into pre-existing cystic cavities leads to FBL (15, 81). A recent study has also suggested that FBLs may serve as a vital marker of HE in patients with ICH associated with CAA (15).

The density of the hematoma on NCCT may potentially suggest distinct phases of bleeding and may be connected with clinical progression following symptom onset. NCCT attenuation is time-independent in ICH, and hematoma density fluctuation is related to clot development and the sedimentation of cellular components in the plasma. The content of hemoglobin primarily determines density on NCCT, with protein-rich plasma appearing hypodense on NCCT in the initial phase of ICH relative to surrounding tissue (82). Clot retraction causes a relative hyperattenuation on NCCT, leading to heterogeneity in hematoma density, which may serve as a valuable predictor of the risk of HE or a poor outcome (83, 84).

6.2.3. Subarachnoid extension

SAHE, a new imaging marker for predicting HE and poor functional outcomes in ICH patients, was recently proposed (16) (Figure 3I). The researchers discovered that SAHE could predict HE in individuals with lobar ICH. SAHE was observed to occur in 27.8% of the development cohort and 24.5% of the replication cohort. A multivariate study demonstrated that SAHE independently predicted the probability of HE in patients with lobar ICH after controlling for confounding variables. SAHE may show the existence of weak vessels as well as active bleeding in the hematoma surrounding the vessels, lending credence to the "avalanche" hypothesis of HE (15). Furthermore, earlier research has indicated that the presence of cortical superficial siderosis on MRI was substantially linked with a

higher volume in individuals with lobar ICH, supporting this assumption indirectly (85–87).

6.3. Imaging markers on MRI

6.3.1. Spot sign

The identification of SpS on MRI was first proposed by Muran et al. (88) in 1998. At that time, the concept of SpS did not exist, and any high-intensity signals on T1-weighted post-contrast images were thought to be due to extravasation of contrast medium. In a study of 108 patients, extravasation was observed in 39 patient. Extravasation on MRI was found to be closely correlated with HE, indicating ongoing bleeding. Aviv et al. (89) later developed an animal model of contrast extravasation (SpS) in acute ICH based on MRI, but no significant correlation was found between SpS and HE. Since there was no corresponding MRI marker for SpS at the time, Katharina et al. (90) conducted further research and found that SpS could be detected using post-contrast T1-weighted and dynamic T1-weighted MRI images. The presence of SpS on MRI was found to be associated with worse clinical outcomes, and the time course of contrast extravasation in dynamic T1 images indicated ongoing bleeding. These findings were consistent with those of Muran et al. (88). Valyraki et al. (17) then defined SpS on MRI for the first time, with the following criteria: (1) spot-like or serpiginous high signal intensity >1.5 mm in at least one dimension, located within the margin of the hematoma and without connection to an outside vessel; and (2) no hyperintensity at the corresponding location on non-enhanced T1-weighted time-of-flight magnetic resonance angiography (MRA). In a study of 147 patients, the presence of SpS on MRI was found to be an independent biomarker of HE, and the presence of ≥2 spots was independently associated with a poor 3-month outcome. Conversely, the lack of SpS was highly predictive of a favorable evolution. Due to a corresponding MRI marker is lacking to date, further investigation of imaging markers on MRI is urgent for identifying ICH patients with high risk of HE.

7. Minimal computed tomography attenuation value

Chu et al. (91) discovered that the MCTAV is an independent predictor of HE and poor functional outcomes. In their study, the MCTAV was measured by manually selecting a region of interest before the software automatically calculated the CT minimal attenuation value. Their results revealed high SEN (64%) and SPE (92%) for identifying patients at risk of HE.

8. Application of imaging markers and suggestions for clinicians

Using imaging markers and patient clinical information to develop scoring systems or nomogram models to identify high-risk HE patients is a clinical method for risk stratification and further predicting functional outcome. Different medical institutions may have varying medical conditions, so it is necessary to choose appropriate imaging markers to predict the risk of HE based on reality. In 2018, Morotti et al. (92) proposed the BAT score, which includes an easy-to-use 5-point prediction score, including positive BS (1 point), any hypodensity (2 points), and time from onset to NCCT <2.5 h (2 points). Their findings showed that the BAT score can identify subjects at high risk of HE with good specificity and accuracy. This tool requires just a baseline NCCT scan and may help clinicians in poor medical institutions distinguish high-risk HE patients. In 2020, Fu et al. (93) proposed a 10-point prediction score, including baseline ICH volume ˃ 30 ml (1 point), time to initial CT scan ≤3 h (2 points), IS (6 points), and BHS (1 point). They demonstrated that the SEN, SPE, PPV, and NPV of the score ≥ 3 for predicting HE were 97.8, 92.7, 90.9, and 98.3% with high accuracy. Similarly, Huang et al. (21) developed a 7-point prediction score, including hours from onset to CT ≤ 6 h (1 point), baseline ICH volume ˃ 30 ml (1 point), positive IS (1 point), positive BS (1 point), positive SwS (1 point), anticoagulant use or an INR > 1.5 (1 point), and IVH extension (1 point). They indicated that the score system had reliable accuracy in predicting HE, and NCCT imaging markers may serve as the key for HE prediction. Yang et al. (94) put forward a new prediction models of functional outcome in acute ICH patients, named ultra-early ICH score, containing admission GCS score (3–4: 2 points; 5–12: 1point), baseline ICH volume ˃ 30 ml (1 point), positive IVH (1 point), infratentorial hemorrhage (1 point), age ≥ 80 (1 point), positive BS (1 point), positive BHS (1 point), and positive IS (1 point). Their results showed that the ultra-early ICH score was a useful clinical assessment tool for risk stratification concerning functional outcomes and provided guidance in clinical decision-making in acute ICH.

Besides, Brouwers et al. (19) proposed a 9-point prediction score that included warfarin use (no [0 point] or yes [2 points]), a shorter time to CT (> 6 h [0 point] or ≤ 6 h [2 points]), CTA SpS (absent [0 point], present [3 points], or unavailable [1 point]), and baseline ICH volume (< 30 ml [0 point], 30-60 ml [1 point], or >60 ml [2 points]). Based on the 9-point prediction score, Huynh et al. (95) proposed a derivation of the PREDICT A/B scores. Number of SpS, time from onset, warfarin use or an international normalized ratio > 1.5, GCS, and NIHSScale were included in the PREDICT A/B scores. PREDICT A showed improved discrimination compared with a 9-point prediction score, but independent validation was required, whereas the performance of PREDICT B varied by definition of HE.

The TRAIGE trial was conducted across 10 stroke centers in China as a randomized, placebo-controlled study aimed at assessing the efficacy of tranexamic acid in preventing acute intracerebral haemorrhage growth (95). Eligible patients were identified using imaging markers such as SpS, BHS, or BS on CT or CTA, and had to be treatable within 8 h of symptom onset. Participants were randomly assigned to receive either tranexamic acid or a placebo in a 1:1 ratio. However, the study results revealed that tranexamic acid did not significantly prevent intracerebral haemorrhage growth among patients at risk of HE and treated within 8 h of stroke onset. As a result, larger studies are necessary to gain a better understanding of the effectiveness of tranexamic acid. Notably, this trial underscores the potential utility of imaging markers in identifying eligible patients for study participation.

Based on the studies mentioned above, we recommend that clinicians use comprehensive scoring systems to identify high-risk HE patients. When only NCCT is available, we suggest using the BAT score. Another option is the 7-point prediction score proposed by Huang et al. (21). These scoring systems can assist clinicians in poor

TABLE 2 Summary of different prediction scores associated with HE and clinical outcomes in ICH.

Author	Scores	Year	Nation	Study Design	Paticipants (*n*)	Components of the scores	Primary outcome	Categorized score		
								0	1–3	4–9
Brouwers et al. (19)	9-point score	2014	U.S.	Prospective cohort Multi-center	1,012	Warfarin sodium use (No: 0; Yes: 2)	HE (%)	5.7	12.4	36.4
						Time to initial CT (h; ≤6: 2; ˃6: 0)	In-hospital mortality (%)	2.9	17.8	23.2
						Baseline ICH volume (ml; <30: 0; 30–60: 1; ˃60: 2)				
						CTA spot sign (Absent: 0; Present: 3; Unavailable: 1)	3-month mortality (%)	5.7	23.2	50.2
						Total 0–9				
Huynh et al. (95)	PREDICT A score	2015	Canada	Retrospective PREDICT study	301	GCS score (14–15: 0; ≤13: 4)	HE (%)	0–2		15–23
						Hours from onset to CT (h; ≤1: 5; 1–2: 4; ˃2–3: 3; ˃3–4: 2; ˃4–5: 1; ˃5: 0)		7.1		70
						Warfarin use or INR >1.5 (No: 0; Yes: 4)				
						CTA spot sign number (0 spot: 0; 1 spot 4; ≥2 spots: 8)				
						Total 0–23				
	PREDICT B score					NIHSS score (0–4: 0; 5–14: 4; ≥15: 7)		0–5		21–28
						Hours from onset to CT (h; ≤1: 5; ˃1–2: 4; ˃2–3: 3; ˃3–4: 2; ˃4–5: 1; ˃5: 0)		5.6		73.3
						Warfarin use or INR >1.5 (No: 0; Yes: 7)				
						CTA spot sign number (0 spot: 0; 1 spot 4; ≥2 spots: 9)				
						Total 0–28				
Morotti et al. (92)	BAT score	2018	Italy	Retrospective Multi-center	1,539	Blend sign (Present: 1; Absent: 0)	HE (%)	< 3		≥ 3
						Any hypodensity (Present: 2; Absent: 0)		11.0		50.8
						Time from onset to CT (h; <2.5: 2; ≥2.5 or unknown: 0)				
						Total 0–5				

(Continued)

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TABLE 2 (Continued)

Author	Scores	Year	Nation	Study Design	Paticipants (*n*)	Components of the scores	Primary outcome	Categorized score			
								0	1–3	4–9	
Fu et al. (93)	10-Point Score	2020	China	Retrospective single center	216	Time to initial CT scan ≤3 h: 2	HE (%)	≥ 3			
						Hematoma volume > 30 ml: 1		SEN	SPE	PPV	NPV
						Island sign:6		97.8	92.7	90.9	98.3
						Black hole sign:1					
						Total 0–10					
Yang et al. (94)	uICH score	2021	China	Retrospective single center	310	Admission GCS score (3–4: 2; 5–12: 1; 13–14: 2)	Poor outcome	AUC	SEN (%)	SPE (%)	Optimal points
						Baseline ICH volume (ml; <30: 0; ≥30: 1)		0.85 (0.80–0.89)	71.7	84.2	2
						Presence of intraventricular hemorrhage (Present: 1; Absent: 0)					
						Infratentorial hemorrhage (Present: 1; Absent: 0)	30-day mortality	0.86 (0.80–0.91)	87.2	69.7	2
						Age (y; < 0: 0; ≥80: 1)					
						Blend sign (Present: 1; Absent: 0)					
						Black hole sign (Present: 1; Absent: 0)	90-day mortality	0.nnnnnn(0.81–0.92)	84.7	73.7	2
						Island sign (Present: 1; Absent: 0)					
						Total 0–9					
Huang et al. (21)	Grading system	2018	China	Retrospective single center	266	Hours from onset to CT (h; ≤6: 1; 6–24: 0)	HE (%)	0	1–3	4–7	
						Baseline ICH volume (ml; <30: 0; ≥30: 1)		3.45	34.48	76.47	
						Blend sign (Present: 1; Absent: 0)					
						Island sign (Present: 1; Absent: 0)					
						Swirl sign (Present: 1; Absent: 0)					
						Anticoagulant use or an INR > 1.5 (No: 0; Yes: 2)					
						Presence of intraventricular hemorrhage (Present: 1; Absent: 0)					
						Total 0–7					

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medical institutions to quickly identify high-risk HE patients and conduct appropriate anti-expansion therapy. When CTA is available, we suggest using the PREDICT A/Bscores identify ICH patients with high-risk HE. We summarized the different prediction scores associated with HE and clinical outcomes in ICH in Table 2.

In summary, the approach of stratifying high-risk HE patients based on imaging markers and patient clinical information is interesting. Comprehensive scoring systems can assist clinicians in different medical institutions to quickly identify high-risk HE patients and conduct appropriate anti-expansion therapy. This is a crucial point to improve poor outcomes, disability, and mortality rates.

9. Challenges and areas of focus for the future

In accordance with baseline hematoma size and location, HE is regarded an independent predictor of prognosis and a prospective target for acute-phase therapy of ICH. In clinical practice, regular monitoring of imaging indicators can identify patients who require anti-expansion therapy. Nevertheless, it is unclear if anti-expansion therapy improves clinical functional result or survival, which is a critical subject for further research. The Antihypertensive Therapy of Acute Cerebral Hemorrhage (ATACH-2) study found that aggressive blood pressure management did not reduce mortality or disability (96). Yet, the hemostatic medication Factor VII's capacity to diminish HE was most potent during the first 2.5 h, as demonstrated in the Factor VII for Acute Hemorrhagic Stroke Trial (FAST) experiment (97, 98). A subsequent analysis of the ATACH-2 study found that reducing blood pressure ultra-early lowers HE and improves outcomes in people with ICH (99).

Recent findings from the Minimally Invasive Surgery Plus Alteplase for Intracerebral Hemorrhage Evacuation (MISTIE) III study showed that a minimally invasive technique was safe for patients with ICH. Nevertheless, it demonstrated no effect in terms of the primary outcome in a subset of individuals. Patients with low risk of HE may be better suited for MIS methods when they become available because to their decreased risk of postoperative rebleeding (100). The BS and BHS were linked to postoperative rebleeding in patients with ICH after minimally invasive surgery, according to retrospective investigations (101, 102). Despite this, individuals with consistently formed hematomas had satisfactory functional results following surgery (103).

Newly suggested recommendations for identifying, reporting, and interpreting these radiological indicators may give more proof of imaging markers' predictive efficacy (104). As a result, future initiatives should aim to improve the standardization of the ever-expanding vocabulary for HE imaging indicators and determine if they should be utilized to select patients for ICH clinical trials. Future imaging research in ICH should focus on developing user-friendly systems that include imaging markers and parameters. When artificial intelligence is integrated into the clinical workflow as a tool to aid clinicians, more accurate radiological assessments can be performed (105–108).

10. Conclusion

The management of ICH presents a significant challenge, and identifying high-risk patients for HE is crucial to improving outcomes. The use of imaging markers for HE prediction can aid in the rapid identification of such patients and may serve as potential targets for anti-HE therapies in the acute phase of ICH. Therefore, further research is needed to establish the reliability and validity of these markers in identifying high-risk patients and guiding appropriate treatment decisions.

Author contributions

Y-WH and H-LH developed the initial idea for this study, contributed to the original draft, and contributed equally and are co-first authors. Z-PL and X-SY searches the relevant references and was responsible for the revision of the draft. Y-WH created the figure of etiology. X-SY provided the funding. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Glossary

ICH	Intracerebral hemorrhage
HE	Hematoma expansion
CT	Computed tomography
CTA	Computed tomographic angiography
MRI	magnetic resonance imaging
SpS	Spot sign
LS	Leakage sign
STS	Spot-tail sign
IS	Island sign
SaS	Satellite sign
IoS	Iodine sign
BS	Blend sign
SwS	Swirl sign
BHS	Black hole sign
FBL	Fluid-blood level
SAHE	Subarachnoid Extension
IVH	Intraventricular hemorrhage
NCCT	Noncontrast computed tomography
HU	Hounsifield unit
MCTAV	Minimal computed tomography attenuation value
ATACH-2	the antihypertensive treatment of acute cerebral hemorrhage
FAST	The factor VII for acute hemorrhagic stroke trial
MISTIE	The minimally invasive surgery plus alteplase for intracerebral hemorrhage evacuation
APOE	Apolipoprotein E
BBB	Blood–brain barrier
SEN	Sensitivity
SPE	Specificity
PPV	Positive predictive value
NPV	Negative predictive value
GSI	Gemstone spectral imaging
IC	Iodine concentration
CAA	Cerebral amyloid angiopathy
TRAIGE	Tranexamic acid for acute ICH growth prEdicted by spot sign

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The role of homocysteine levels as a risk factor of ischemic stroke events: a systematic review and meta-analysis

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Introduction: Among numerous risk factors, homocysteine (Hcy) has been linked to cerebral infarction; however, results have been inconsistent. This review aimed to conduct a meta-analysis of published studies to investigate the relationship between plasma Hcy levels and the risk of ischemic stroke.

Methods: A systematic literature search was conducted until November 2022 to obtain articles reporting Hcy levels in ischemic stroke patients. Review Manager software was used to perform all statistical analyses (version 5.3).

Results: Initial investigation yielded 283 articles. The final evaluation included 21 articles, including two prospective studies, one retrospective cohort, and 18 case–control studies. These studies included 9888 participants, of which 5031 were admitted patients with ischemic stroke. An integrated analysis revealed that ischemic stroke patients had significantly higher levels of Hcy than controls (mean difference (MD) = +3.70, 95% confidence interval (CI) = 2.42–5.81, $p < 0.001$).

Conclusion: This meta-analysis and systematic review indicate that ischemic stroke patients have significantly higher homocysteine levels than controls. Detecting hyperhomocysteinemia and reducing homocysteine levels should be explored among individuals at increased risk for ischemic stroke.

KEYWORDS

homocysteine, ischemic stroke, risk factor, systematic review, meta-analysis

Introduction

The cerebrovascular disease has emerged as the leading cause of disability and the second leading cause of death worldwide. Ischemic stroke is one of the most common cerebrovascular diseases, constituting 85% of all strokes (1). Older age, gender, hypertension, diabetes mellitus, hypercholesterolemia, and smoking are the traditional risk factors for cerebrovascular disease (2). Among a variety of risk factors, studies have found that homocysteine (Hcy) is an independent risk factor and correlated with cerebral infarction due to intracranial small-vessel disease and extracranial vascular disease, including myocardial infarction and peripheral artery disease (3–6).

Homocysteine (Hcy) is a naturally sulfhydryl-containing amino acid and is closely linked with endothelial dysfunction and extracellular matrix proliferation that may cause vessel damage (7). Recent studies reported a possible association between hyperhomocysteinemia and thrombotic vascular events,

including ischemic stroke (8–10), but these studies have suggested mixed conclusions, and the mechanism by which homocysteine affects stroke prognosis is still unclear. In recent years, researchers have conducted numerous case–control studies to explore the possible correlation between Hcy and cerebral infarction (11, 12). Nevertheless, the results have been inconsistent. Most of the published studies on Hcy and ischemic stroke only had modest sample sizes and were not well-designed, affecting their significance. Current guidelines did not recommend any treatment for Hcy levels. However, if the role of Hcy levels may affect stroke outcomes, controlling Hcy levels may be a novel treatment option for stroke treatment and prevention.

Therefore, the aim of this review was to perform a meta-analysis of published studies to assess the relationship between plasma Hcy levels and the risk of ischemic stroke.

Methods

This review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (13).

Literature search and selection criteria

Initially, three independent reviewers screened the databases of the included studies on PubMed, and MedRvix up to November 2022, using specific keywords: "ischemic stroke" OR "cerebral infarct" AND "homocysteine." We used the following criteria to identify eligible studies that investigated the association between Hcy levels and ischemic stroke: (1) studies that reported the relationship between baseline plasma Hcy levels (measured at admission) and patients with ischemic stroke and (2) studies that compared ischemic stroke patients and healthy controls (case–control). The literature search was also restricted to English-language articles only. The exclusion criteria were as follows: (1) single-arm trials (no control/comparison group); (2) outcomes out of interest (studies that did not estimate the mean differences between ischemic stroke patients and healthy controls); and (3) data cannot be extracted (incomplete data). The primary outcome was the differences in the plasma Hcy levels between ischemic stroke patients and the control group, and the secondary outcome was the differences in the plasma Hcy levels between male and female ischemic stroke patients.

Data extraction and quality assessment

In total, three authors independently screened and examined the titles and abstract, followed by a full-text review using the inclusion and exclusion criteria. In the event of disagreement between the three authors, the main author would help to resolve the issue and make a final decision. Studies that entirely fulfilled our inclusion criteria were retrieved and additional articles were added based on the bibliography of the articles retrieved through the outlined search strategy. If the reviewers could not reach an agreement, the first author will be consulted for the final decision.

We extracted and tabulated the following data: author(s), year of publication, study design, country of origin, baseline characteristics, homocysteine levels (mean ± standard deviation), and clinical outcomes. The quality of each included study was assessed using the Oxford Center for Evidence-Based Medicine Quality ratings and classified the evidence ratings ranged from one to five, with one representing high-quality studies such as randomized controlled trials (RCT) and five representing case reports (14).

Statistical analysis

All the analyses were performed using Review Manager software (version 5.3). Standardized mean difference (SMD) with a 95% confidence interval (CI) was used for continuous variables to compare the homocysteine levels between groups. The I2 tests measured heterogeneity among studies, and studies with I2 higher than 50% were considered to have high heterogeneity. A fixed-effects model was used when there was no significant heterogeneity among studies; otherwise, a random-effects model was used when data were considered heterogeneous. Two-sided *P*-values of <0.05 were regarded as statistical significance (15, 16).

Results

Study characteristics

The search strategy initially generated 283 articles. After removing duplicates and abstract screening, 104 full-text articles were assessed for eligibility. Finally, 21 articles were included in the final review, including two prospective studies, one retrospective cohort, and 18 case–control studies. Figure 1 shows the PRISMA flow chart of study selection.

This process resulted in the selection of 21 studies involving a total of 9888 participants, of whom 5031 were patients admitted with ischemic stroke, for the meta-analysis. Of the included studies, first author, publication year, total sample participants, country location, ethnicity, age, and study quality level were assessed. The studies included in the meta-analysis were generally of moderate quality rating (Table 1).

Homocysteine levels in patients with ischemic stroke

This study compared the differences in the plasma Hcy levels between ischemic stroke patients and the control group, and other features were listed (Table 2). There was high heterogeneity among the studies reporting differences in Hcy levels between ischemic stroke patients and control ($I^2 = 100\%$). Thus, a random-effects model was used to analyze the data. An incorporated analysis showed that the AIS patients had significantly higher levels of Hcy compared to the controls (MD = +3.70, 95% CI = 2.42–5.98, $p < 0.001$) (Figure 2). Additional analysis of sex differences showed that male acute ischemic stroke patients had higher levels of Hcy

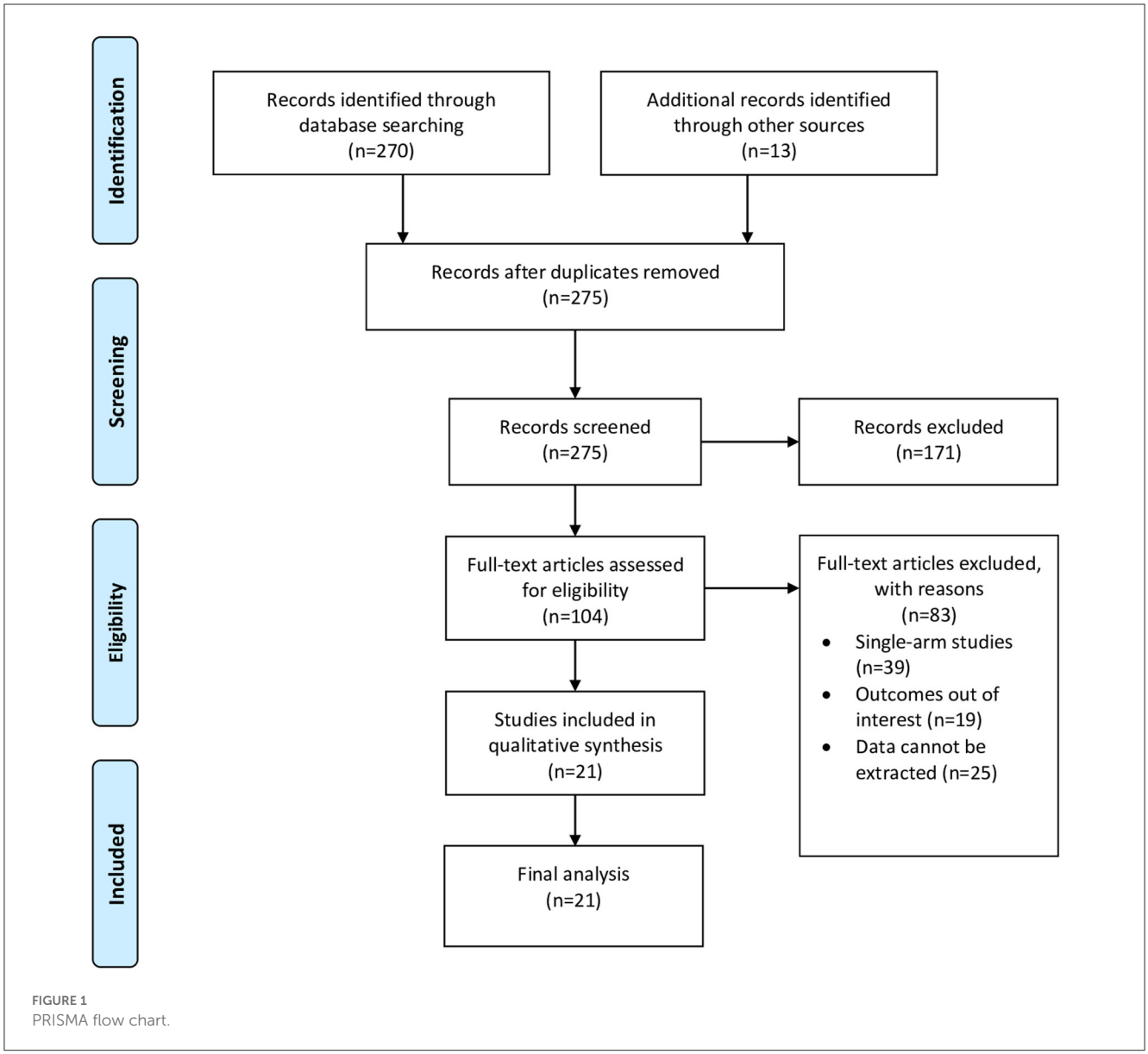

FIGURE 1
PRISMA flow chart.

compared to female patients (MD = +0.42, 95% CI = −1.20–2.05, $p = 0.61$) (Figure 3).

Discussion

Homocysteine is a non-dietary amino acid that can be transformed into cysteine or recycled into methionine, a necessary amino acid, with the assistance of certain B vitamins. Normal homocysteine ranges in men and women vary between 5 and 10 micromol/L (micromoles per liter). If homocysteine levels surpass 10 micromol/L, this condition is called hyperhomocysteinemia (38, 39). Data from our systematic review and meta-analysis suggested the following: (1) patients with ischemic stroke had greater homocysteine levels than controls and (2) homocysteine could be an independent risk factor for the outcome of ischemic stroke patients. Homocysteine levels are often classified as mild (slightly above 10 micromol/L), moderate (16–30 micromol/L), intermediate (31–100 micromol/L), and severe (above 100 micromol/L) (40). Even mild hyperhomocysteinemia may increase the risk for ischemic stroke, as demonstrated by numerous studies in this systematic review and meta-analysis (18, 23, 25, 27, 28, 31, 36, 37). In total, three studies did not find homocysteine levels that meet the criteria for hyperhomocysteinemia, but all showed a tendency for greater homocysteine levels in stroke patients compared to controls (29, 30, 34). A prior study concludes that the effect of blood homocysteine level on stroke severity and outcome begins to appear between 8 and 10 micromol/L (41).

A higher homocysteine level raises the risk of vascular diseases, including stroke. Conversely, a decrease in homocysteine levels is correlated with a reduced risk of ischemic stroke (42). Elevated homocysteine levels can lead to stroke through a variety of pathways. Homocysteine promotes the transcription of the factor in the neural tissue, which enhances inflammation

TABLE 1 Baseline characteristics of patients in the included studies.

Authors	Study type	Country location	No. of participants, (n)	Ethnicity	Age, Median (IQR, y) or Mean ± SD	Study quality level
Alfieri et al. (17)	Prospective cohort	Brazil	352	Caucasians	IS group: 67.7 ± 12.1, Control group: 63.1 ± 11.3	2
Jin et al. (18)	Case-control	China	3575	Asians	IS group: 62.71 ± 11.86, Control group: 50.82 ± 8.87	3
Ma et al. (19)	Retrospective Cohort	China	314	Asians	IS group: 53.8 ± 6.2, Control group: 54.0 ± 7.0	3
Shademan et al. (20)	Case-control	Turkey	240	Asians	IS group: 58.2 ± 8.5, Control group: 55.1 ± 6.6	3
Yurekli et al. (21)	Prospective trial	Turkey	118	Asians	IS group: 61.07 ± 6.28, Control group: 58.71 ± 5.66	2
Wang et al. (22)	Case-control	China	202	Asians	IS group: 61.07 ± 11.56, Control group: 62.49 ± 8.93	3
Kawamoto et al. (23)	Case-control	Japan	91	Asians	IS group: 81 ± 7, Control group: 79 ± 6.5	3
Yoldas et al. (24)	Case-control	Turkey	80	Asians	IS group: 69 ± 11, Control group: 70 ± 9	3
Salem-Berrabah et al. (25)	Case-control	Tunisia	147	Africans	IS group: 57.62, Control group: 30 to 70 years	3
Omrani et al. (26)	Case-control	Iran	186	Arabs	IS group: 62.2 ± 9.8, Control group: 61.8 ± 9.9	3
Wei et al. (27)	Case-Control	China	1108	Asians	IS group: 59.34 ± 9.25, Control group: 59.88 ± 10.12	3
Luo et al. (28)	Case-Control	China	601	Asians	IS group: 60.70 ± 12.33, Control group: 60.17 ± 10.32	3
Modi et al. (29)	Case-Control	India	87	Asians	NR	3
Xiao et al. (30)	Case-Control	China	304	Asians	IS group: 60.37 ± 12.02, Control group: 60.45 ± 12.23	3
Narayan et al. (31)	Case-Control	India	175	Asians	IS group: 53.3 ± 14.6, Venous stroke group: 30.9 ± 6.6, Control group: 51.8 ± 9.3	3
Al-Allawi and Jubrael. (32)	Case-Control	Iraq	120	Arabs	IS group: 60, Control group: 62	3
Lu et al. (33)	Case-Control	China	320	Asians	IS group: 63.91 ± 11.49, Control group: 61.65 ± 11.47	3
Zheng et al. (34)	Case-Control	China	418	Asians	MCA stroke group: 64 ± 12, CA stroke group: 62 ± 11, BA stroke group: 60 ± 13, Control group: 64 ± 11	3
Chen et al. (35)	Case-Control	China	610	Asians	IS group: 64.40 ± 12.90, Control group: 65.16 ± 11.95	3
Zhou and Qi. (36)	Case-Control	China	216	Asians	IS group: 66.32 ± 11.51, Control group: 64.46 ± 12.77	3
Chen et al. (37)	Case-Control	China	730	Asians	IS group: 65.7 ± 11.5, Control group: 66.3 ± 10.2	3

BA, Basilar Artery; IS, Ischemic Stroke; MCA, Middle Cerebral Artery; NR, Not Reported in detail; PCA, Posterior Cerebral Artery.

by elevating the concentration of inflammatory cytokines. Homocysteine accumulation within cells has been demonstrated to impede methyltransferases, reduce deoxyribonucleic acid (DNA) repair, and promote apoptosis. Autooxidation of homocysteine metabolites generates H_2O_2 and results in necrotic cell death (43, 44). Plasma homocysteine levels are frequently associated with the development of atherosclerosis and the degradation of vascular endothelium. Homocysteine induces the formation of serine elastase in vascular smooth muscle cells, which results in elastolysis by dissolving the extracellular matrix and generating reactive oxygen species (45).

One of the studies in this systematic review and meta-analysis comparing large-artery atherosclerosis stroke patients and healthy controls found a significant difference in homocysteine blood levels (18). Similar results were reported in a previous meta-analysis comparing homocysteine blood levels among

TABLE 2 Patients group and clinical characteristics of patients in the included studies.

Authors	Ischemic stroke group (no. of patients)	Control group (no. of patients)	Ischemic stroke group Hcy levels, μmol/L (Mean ± SD)	Control group Hcy levels, μmol/L (Mean ± SD)	Stroke subtypes	Follow-up	Covariates adjustment	Other outcomes
Alfieri et al. (17)	176	176	16.6 ± 1.3	12.0 ± 1.5	NR	3 months	Age, sex, ethnicity, BMI, smoking, and previous medications (antihypertensive, hypolipemiant, and hypoglycemic drugs)	The main findings of the study are that IS associated with increased WBC counts, high hsCRP, IL-6, lipid hydroperoxides (LOOH), NOx, homocysteine, ferritin, ESR, glucose, and insulin, and lowered iron, 25(OH)D level, total cholesterol, and HDL cholesterol
Jin et al. (18)	1810 (male: 965; female: 845)	1765 (male: 570; female: 1195)	13.67 ± 6.62 (male: 13.86 ± 6.74; female:14.45 ± 6.26)	12.49 ± 4.36 (male: 11.93 ± 5.46; female: 12.86 ± 5.74)	large-artery atherosclerosis (LAA)	NR	Age, sex	In LAA-IS patients, the TT homozygous genotype correlated with an increased risk of developing LAAIS, The plasma homocysteine level was genotype-dependent according to the following trend: TT > CT > CC
Ma et al. (19)	92 hypertensive patients with IS	114 hypertensive patients without IS	61.1 ± 8.8	55.7 ± 10.2	NR	6 months	NR	In hypertensive patients with IS, serum cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), ischemia-modified albumin (IMA), lipoprotein-associated phospholipase A2 (Lp-PLA2), glial fibrillary acidic protein (GFAP), and homocysteine (HCY) levels were significantly higher compared to controls ($p < 0.05$)
Shademan et al. (20)	120	120	16.1 ± 1.20	13.2 ± 0.82	NR	NR	Blood pressure, glucose, and cholesterol	The mean serum levels of apolipoprotein B 48, interleukin-1β, and Homocysteine, were significantly increased in the experimental group compared to the control group with a *p*-value of 0.001
Yurekli et al. (21)	54	64	29.28 ± 10.9	12.83 ± 6.8	NR	24 h after admission	NR	Compared to the control group, IS patients had lower serum vitamin D ($p < 0.0001$) and brain-derived neurotrophic factor ($p < 0.0001$) levels and higher homocysteine levels ($p < 0.0001$). There was a correlation between vitamin D levels and BDNF levels in patients with IS
Wang et al. (22)	101	101	18.48 ± 10.29	15.27 ± 6.35	NR	NR	Age, sex, BMI, TG, TC, HDL, and LDL	Serine hydroxymethyl transferase 1 (SHMT1) gene hypermethylation was significantly associated with high Hcy concentration in ischemic stroke patients
Kawamoto et al. (23)	44	47	14.6 ± 5.6	12.9 ± 6.6	NR	NR	Age, gender, albumin, creatinine, hypertension, diabetes, smoking, BMI, TG, TC, HDL, and uric acid	There was an association between elevated Hcy levels (>10 μ**mol/L)** and IS among the elderly Japanese
Yoldas et al. (24)	40	40	21.0 ± 0.6	11.2 ± 1.1	NR	NR	NR	Subjects with stroke have higher circulating serum hsCRP and homocysteine levels
Salem-Berrabah et al. (25)	50 (male: 30; female: 15)	97 (male: 50; female: 46)	15.83 ± 10.60 (male: 16.73 ± 12.45; female:14.03 ± 5.23)	13.78 ± 6.29 (male: 14.7 ± 6.03; female: 12.78 ± 6.47)	NR	NR	NR	In Tunisian subjects, the risk of developing ischemic stroke in hyperhomocysteinemic subjects was 2.4 times more than in subjects with normal Hcy levels (OR = 2.4; 95% CI: 1.13–5.06; $p < 0.05$).
Omrani et al. (26)	93	93	20.59 ± 19.7	14.1 ± 9.5	NR	NR	Smoking	In this study, 41% of patients had hyperhomocysteinemia. Hcy plasma levels in the acute phase of ischemic stroke (within 24 h) were significantly higher than normal limits

(Continued)

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Authors	Ischemic stroke group (no. of patients)	Control group (no. of patients)	Ischemic stroke group Hcy levels, μmol/L (Mean ± SD)	Control group Hcy levels, μmol/L (Mean ± SD)	Stroke subtypes	Follow-up	Covariates adjustment	Other outcomes
Wei et al. (27)	548	560	12.14 ± 2.61	8.92 ± 2.43	NR	NR	Gender, age, smoker, diabetes and hypertension	Homocysteine was significantly higher in ischemic stroke patients than in the controls ($p < 0.001$). Higher levels of homocysteine were reported in patients with ischemic stroke who had the rs2666433AA genotype compared to those who carried the rs2666433 GG+GA genotypes ($p < 0.001$)
Luo et al. (28)	298	303	13.98 ± 7.15	8.96 ± 7.02	NR	NR	Gender, age, smoking situation, diabetes, hypertension	Homocysteine was significantly higher in ischemic stroke patients than in the controls ($p < 0.001$)
Modi et al. (29)	57 (male: 41; female: 16)	30 (male: 22; female: 8)	9.91 ± 2.25 (male: 10.24 ± 2.34; female: 9.08 ± 1.81)	8.00 ± 2.74 (male: 8.45 ± 2.72; female: 6.79± 2.60)	NR	NR	Gender, smoking, hypertension, obesity	Hyperhomocysteinemia is a significant independent risk factor for ischemic stroke ($p < 0.01$). A considerable positive correlation was also found between hypertension, smoking, and elevated levels of homocysteine
Xiao et al. (30)	152	152	1.18 ± 0.23	1.14 ± 0.16	NR	NR	Telomere length, glucose, TC, HDL	Homocysteine was significantly higher in ischemic stroke patients than in the controls (p: 0.047). Telomere length and homocysteine (HCY) were inversely associated in ischemic stroke patients ($r = -0.176$, p: 0.03)
Narayan et al. (31)	75 IS patients and 25 venous stroke patients	75	IS group: 12.88 ± 10.27, venous stroke group: 8.08 ± 4.17	8.62 ± 6.13	Ischemic stroke and venous stroke	NR	NR	Homocysteine was significantly higher in ischemic stroke patients than in the controls (p: 0.02). Ischemic stroke and venous stroke patients were younger than 45 years old
Al-Allawi and Jubrael. (32)	70	50	20.9 ± 22.2	12.3 ± 10.2	NR	NR	NR	Homocysteine was significantly higher in ischemic stroke patients than in the controls (p: 0.02). TT and CT genotypes had greater homocysteine levels than the CC genotype ($p < 0.001$ and p: 0.04, consecutively). No interquartile ranges for age were available
Lu et al. (33)	152	168	16.628 ± 12.0426	14.78 ± 9.494	NR	NR	Age, gender, smoking, alcohol consumption, SBP, DBP, blood glucose, TC, TG, LDL, HDL, UA, plasma fibrinogen level	NR
Zheng et al. (34)	209	209	MCA stroke group: 8.89 ± 2.32, PCA stroke group: 7.99 ± 2.20, BA stroke group: 8.09 ± 2.54	8.35 ± 1.93	MCA, PCA, and BA stroke	NR	NR	MCA stroke patients had significantly higher homocysteine levels than PCA ($p = 0.016$) and BA stroke patients (p: 0.013)
Chen et al. (35)	400	210	8.93 ± 1.32	9.59 ± 1.74	NR	NR	NR	NR
Zhou and Qi. (36)	108	108	14.43 ± 5.43	11.14 ± 3.78	NR	NR	NR	Homocysteine was significantly higher in ischemic stroke patients than in the controls ($p < 0.001$)
Chen et al. (37)	382	348	12.43 ± 6.09	10.12 ± 5.19	NR	NR	NR	Homocysteine was significantly higher in ischemic stroke patients than in the controls ($p < 0.001$). Homocysteine levels were statistically lower in ischemic stroke patients with the GG or AG genotype than in those with the AG or AA genotype

BA, Basilar Artery; IS, Ischemic Stroke; MCA, Middle Cerebral Artery; NR, Not Reported in detail; PCA, Posterior Cerebral Artery; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure, TC, Total Cholesterol, TG, Triglycerides, LDL, low-density lipoprotein, HDL, high-density lipoprotein, UA, uric acid.

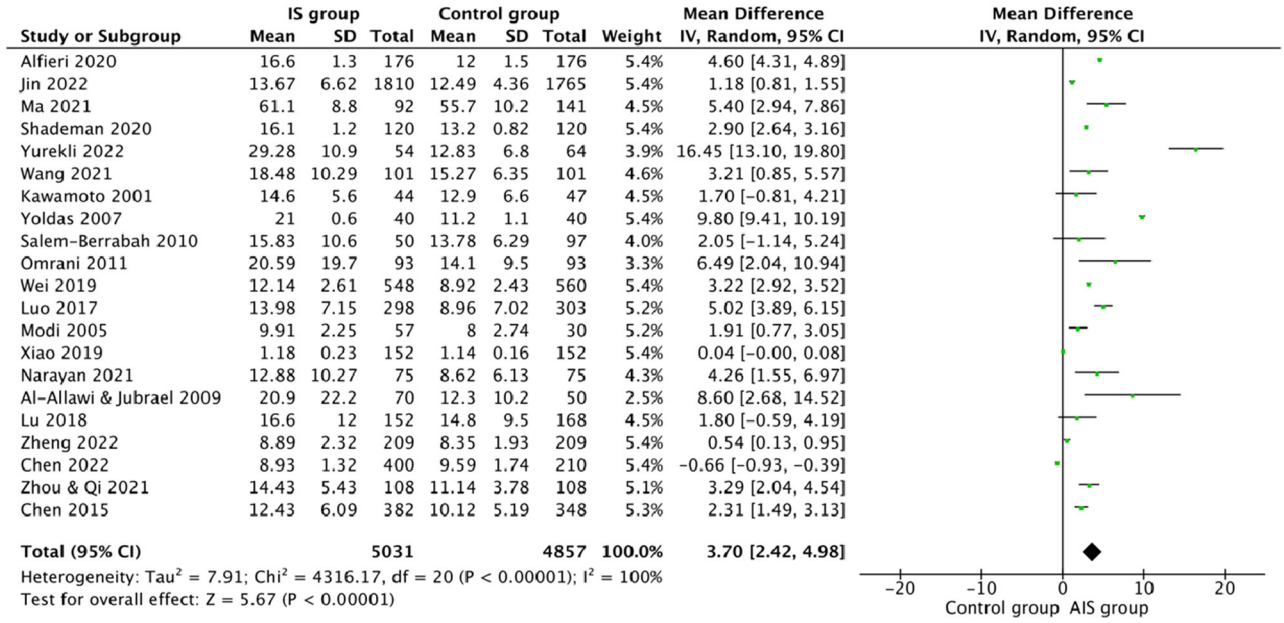

FIGURE 2
Forest plots for comparing plasma Hcy levels between ischemic stroke (AIS) patients and controls.

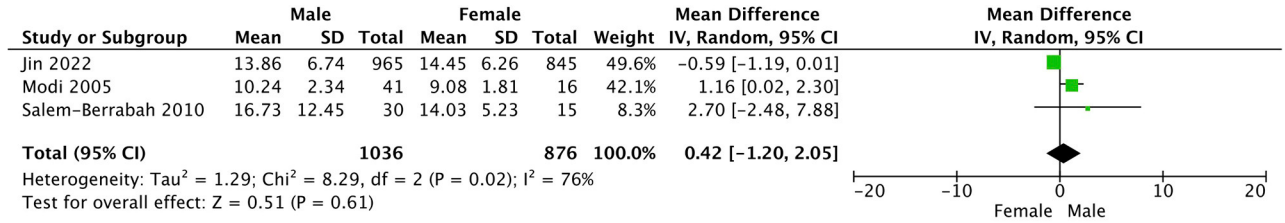

FIGURE 3
Forest plots of sex differences comparing plasma Hcy levels in ischemic stroke (AIS) patients.

acute stroke patients (2,243 patients) and a control group (871 patients). Hyperhomocysteinemia is most often related to the subtypes "small-vessel occlusion" and "large-artery atherosclerosis" (46).

Depending on their locations, individuals with middle cerebral artery (MCA) stroke had significantly higher homocysteine levels than patients with the posterior cerebral artery (PCA) and basilar artery (BA) stroke (34). Higher homocysteine levels in MCA stroke patients compared to BA stroke patients may be indicative of a higher risk of post-stroke cardiovascular disorders in MCA stroke patients related to a hypercoagulable state (47).

Hyperhomocysteinemia is also a risk factor for other stroke subtypes, including intracerebral hemorrhage, the second-leading subtype of stroke (48). In an earlier meta-analysis involving 667 patients with intracerebral hemorrhage, 1821 patients with ischemic stroke, and 2500 healthy controls, homocysteine levels in intracerebral hemorrhage patients were significantly higher than in healthy controls, indicating that the exact pathophysiology of intracerebral hemorrhage inevitably involves increased homocysteine levels (49). The plasma homocysteine level was found to be an exacerbating factor in atherosclerosis, resulting in the pathogenesis of endothelial degeneration and vessel wall necrosis, which could increase the risk of ischemic stroke as well as intracerebral hemorrhage (50). Additionally, a raised homocysteine level was significantly associated with an increased risk of recurrent stroke within 15 months after the initial cerebrovascular event (51). A plasma homocysteine level above the 75th percentile 3 months following an ischemic stroke was predictive of vascular events, including stroke recurrence (52).

Vitamin B deficiency is a potential challenge that might impair homocysteine metabolism and lead to hyperhomocysteinemia (53). Nonetheless, vitamin B supplementation and homocysteine reduction remain the subjects of several debates. In the

Vitamins to Prevent Stroke (VITATOPS) trial, daily B vitamins supplementation did not appear to be over the placebo in reducing the incidence of major vascular events (54). It was hypothesized that antiplatelet therapy, administered to approximately 80% of patients in the VITATOPS trial, might have modulated the beneficial impact of B vitamins on homocysteine levels. Patients who were receiving antiplatelet therapy at the baseline were separated from those who were not in the *post-hoc* analysis. There was no significant difference in the primary outcome between the placebo and vitamin B groups in patients receiving antiplatelet medication at the baseline (14.8% vs. 15.7%). However, for patients who did not receive antiplatelet therapy at the baseline, vitamin B treatment correlated with a significant reduction in primary outcome events (16.8% vs. 21.0%) (55). According to the Vitamin Intervention for Stroke Prevention (VISP) trial, moderate homocysteine reduction did not affect vascular outcomes (56). However, there were a few issues with the VISP trial. It appears that VISP gave too much cobalamin in the low-dose vitamin arm of the study (6 mcg daily; at least the recommended daily intake [RDI] or, by some measures, three times the RDI) as well as insufficient cobalamin in the high-dose vitamin arm (400 mcg daily) for geriatric patients (57). A dose–response study revealed that geriatric patients with cobalamin levels below 221 pmol/L require 1000 g daily for optimal absorption (58). It became clear that the ability to absorb sufficient levels of cobalamin was the primary determinant of response to vitamin therapy in homocysteine reduction. Mecobalamin, one of the active analogs of cobalamin, has been shown to reduce plasma homocysteine concentrations. An earlier study revealed that after 4 weeks, 8 weeks, 3 months, and 6 months of supplementation, the homocysteine level in the group receiving 500 μg of mecobalamin three times a day was lower than in the group receiving only conventional therapy. In addition, the treatment group had significantly higher scores on the National Institutes of Health Stroke Scale (NIHSS) after 3 and 6 months of mecobalamin supplementation than the control group. (59). Similar to cobalamin, folate is an essential regulator in the homocysteine metabolic process; a previous meta-analysis comprising 14 randomized controlled trials with a total of 39,420 participants showed that homocysteine reduction after folic acid supplementation was significantly higher in regions without folate fortification than in regions with folate fortification (60).

Despite all the contrasts, multiple studies indicate that daily vitamin B intake has a strong preventive effect against stroke or transient ischemic attack (61). Reducing homocysteine levels prior to the onset of atherosclerosis may have preventative benefits for vascular events. In other words, homocysteine must be decreased as promptly as possible. Yet another issue that must be addressed is attempting to determine the impact of modifiable risk factors, including hyperhomocysteinemia, on medical care, such as suggesting homocysteine-lowering interventions, including supplementation with vitamin B, to decrease the probability of stroke or achieving better prognosis of stroke patients.

There were some limitations in our study. (1) Most of the included studies only measured homocysteine levels at hospital admission. There was a lack of data on changes in homocysteine levels during follow-up. Therefore, further studies assessing the average time of measurement of homocysteine levels following an ischemic stroke or during hospitalization would help understand whether homocysteine is a risk factor or a consequence of stroke. (2) Our primary outcome was to compare the homocysteine levels between the ischemic stroke and control group. Further studies are needed to analyze other covariates (different types of strokes and comorbidity) or predict the risk estimates of hyperhomocysteinemia.

Conclusion

This meta-analysis and systematic review indicate that ischemic stroke patients have significantly higher homocysteine levels than controls. Detecting hyperhomocysteinemia and reducing homocysteine levels should be explored among individuals at increased risk for ischemic stroke.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

RP: supervision, study concept, writing of the initial draft, and data extraction. VW: writing of the initial draft, data extraction, analysis, and interpretation. VV: full-text review, manuscript preparation, and data extraction and analysis. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effects of herpes zoster vaccination and antiviral treatment on the risk of stroke: a systematic review and meta-analysis

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Background: Evidence suggests that there is an increased risk of stroke after herpes zoster (HZ). However, reports on the effects of HZ vaccination (HZV) and antiviral treatment on stroke risk are inconsistent. Thus, we examined these associations in a meta-analysis.

Methods: To identify relevant studies, we searched three databases for articles published up to January 2023. Random-effect models were examined to determine overall pooled estimates and 95% confidence intervals (CIs).

Results: This review included 12 observational studies (six on HZV and seven on antiviral treatment). When comparing vaccinated and unvaccinated patients, vaccination was found to be associated with a lower risk of stroke (OR, 0.78; 95% CI 0.68–0.9; $P = 0.001$). A meta-analysis of self-controlled case series (SCCS) revealed evidence of a reduced OR in individuals who received the vaccine (OR, 1.14; 95% CI 0.94–1.37; $P = 0.181$) compared with unvaccinated individuals (OR, 1.36; 95% CI 1.15–1.61; $P < 0.001$). Compared with untreated patients, antiviral therapy was not associated with a reduced risk of stroke (OR, 1.13; 95% CI 0.94–1.36; $P = 0.201$). The meta-analysis of the SCCS showed no evidence of a reduced OR in individuals who received antiviral therapy (OR, 1.33; 95% CI 1.17–1.51; $P < 0.001$) compared to untreated individuals (OR, 1.45; 95% CI 1.25–1.69; $P < 0.001$).

Conclusions: This meta-analysis suggests that the HZV, but not antiviral treatment, decreases the odds of developing stroke.

KEYWORDS

infection, vaccine, cerebrovascular, virus, pathogen

Introduction

Primary infection with varicella zoster virus (VZV) usually occurs in childhood, causing chickenpox characterized by a vesicular pruritic rash, viremia, and fever (1). VZV becomes latent in the dorsal root ganglia and nerve cells and can reactivate to cause herpes zoster (HZ), which typically manifests as localized, painful, dermatomal vesicles or blisters (2). The incidence of HZ has increased from 1.7 in 1993 to 7.2 per 1,000 person-years in 2016, with a substantial negative impact on the health-related quality of life (3). In the last decade, infectious diseases have been identified as a new risk factor for stroke. Several pathogens

have been recognized as being directly associated with the development of stroke (4–6). Preclinical studies have demonstrated that VZV triggers a variety of inflammatory effects that may contribute to thrombogenesis, atherosclerosis, and vasculopathy and thus to an increased risk of stroke (7–9). Recent research on the effect of HZ on stroke has reported an increased risk of stroke or myocardial infarction in HZ patients, especially ophthalmic zoster patients (10, 11). Given the high morbidity and mortality of stroke, any potential prevention strategy becomes increasingly important.

With the introduction of the zoster vaccine live (ZVL, Zostavax) in 2006 and the recombinant zoster vaccine (RCV, Shingrix) in 2017, HZ vaccination (HZV) has reduced the risk of developing HZ and postherpetic neuralgia (12, 13). Some studies have examined the association between HZV and post-HZ stroke, but the findings have been inconsistent (14–19). One study had a within-person study design but did not find a protective role of HZV (14). The most recent case–control study conducted to date found a reduced risk of stroke in vaccinated patients compared with unvaccinated patients (19). Additional studies have explored whether antiviral treatment modifies the risk of stroke after HZ. Some studies have demonstrated that antiviral treatment following HZ is associated with a reduced risk of stroke (20, 21), while others have found no difference in stroke risk between patients treated (or not) with antivirals (16, 22–25). To the best of our knowledge, the latest published review on this topic included articles in PubMed up to January 2017, including only two observational studies evaluating the association between antiviral treatment and stroke. Furthermore, this study did not conduct a meta-analysis (26); hence, the researchers were unable to provide an overall quantitative summary of their results. The effect of HZV and antiviral treatment on post-HZ stroke remains unclear. Therefore, we conducted a systematic review and meta-analysis on this topic, including all observational studies published up to January 2023 to examine whether HZV and antiviral treatment modify the risk of post-HZ stroke.

Methods

This meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (27).

Search strategy

This systematic review examined English-language publications in the EMBASE, PubMed, and Cochrane Library databases. The literature was searched using the following keywords from inception dates to 16 January 2023: "Herpes Zoster OR Shingles OR Zoster OR VZV OR zona" and "stroke OR cerebral arterial disease OR myocardial infarction OR ischemic attack OR cerebral ischemia." The reference lists of identified publications and relevant reviews were also searched manually.

Study selection

Peer-reviewed publications were considered eligible for data extraction if they were observational studies with cross-sectional, case–control, case–crossover, self-controlled case series (SCCS), or cohort study designs; compared vaccinated with unvaccinated patients and/or antivirally treated with untreated patients; reported odds ratios (ORs), relative risks (RRs), incidence ratios (IRs), and/or hazard ratios (HRs) of associations; and included adequate data to derive risk estimates. Reviews, case reports, conference abstracts, editorials, correspondence, basics, and animal studies were excluded.

Data extraction and quality assessment

An Excel spreadsheet was used to record the details of the included studies, including the first author's name, year of publication, country, study design, study period, age, number of observation groups, information regarding HZ exposure, diagnostic criteria for stroke (stroke or myocardial infarction), outcome measures, and statistical adjustments.

Two authors evaluated study quality using the Newcastle–Ottawa Quality Assessment Scale (NOS), which was developed for assessing observational studies (28). This scale is divided into three domains: participant selection (four questions), study group comparability (two questions), and outcome (three questions), with all questions having a value of one. Studies with a quality score ≥ 7 were considered to be of high quality.

Data analysis

Meta-analysis was performed using STATA version 10.0 (StataCorp, USA). Heterogeneity among the included studies was assessed using the I^2 statistic (29). I^2 values of 25%, 50%, and 75% represent low, medium, and high heterogeneity, respectively (29). Due to differences in the study populations and methodology, effect estimates were combined using the random-effects generic inverse variance method of DerSimonian and Laird (30). A pooled OR was calculated. Publication bias was not assessed because fewer than 10 studies were included in the meta-analysis (31). Statistical significance for all analyses was set at a P-value of <0.05.

Results

Search results

Using the keywords, our comprehensive search identified 1,744 articles after excluding 239 duplicates, of which 996 were excluded after the initial screening of titles and abstracts. Then, the full text of 54 articles was reviewed to determine their eligibility. As a result, our analysis included 12 studies [six (14–19) on HZV and seven (16, 20–25) on antiviral exposure]. The screening and reason for exclusion at each step are shown in the PRISMA flow diagram (Figure 1).

Characteristics of the included studies investigating the association between HZV and stroke

Table 1 shows the characteristics of the six studies that investigated the association between HZV and stroke risk; there were three (14–16) SCCS studies, two (17, 18) cohort studies, and one (19) case–control study. Publication years ranged from 2015 to 2022, and five studies were conducted in the United States. Only one (18) was a hospital-based study; the others were population-based studies that analyzed database data. Participants in four studies (14–17) were older than 65 years old. Four studies (14–17) evaluated only ZVL (Zostavax), one study (18) evaluated only RZV (Shingrix), and the remaining study (19) evaluated both ZVL and RZV. Based on the NOS quality assessment scores, all studies were deemed to be of high quality. The score breakdown is presented in Supplementary Tables S1, S2.

Meta-analysis of HZV and risk of stroke

Three studies (17–19) evaluated the effect of HZV on stroke by comparing vaccinated and unvaccinated patients; the pooled data demonstrated that patients who received HZV were less likely to

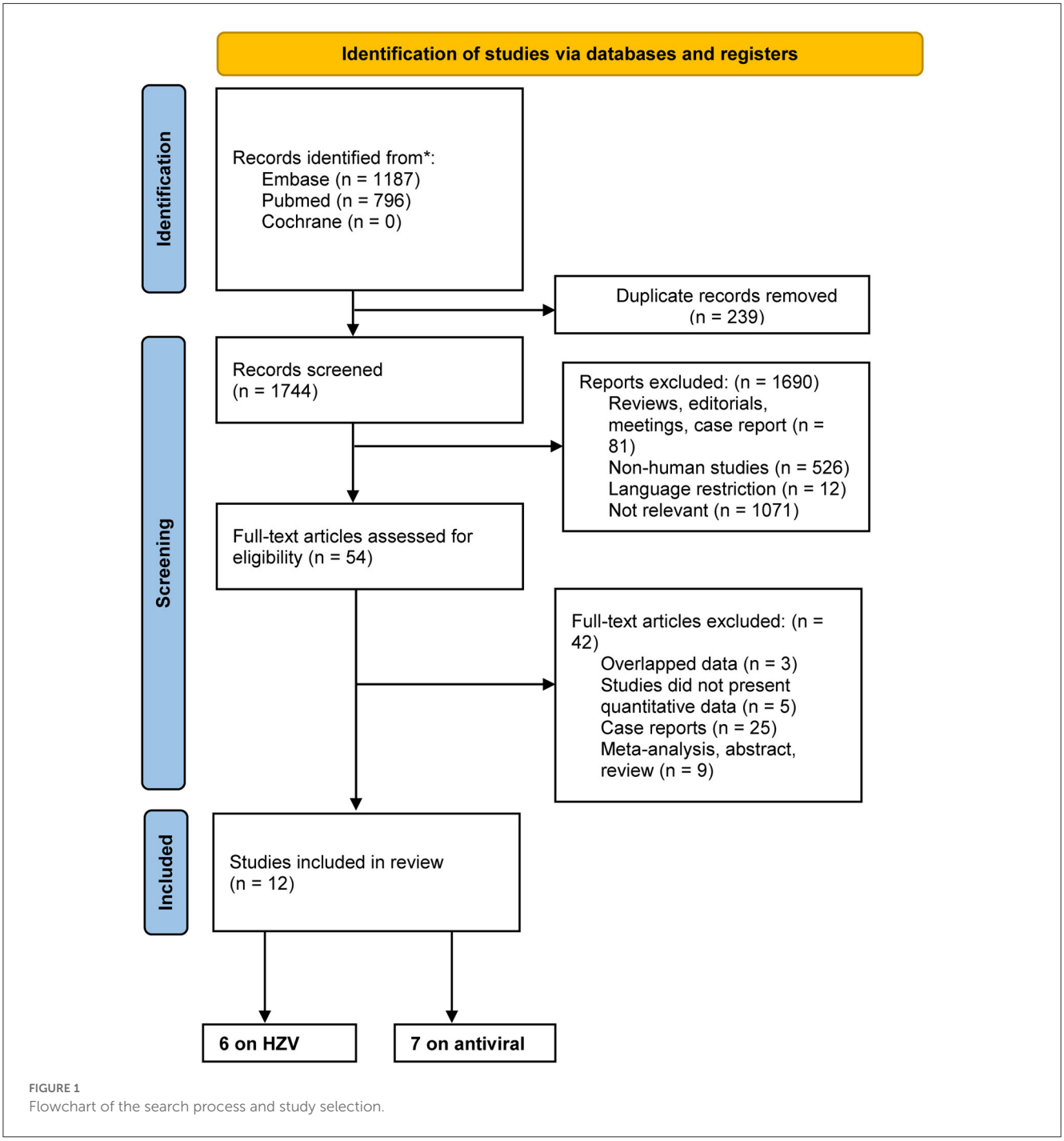

FIGURE 1
Flowchart of the search process and study selection.

TABLE 1 Characteristics of the included studies investigating the association between HZV and cerebrovascular events.

References, study location	Study design	Study period	Age (y)	Comparison	Number of events	Definition of stroke	Ascertainment of HZV exposure	Type of HZV	Adjustment	Quality
Minassian et al. (14), USA	SCCS	2006–2011	≥65	Pre-vaccination vs. after-vaccination	42,954	ICD-9-CM	Medicare part D drug files	ZVL	Age	9
Totterdell et al. (15), Australia	SCCS	2016–2018	70–79	Pre-vaccination vs. after-vaccination	2,166	Medicine insight data	Medicine insight	ZVL	Age	8
Yang et al. (16), USA	SCCS	2008–2017	≥65	Pre-vaccination vs. after-vaccination	87,405	ICD-9-CM or ICD-10-CM	Medicare provider analysis and review	ZVL	FDR adjusted	9
Yang et al. (17), USA	Cohort	2008–2017	≥65	Vaccinated vs. unvaccinated	50,681	ICD-9-CM or ICD-10-CM	Medicare provider analysis and review	ZVL	Propensity score matching	9
Nelson et al. (18), USA	Cohort	2018–2019	≥50	Vaccinated vs. unvaccinated	308	ICD-10-CM	Electronic health record	RZV	Age, gender, study site, a dermatology visit, an optometry visit, and prior zoster vaccine live vaccination, hypertension, diabetes, hyperlipidemia, and ischemic conditions	9
Parameswaran et al. (19), USA	Case-control	2010–2020	≥18	HZ vs. no HZ	14,523	ICD-9 or ICD-10	Veterans affairs corporate data	ZVL or RZV	Age, gender, zoster history, congestive heart failure, diabetes, renal failure, cancer, peripheral vascular disease, paralysis, COPD, HIV/AIDS,/metastatic cancer, myocardial infarction, CVA, dementia, rheumatologic disease, and liver disease	8

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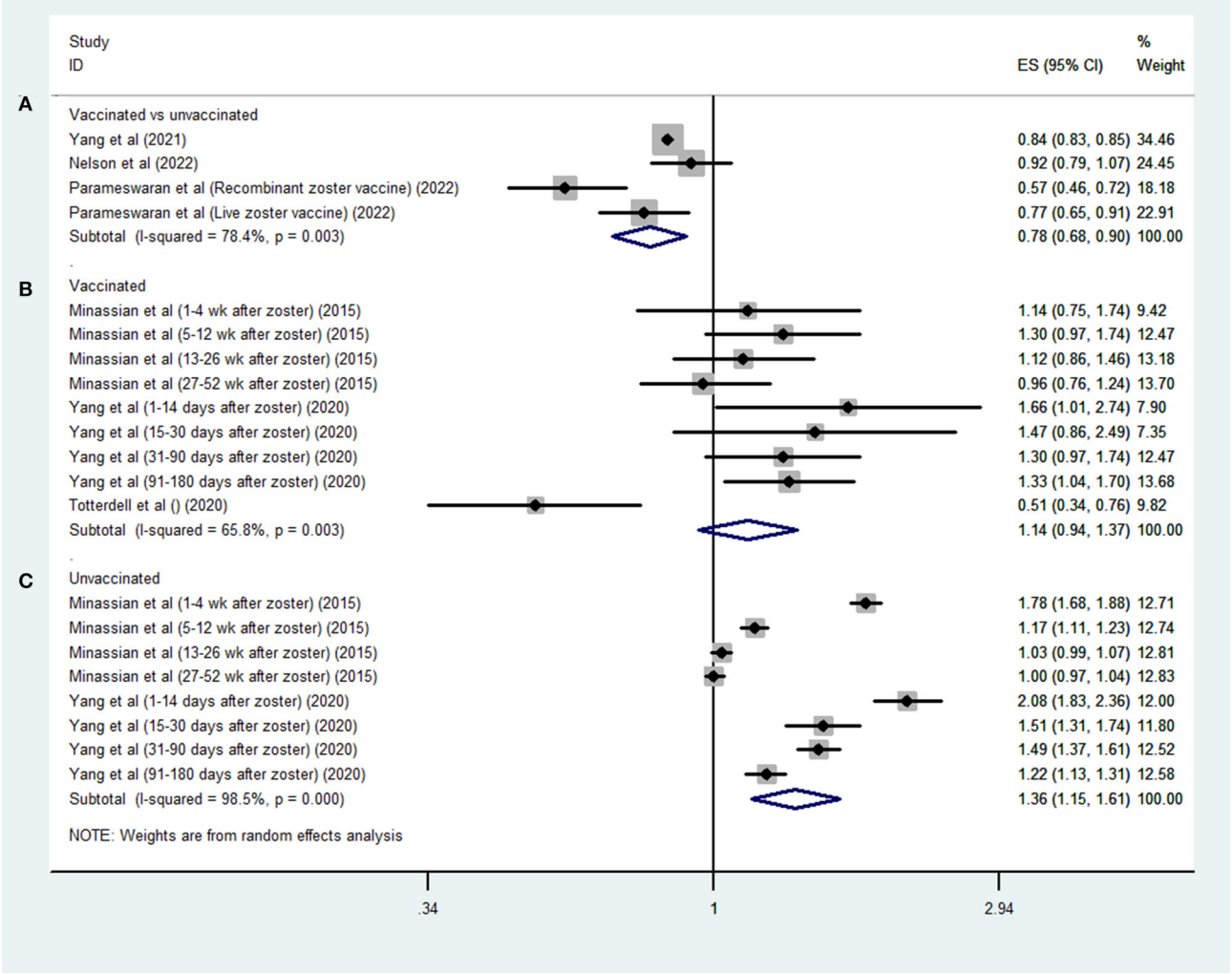

FIGURE 2
Forest plot of the overall risk of stroke in relation to HZV in **(A)** vaccinated vs. unvaccinated patients; **(B)** unvaccinated patients' own control; and **(C)** vaccinated patients' own control.

suffer from a stroke than those who did not (OR, 0.78; 95% CI 0.68–0.9; $I^2 = 78.4\%$; $P = 0.001$; Figure 2A).

Three SCCS studies (14–16) assessed the risk of stroke in defined periods after HZ compared with other periods. Among the vaccinated patients, there was no positive association between HZ infection and stroke risk (OR, 1.14; 95% CI 0.94–1.37; $I^2 = 65.8\%$; $P = 0.181$; Figure 2B); however, a higher risk of stroke was observed among unvaccinated patients after HZ infection (OR, 1.36; 95% CI 1.15–1.61; $I^2 = 98.5\%$; $P < 0.001$; Figure 2C).

Characteristics of the included studies on the association between antiviral treatment and stroke

Table 2 presents the details of the seven studies that investigated the association between antiviral treatment and stroke risk; there were two SCCS studies (16, 23) and five cohort studies (20–22, 24, 25). The studies were published between 2010 and 2022. Three studies (16, 24, 25) were conducted in the United States, two (20, 21) in Asia, and two (22, 23) in Europe. Only one (25) was a hospital-based study; the others were population-based studies that analyzed database data. According to the NOS quality scores, six studies were deemed to be of high quality, with only one categorized as low quality. The score breakdown is presented in Supplementary Tables S3, S4.

Meta-analysis of antiviral treatment and risk of stroke

Four studies (20–22, 25) evaluated the effect of antiviral treatment on stroke by comparing treated and untreated patients with HZ; the pooled data demonstrated that antiviral treatment was

TABLE 2 Characteristics of the included studies investigating the association between antiviral treatment and cerebrovascular events among HZ patients.

References, study location	Study design	Study period	Age	Ascertainment of HZ	Comparison	Definition of cerebrovascular events	Ascertainment of antiviral treatment	Adjustment	Quality
Lin et al. (20), Taiwan	Cohort	2003–2004	≥18	ICD-9-CM	Antiviral vs. No-antiviral	ICD-9-CM	Taiwan's National Health Insurance Research Database	No	7
Sreenivasan et al. (22), Denmark	Cohort	1995–2008	≥18	ICD-10	Antiviral vs. no-antiviral	ICD-10	Danish National Register of Medicinal Product Statistics	Age, gender, and calendar period	7
Langan et al. (23), UK	SCCS	1987–2012	≥18	ICD-10	Pre-antiviral vs. after-antiviral	ICD-10	Clinical Practice Research Datalink	Age	7
Calabrese et al. (24), USA	Cohort	2006–2013	≥65	ICD-9-CM	Antiviral vs. no-antiviral	ICD-9-CM	Medicare claims data	Age, gender, race, diabetes, hypertension, atrial fibrillation, transient ischemic attack, glucocorticoid use	9
Yang et al. (16), USA	SCCS	2008–2017	≥65	ICD-9-CM or ICD-10-CM	Pre-antiviral vs. after-antiviral	ICD-9-CM or ICD-10-CM	Medicare Provider Analysis and Review	FDR adjusted	8
Kim et al. (21), Korea	Cohort	2003–2014	≥18	ICD-10	Antiviral vs. no-antiviral	ICD-10	NHIS-NSC data	Gender, household income, medical history, steroid, antithrombotic, statin	9
Meyer et al. (25), USA	Cohort	2006–2016	≥65	Clinical charts	Antiviral vs. No-antiviral	Clinical charts	Clinical charts	No	5

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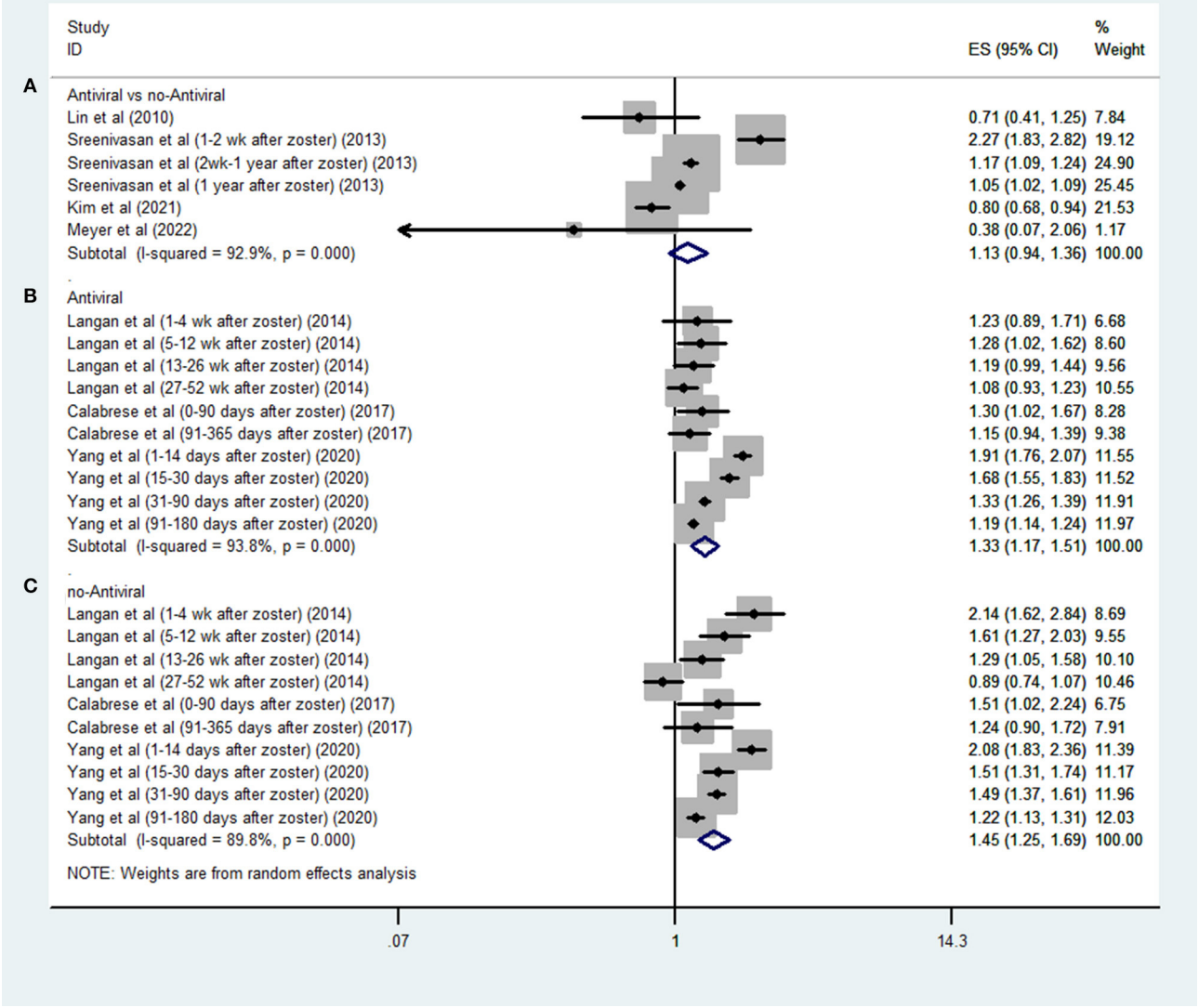

FIGURE 3
Forest plot of the overall risk of post-HZ stroke in relation to antiviral treatment (HZV): **(A)** antiviral vs. no-antiviral; **(B)** no-antiviral self-control; and **(C)** antiviral self-control of.

not associated with a reduced risk of stroke in these patients after HZ (OR, 1.13; 95% CI 0.94–1.36; $I^2 = 92\%$; $P = 0.201$; Figure 3A).

Three SCCS studies (16, 23, 24) evaluated the effect of antiviral treatment on the risk of stroke in defined periods after HZ compared to other periods; the pooled data demonstrated that both treated (OR, 1.33; 95% CI 1.17–1.51; $I^2 = 93.8\%$; $P < 0.001$; Figure 3B) and untreated (OR, 1.45; 95% CI 1.25–1.69; $I^2 = 89.8\%$; $P < 0.001$; Figure 3C) patients were at a higher risk of stroke after HZ.

Discussion

This systematic review and meta-analysis comprehensively investigated the current evidence on the effects of HZV and antiviral treatment on the risk of stroke; the pooled results showed that HZV was associated with a decreased risk of stroke, whereas no such protective modified effect was observed in patients with HZ who received antiviral treatment. The marked methodological variation among the studies and the limited number of included studies warrant a cautious interpretation of these findings.

Previous studies (10, 11, 26, 32) have focused on the relationship between HZ and stroke risk. Several biological mechanisms could explain such an association. One possible explanation is viral replication in the cerebral arteries. HZ virus can invade the arterial walls and thereby induce vasculopathy, which ultimately results in thrombosis, occlusion, infarction, aneurism, and hemorrhage (33). Inflammation also plays an important role in the etiology of stroke. A clinical study found inflammatory cells in the adventitia and intima in both early and late VZV vasculopathy (34). The inflammatory cytokines secreted by these inflammatory cells can potentially disrupt pre-existing atherosclerotic plaques

(35). Consistent with the preclinical findings, the recent meta-analysis (10) based on 12 epidemiologic studies demonstrated an increased risk of stroke in the short term after herpes zoster infection. Therefore, prevention and treatment of HZ may modify the associated risk of stroke.

In previous studies, the live HZV vaccine was 51%−65% efficacious against zoster and post-herpetic neuralgia, and this increased to 90% efficacy for the recombinant zoster vaccine (12, 13). The protective effect of HZV was observed in our analysis by comparing the incidence of stroke between vaccinated and unvaccinated individuals. However, the pooled analysis of the SCCS studies did not support an effect of HZV in terms of modifying the risk of stroke. This may result from the designs of such studies. SCCS is a novel strategy to control for between-person confounders by comparing the risk and reference periods in each patient (36). Risk periods are defined as during or after an exposure. Considering the proven risk of stroke after HZ, the null association in vaccinated patients with HZ implies a protective effect of HZV. Meanwhile, the meta-analysis of the SCCS studies found an increased risk of stroke in unvaccinated patients with HZ.

Antiviral drugs are mainly used to treat acute HZ, and they can relieve pain, accelerate the healing of skin lesions, and reduce the spread of the virus (37). Theoretically, it follows that antiviral treatment may have the potential to reduce post-zoster stroke by reducing inflammation. However, our findings did not support the protective role of antiviral treatment on stroke, which may be due to the following reasons. First, antiviral treatment is likely to be used mainly in patients with severe symptoms. It is reasonable to speculate that a more severe disease confers a higher risk of stroke; further studies should consider the severity of HZ. Second, it is recommended that antiviral treatment should be started within 3 days of the onset of HZ. Early antiviral therapy has been proven to reduce the risk of post-herpetic neuralgia and other complications (38). Only one study included in our analysis evaluated the effect of the timing of antiviral treatment on the risk of cerebrovascular disease and found a protective role for prompt but not for delayed antiviral treatment (25). Therefore, delayed antiviral treatment may underestimate the beneficial effect of antiviral treatment on stroke. Third, patient age varied among the included studies, and increasing age is associated with a higher risk of stroke (39). Due to the low incidence of stroke in young people, the wide age range of the subjects enrolled in several of the included studies may have reduced our chance of finding a protective effect. Accordingly, one included study (21) performed a further age-stratified analysis and observed a protective effect of antiviral treatment only in patients aged ≥50 years. Hence, the protective effect of antiviral treatment may be age-dependent.

To the best of our knowledge, this study is the first systematic review of the effects of HZV and antiviral treatment on the risk of stroke. However, several limitations should be taken into account. First, the small number of included studies may have influenced the accuracy of our findings. Second, residual unknown confounders are always a concern in observational studies. Further well-designed studies that consider more covariates should examine these associations. Finally, the included studies were very heterogeneous in terms of data sources, definitions of stroke, age of enrolled subjects, and type of vaccination examined.

In conclusion, our findings suggest that HZV, but not antiviral treatment is associated with a reduced risk of post-HZ stroke. However, these conclusions should be interpreted with caution because of the high study heterogeneity and potential unknown confounders. Further well-designed studies with larger samples are needed to verify our findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

A-jL and Y-hJ searched the library and drafted the manuscript. Y-bD and H-yJ extracted the data and revised all articles. A-jL designed the manuscript. All authors reviewed the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1176920/full#supplementary-material

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Progress in the clinical application of constraint-induced therapy following stroke since 2014

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Stroke is a group of cerebrovascular diseases with high prevalence and mortality rate. Stroke can induce many impairments, including motor and cognitive dysfunction, aphasia/dysarthria, dysphagia, and mood disorders, which may reduce the quality of life among the patients. Constraint-induced therapy has been proven to be an effective treatment method for stroke rehabilitation. It has been widely used in the recovery of limb motor dysfunction, aphasia, and other impairment like unilateral neglect after stroke. In recent years, constraint-induced therapy can also combine with telehealth and home rehabilitation. In addition, constraint-induced therapy produces significant neuroplastic changes in the central nervous system. Functional magnetic resonance imaging, diffusion tensor imaging, and other imaging/electrophysiology methods have been used to clarify the mechanism and neuroplasticity. However, constraint-induced therapy has some limitations. It can only be used under certain conditions, and the treatment time and effectiveness are controversial. Further research is needed to clarify the mechanism and effectiveness of CI therapy.

KEYWORDS

stroke, CI therapy, rehabilitation, motor dysfunction, aphasia

1. Introduction

Stroke is a group of cerebrovascular diseases with high prevalence and mortality rate (1). In the United States, about 795,000 people experience a new or recurrent stroke each year, and the overall stroke prevalence among Americans over 20 years of age is estimated at 3.3% (2). Globally, the prevalence of stroke was 89.13 million, and 7.08 million deaths can be attributed to stroke annually (2). Stroke is the second leading cause of death worldwide, with an estimated 5.5 million mortality rate annually, and its high morbidity results in long-term disability in up to 50% of survivors (1). Stroke can induce many impairments, including motor and cognitive dysfunction, aphasia/dysarthria, dysphagia, and mood disorders, which may reduce the quality of life (QoL) among the patients (3–5).

Constraint-induced (CI) therapy has been proven to be an effective treatment method for stroke rehabilitation. It was originally used for the rehabilitation of upper limb motor function, and gradually expanded to that of lower limb motor function recovery and aphasia treatment (6–10). Among them, constraint-induced movement therapy (CIMT) is a rehabilitation treatment method based on neuroscience and primate behavior research, which is effective in the rehabilitation of motor function after stroke (10). Constraint-induced aphasia therapy (CIAT), also known as intensive language-action therapy (ILAT), is an effective treatment for aphasia (11).

A literature search was conducted based on a selective search in the PubMed/MEDLINE databases to search the literature from 2014 up to 2022. We used search terms related to "stroke," "constraint-induced movement therapy," "intensive language-action therapy", "constraint-induced aphasia therapy," and "constraint-induced therapy," to review the clinical application of CI therapy in upper and lower limb motor dysfunction, aphasia, and other impairments after stroke. The literature search was limited to articles published in English, and the full text was available. We mainly included clinical studies on adults and excluded studies that the CI therapy was not an important method. The general writing framework was shown in Figure 1.

2. Clinical study of CI therapy in the treatment of upper limb

Upper limb motor dysfunction after stroke is a common complication, about 65% of patients were unable to engage the affected hand in daily activities 6 months after stroke (12). The CIMT for upper limb program consists of three components: ① repetitive, task-oriented training of the more-affected limb (shaping, and task practice), ② application of the "transfer package" of adherence-enhancing behavioral strategies that facilitate the transfer of therapeutic outcomes from the treatment setting to daily living situations (such as home diary, problem solving, and behavioral contract), and ③ constraining use of the more-affected limb, sometimes by restraining the less-affected limb (13, 14). CIMT applies movement techniques, behavioral techniques, and restriction methods to increase the frequency of using the more-affected limb by limiting the use of the less-affected limb, improve the quality of movement of the more-affected limb in real life, prevent or correct learned non-use, and ultimately improve the motor function of the more-affected limb (15). The efficacy of CIMT is considered to be associated with changes in brain plasticity (10, 16). The recovery process of CIMT was shown in Figure 2 (10, 13–16). The traditional CIMT approach requires restraint of the less-affected limb for 90% of the waking time and about 6 hours of training each weekday for 2 weeks (17). However, it was difficult to implement clinically; in addition, patients and therapists reported difficulties applying this approach (18). Therefore, the modified CIMT (mCIMT) has been created. While compared to the traditional CIMT, evidence suggested that mCIMT had similar functional recovery of the affected limb (18, 19).

2.1. Current status of effectiveness

The effectiveness of CIMT can be considered through various rehabilitation evaluation scales. Some studies have found improvements in motor function and affected limb use after CIMT intervention compared to pre-treatment (20, 21). Some studies comparing conventional rehabilitation therapy with CIMT (or CIMT combined with conventional rehabilitation), the results had shown improvements in motor function, spasticity, and occupational performance with CIMT (or CIMT combined with conventional rehabilitation) (22–26). In addition, the improvement of upper limb function could be related to the performance of activities of daily living (ADL) with CIMT (20), and CIMT might improve depressive symptoms (21).

Some studies compared CIMT with other therapies. A study showed significant improvement in spasticity and upper limb motor function in the mCIMT group compared with the proprioceptive based training group (18). Another study showed significant improvements in motor function and ADL in the CIMT group compared with the unconstraint task-oriented training group (27). However, some studies had shown that CIMT did not significantly improve function in patients compared to other therapies (28, 29), but the CIMT did not increase fatigue (28). Considering that CIMT is superior to some, but not all of the therapies; the best treatment method for the patient needs to be selected according to the condition and needs.

CIMT can be combined with other therapies. A study combined mCIMT with virtual reality training, the upper limb motor function improved (30). Another study used mCIMT or intensive conventional rehabilitation based on botulinum-A toxin injection, the results showed that the motor function and ADL of botulinum-A toxin injection combined with the mCIMT group were significantly improved between groups (31). In addition, a study combined short-term CIMT with visual biofeedback training, grasp and pad pinch function improved significantly compared to the conventional occupational therapy group (32). Yoon et al. combined mirror therapy with CIMT, and the results showed that the improvement of upper limb motor function was more significant than that of CIMT alone (33). It can be considered that CIMT combined with other treatment methods may have additional effects.

Trunk compensatory strategies may hinder long-term functional recovery of the upper limb (34). CIMT program could add trunk restraint. Some studies have demonstrated that CIMT combined with trunk restraint is significantly superior to CIMT alone in terms of upper limb motor function, ADL, and the use of the hemiplegic upper limb (35–37). In addition, another study combined auditory feedback for trunk control with mCIMT, the results suggested the upper limb function improved significantly compared to mCIMT alone (34). However, a study suggested that adding trunk restraint to mCIMT had no additional benefit (38). The effectiveness and mechanism of trunk control require further research.

Sometimes group modality may provide a foundation for communication and emotional support, stimulate the healing process, and transfer these improvements into functional independence and participation in daily activities (39). Some studies comparing group and individual modalities of CIMT indicated that motor function, amount of upper limb use, and functional independence increased more significantly in the group modality (39, 40). In addition, a study had shown that the amount of upper limb use daily significantly improved with group-based CIMT (41). The group modality can improve communication between patients, and may save the treatment time of the therapists to provide recovery for more patients;

Abbreviations: CI therapy, Constraint induced therapy; CIMT, Constraint induced movement therapy; mCIMT, Modified CIMT; CIAT, Constraint induced aphasia therapy; ILAT, Intensive language-action therapy; ADL, Activities of daily living; QoL, Quality of life; tDCS, Transcranial direct current stimulation; TMS, Transcranial magnetic stimulation; rTMS, Repetitive TMS; MEP, Motor-evoked potential; CST, Corticospinal tract; fMRI, Functional magnetic resonance imaging; BOLD, Blood oxygenation-level-dependent; M-MAT, Multimodality aphasia therapy.

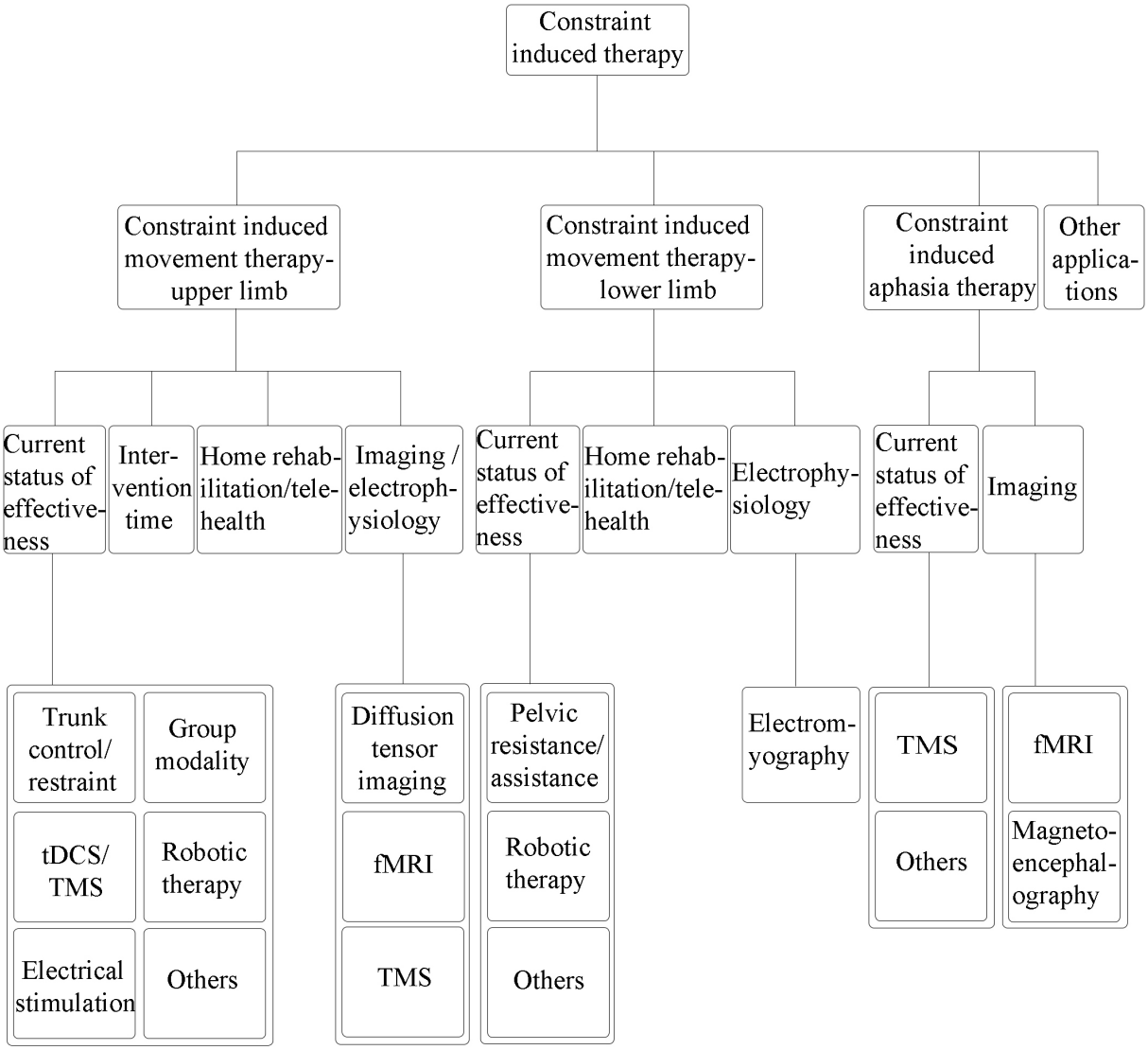

FIGURE 1
General writing framework of the article.

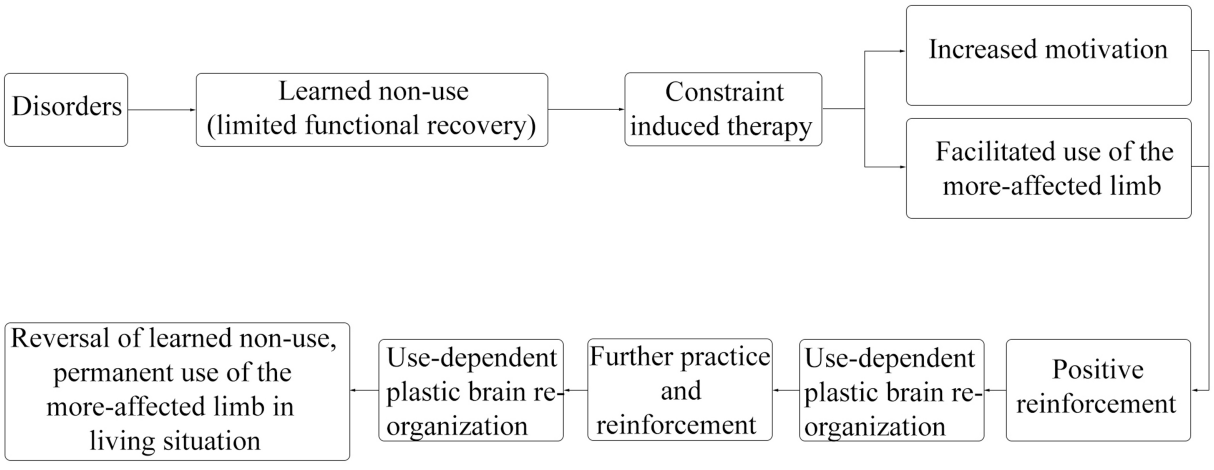

FIGURE 2
Recovery process of the CI therapy for upper limp.

further research is needed to find out the most suitable group modality therapy for clinical use.

Some studies have combined transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS) with CIMT. Two studies showed that tDCS combined with mCIMT group improved upper limb motor function compared with mCIMT alone group (42, 43). However, another study suggested that tDCS combined with mCIMT just improved the amount of the paraplegic upper limb use, with no statistical difference in motor function compared to mCIMT (44). In addition, one study combined CIMT with different tDCS (anodal stimulation in ipsilesional primary motor cortex versus anodal stimulation in ipsilesional premotor cortex versus sham stimulation), the motor function and ADL were improved and the muscle tone was decreased significantly in the premotor cortex group compared with the other two groups (45). Moreover, a study combining dual tDCS and peripheral neuromuscular electrical stimulation in a treatment group based on CIMT found significant improvements in motor function and use of the paralyzed upper limb compared with CIMT alone (46). Another study combining low-frequency repetitive TMS (rTMS) with intensive occupational therapy showed significant improvement in motor function compared to CIMT (47). tDCS/TMS has been widely used and can be combined with CIMT. However, it may not be ruled out that other therapies combined with tDCS/TMS are more effective. Moreover, different brain regions have different gains from stimulation, so further research is needed to find the most suitable method.

Some studies have involved robotic therapy. A study compared robot-assisted therapy to CIMT, and the results suggested that both of them could improve the function of the patients, but there was no significant difference in motor function between groups (48). Some studies that added CI therapy to robot-assisted therapy showed a reduction in compensatory trunk movement during the task, with more significant improvements in motor function and ADL compared with robot-assisted therapy alone (49, 50). Robotic-based rehabilitation is a hot research field, and the studies have shown that it can be combined with CI therapy. Robot-based therapy can provide precise control and real-time monitoring of the patients; through further research, we may find out suitable treatment methods for patients and achieve precise rehabilitation.

Electrical stimulation is also a common method in rehabilitation. A study combining modified CI therapy and peripheral nerve stimulation suggested that the improvement of motor function was more significant than that of modified CI therapy alone (51). Another study used electromyography-triggered neuromuscular stimulation on the patient with an unfavorable prognosis, the result suggested that there was no significant difference compared to usual care (22). It is considered that electrical stimulation may have an additional effect in patients eligible for CIMT, but in patients with low function, it may not possible to improve function by electrical stimulation alone.

In addition to rehabilitation methods, patient management is also essential. Self-regulation is designed to improve patients' self-awareness and assist in identifying their functional problems, thus facilitating the recovery process (52). A study combining self-regulation and mCIMT has found additional effects on functional recovery in patients after stroke (52). In addition, a study used the mobile health platform to help patients improve self-management and timely communication. The study combined CIMT with the use of mobile health platform, the results showed significant improvements in motor function and ADL compared to conventional rehabilitation program (53).

2.2. Discussion on the intervention time

Several studies have compared early and late delivery of CIMT. A study showed that the early applied CIMT group had greater improvement in motor function than the late applied group (54). But another study found that early delivery of CIMT was as good as late intervention; however, the early CIMT intervention group showed a faster recovery curve than the late intervention group (55). Considering that according to the patient's condition, CIMT can be intervened early; if CI therapy has not been used in the early stage, it can also be added when necessary, and there is no need to worry about the late intervention of CIMT may be ineffective.

2.3. Discussion on the home rehabilitation and telehealth

Home rehabilitation and telehealth are current research hotspots. In the post-coronavirus disease 2019 era, the development of home rehabilitation is particularly important. CI therapy can also be combined with telehealth and home rehabilitation, and gradually applied to out-of-hospital care. With telehealth, treatment services can provide to individuals who may not be able to visit clinics, and there is an internet-based CIMT, which is the mCIMT approach combined with telehealth (56). In addition, telehealth can take the approach of games, and its efficacy can be similar to that of in-clinic rehabilitation (57). And home rehabilitation also can be via an in-home game program (58).

A study using mCIMT in combination with telehealth in high/low functioning patients showed significant improvements in motor and ADL functions in both groups (56). Another study showed the telehealth CIMT group was no worse than the face-to-face CIMT group in using the more-affected upper limb (59). In addition, a study comparing in-home CIMT with conventional rehabilitation found that in-home CIMT could improve the use of the affected upper limb more effectively than conventional therapy, but was not superior in motor function improvement (60). However, the results were controversial. Another study showed that there was no significant difference between in-home CIMT and conventional rehabilitation in motor function and participation (29). Furthermore, a study analyzed factors associated with QoL in different CIMT programs (in person/in home), and found that improvement in QoL was associated with gains in upper-limb use but not with motor function (61). Considering that telehealth and home rehabilitation combined with CIMT are useful for stroke patients who need long-term rehabilitation, but may need to improve treatment protocol to ensure the efficacy; further research can be done to develop more programs to provide convenience for patients.

2.4. Imaging and electrophysiology – discussion on the mechanism

Diffusion tensor imaging can be utilized to show the effects of CIMT on the fibers of the corticospinal tract (CST). A study showed

that patients with disrupted or displaced CST had lower motor function in pre-treatment than those with unaltered CST. However, this had no significant difference in their ability to benefit from CI therapy (62). Another study showed similar results. The integrity of CST correlated with patients' motor function, and there was no significant difference between left and right hemiplegia. The post-treatment benefit was not associated with CST integrity or lesion volume (63).

Some studies applied functional magnetic resonance imaging (fMRI). A study showed the CIMT led to increased activity of the lesioned hemisphere dorsal premotor cortex compared to the untreated group, and no changes in laterality index were observed in the primary motor cortex (64). Upper limb dominance did not affect the improvement of upper limb function after CIMT (65). However, fMRI showed that the images were different according to the dominant/non-dominant side of the upper limb paralysis. When less-affected upper limb constraint was added to the right-handed left/right hemisphere stroke patients during the paralyzed arm elevation, the study had shown that in right hemisphere stroke patients, it led to the silence of contralesional cortical areas while maintaining ipsilesional activation of the sensorimotor cortex. And in patients with left hemisphere stroke, the same situation led to bilateral reduction of cortical activation (66). Considering that further studies on hand dominance are needed, it is also possible that left/right hemisphere stroke has different functional mechanisms.

TMS can be used for electrophysiological evaluation. Motor-evoked potentials (MEPs) were significantly improved, and the ipsilesional silent period declined in the mCIMT group compared to baseline in acute stroke (67). However, there were no long-term differences in motor function or electrophysiological parameters between mCIMT and standard therapy groups (67). Another study showed that when compared pre-and post-treatment MEPs, there were no significant improvements in resting motor threshold, central motor conduction time, and amplitude with conventional rehabilitation; and the MEP parameters in CIMT group were significantly improved (26). In addition, acute stroke could cause the interhemispheric excitability imbalance. It is considered that tDCS can reduce the interhemispheric excitability imbalance through the change of MEP (68). Furthermore, a study compared early and late applied CIMT, the results showed that greater cortical recombination occurred in the late group in terms of map size and position, considering that the recovery mechanism may have changed over time (54).

Imaging and electrophysiology are important methods to clarify the mechanisms that reflect neuroplasticity changes in CIMT and other recovery methods. At present, much of the latest research in this field tends to be animal experiments (69), and more human studies are needed. It is also important to edit appropriate functional tasks in fMRI.

3. Clinical study of CI therapy in the treatment of lower limb

Lower limb motor dysfunction after stroke is also a common disorder. There are up to 35% of stroke patients with initial lower-limb paralysis who do not regain physical function, and 20–25% of them are unable to walk without full physical assistance (12). CIMT for the lower limb was modified from the original upper limb CIMT (14). CI therapy for lower limb has been widely used in neurological disorders (10).

3.1. Current status of effectiveness

In CIMT for lower limb, the number of practice tasks, rather than practice time, may play an important role in functional recovery. Therefore, it may be more convenient to use the CIMT protocol with the number of repetitions than the CIMT protocol with the number of practice hours, so the mCIMT scheme is preferable (70). In addition, a study found improvements in the use and function of the paralyzed lower limb after CIMT (71). Another study showed that CIMT significantly improved patients' balance function, lower limb motor function, and walking speed compared to conventional rehabilitation, and many of these improvements were sustained after 3 months (72).

Lower limb restraint can be accomplished with "pelvic resistance/assistance." In the "pelvic resistance" condition, the lateral weight shift to the paralyzed side was improved compared to the "pelvic assistance" condition, while the "pelvic resistance" also improved overground gait speed and standing phase symmetry (73). Park et al. suggested that lower limb muscle activity, weight shift toward the affected side, and overground walking speed were significantly improved in the condition of a gradual increase of "pelvic assistance" force, which was better than that under the sudden increase. It was considered that the "gradual increase" during constrained induced walking might improve weight shift and enhance forced use of the paralyzed lower limb (74). Another study showed that pelvic resistance in the standing stage showed a greater increase in hamstring muscle activity in the paretic lower limb and improvement of the step length symmetry compared with constant resistance applied throughout the gait cycle (75). Restraint devices were omitted in lower limb CIMT, mainly due to safety issues like high risk of falls; meanwhile, wearing the device during the intervention led to unnatural gait and postural patterns (14). Resistance applied to the pelvis in the above studies provided a similar restraint effect to upper limb CIMT, which may have an additional effect on functional improvement.

CIMT for lower limb can also involve robotic therapy. A study used a rehabilitation robot to apply resistance to the less-affected lower limb, while assistance was applied to the more-affected side, and performed gait analysis. The results suggested that "Lokomat® constraint gait training" might improve knee flexion of the paralyzed lower limb, and the effect was better than that of conventional robotic gait training (76). The robot-assisted system can provide precise force changes. It can provide appropriate assistance and resistance force, may solve the problem of traditional lower limb CIMT with no resistance, and can be considered for clinical promotion.

3.2. Discussion on the home rehabilitation and telehealth

Home rehabilitation can also be used in lower limb motor dysfunction, and can adopt the game mode. One study compared game-based CIMT with game-based training, the results suggested that both of game-based CIMT and training could improve static and

dynamic balance, and the CIMT had a greater effect on static balance control (77).

3.3. Electrophysiology – evaluation with electromyography

Studies related to lower limb CI therapy can be conducted by electromyography. Some studies have compared whether forcible use of the paralyzed lower limb by restraining the non-paralyzed lower limb, could improve the functional ability of the patients. One study showed that step length symmetry could be significantly improved during treadmill walking with constraints (78). Furthermore, during the stance phase, the electromyography of some lower limb muscles increased significantly at the early adaptation period. Meanwhile, under the constraint condition, the retention during the post-adaptation period was significantly greater than that under the treadmill-only condition (78). Another study has shown that applying controlled resistance force to the non-paralytic lower limb during early swing phase increased the use of paralytic lower limb and improved spatiotemporal symmetry of gait (79). In addition, compared to baseline, significant electromyography increases were observed in some muscles of the paralyzed lower limb when resistance force was applied during the early swing phase, and 30% maximum voluntary contraction resistance caused the highest level of muscle activity compared to 10% or 20% maximum voluntary contraction resistance (79). Studies on electrophysiology and imaging of lower limb CIMT are less common than those of upper limb CIMT, so more relevant studies should be conducted to help clarify the mechanism and neuroplasticity of CIMT for lower limb.

4. Clinical study of CI therapy in the treatment of aphasia

Aphasia is an acquired language disorder that affects all aspects of language-based communication: comprehension of speech, reading, writing, and speaking, and is a common disorder that affects the QoL among stroke patients (80). Aphasia treatment may require extensive training, behavioral and communicative relevance of the interaction during treatment, and should focus on the patients' communication needs and possibilities. These principles have been adopted by a new treatment method called CIAT (81).

4.1. Current status of effectiveness

CIAT can be used in the treatment of aphasia after acute stroke (82). Meanwhile, patients with chronic aphasia for more than 1 year can also expect language improvement through CIAT (83). The benefits gained by CIAT may sustain long after treatment ended (84).

Studies have found that CIAT could improve the subjective language abilities (85) and depressive symptoms (86). Stahl et al. comparing CIAT and naming therapy suggested that CIAT significantly improved language performance, independent of the duration of the intervention (87). In addition, a study compared CIAT with multimodality aphasia therapy (M-MAT) and usual care, showed CIAT and M-MAT were better than usual care for aphasia. After intervention, M-MAT was beneficial for patients with severe aphasia, CIAT was beneficial for patients with moderate aphasia, but there was no difference between them for patients with mild aphasia (80). Through these studies, CIAT can be considered to improve aphasia, but different levels of aphasia may need different treatment methods. Furthermore, one study compared the efficacy difference between high-intensity and moderate-intensity CIATs. The results indicated that there was no statistical significance between them (88). It was considered that only increasing the daily treatment time might not gain additional effect.

Some studies showed CIAT could combine with rTMS. A study combined rTMS with CIAT, and compared to CIAT, found no additional effect of rTMS (89). Nevertheless, previous studies have found that both of CIAT and CIAT combined with rTMS could improve naming (90, 91). The results of the studies may be related to the small sample size, and further research is needed to determine whether it is necessary to combine rTMS based on CIAT.

4.2. Imaging – discussion on the mechanism

Functional imaging was used for the studies. Some studies used intermittent theta burst stimulation and CIAT. The language measurements suggested that intermittent theta burst stimulation combined with mCIAT indicated improvements, and these improvements were correlated with changes in the blood oxygenation-level-dependent (BOLD) fMRI in left inferior parietal lobe and right inferior frontal gyrus (92) or in right postcentral gyrus and bilateral supplementary motor area (93). Some other studies also have shown that the BOLD signal changes with fMRI correlated with improvement in the clinical aphasia test after CIAT (11, 94). However, the connection between aphasia therapy and neuroplasticity changes is controversial. One study found that language ability improved in stroke patients with CIAT, but the changed fMRI areas were mainly related to behavioral performance. Considering that language-related cortical plasticity may not have a specific effect on CIAT (95). A study used magnetoencephalography to suggest that CIAT improved language skills in patients, and language recovery was associated with changes of neuroplasticity in both cerebral hemispheres (96). CIAT was considered to be associated with language-related changes in neuroplasticity, but the results have not been consistent. Further studies on functional imaging are needed to clarify the mechanism of CIAT.

5. Other applications

Unilateral spatial neglect is a common consequence of stroke survivors, most of which occur after right hemisphere stroke, resulting in neglect of the left visual hemifield (97). One of the main reasons why CI therapy is effective is that it overcomes the learned non-use, and considering that CI therapy as an approach to treating unilateral spatial neglect is worth trying (97). Sleep may interfere with functional recovery. A study has shown that circadian preference and sleep quality affects the functional improvement among stroke patients after CI therapy (98).

6. Current problems

However, CI therapy has some limitations. It can only be used under certain conditions and cannot cover all patients. Patients who can use CIMT for upper limb always require certain motor functions, such as the active extension of the thumb and two or more fingers (≥10°) of the affected hand (22). Moreover, the treatment time and effectiveness are also controversial. The traditional CIMT including restraint of the less-affected upper limb to facilitate the use of the more-affected limb during 90% of the waking time (17), which was difficult to implement clinically. However, a study has shown no significant correlation between constraining time and functional outcomes (99). The necessity and the appropriate time of constraint need further study. In addition, a study has shown that CIMT improved motor function immediately after treatment, but no significant effect was observed after 6 months compared to conventional therapy (100).

7. Conclusion

CI therapy is widely used in stroke rehabilitation, and different CI therapies can meet diverse needs for recovery of patients. It can be combined with other treatment methods to provide additional benefits. Many studies have now demonstrated the effectiveness of CIMT not only by rehabilitation evaluation scales but also by electrophysiological and imaging methods. With the development of technology, CI therapy is linked to telerehabilitation, responding to the needs of patients with chronic dysfunction and/or inconvenient access to the clinic. However, CI therapy has some limitations. Requirements on basic motor function may limit its application in some patients. In addition, limiting the use of the non-paralyzed limb may affect the patient's ADL and cause inconvenience. Moreover, its long-term effects need to be further studied. Meanwhile, further research is also needed to clarify the mechanism and effectiveness of CI therapy. In addition, the protocol needs to be improved. Furthermore, it needs to be integrated with modern technology and applied in clinical practice.

Author contributions

YC drafted and revised the manuscript. NM made figures and helped in revision. XL and YLia performed the literature search and extracted the articles. YLi, GX, and JZ helped in writing and editing. ZL conceived and designed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Variants in genes related to inflammation and endothelial function can increase the risk for carotid atherosclerosis in southwestern China

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Aim: To investigate the potential association between polymorphisms in genes involved in endothelial function, inflammation and carotid atherosclerosis.

Methods: This was a three-center, population-based sectional survey conducted in Sichuan province of southwestern China. We randomly selected 8 different communities in Sichuan, and the residents in each community volunteered to participate in the survey by face-to-face questionnaire. A total of 2,377 residents with high stroke risk population in the 8 communities were included. Carotid atherosclerosis was evaluated by carotid ultrasound, and the 19 single nucleotide polymorphisms (SNPs) in 10 endothelial function as well as inflammation relevant genes were measured in the high stroke risk population. Carotid atherosclerosis was defined by the presence of carotid plaque or any carotid stenosis ≥15% or mean intima-media thickness (IMT)>0.9mm. Generalized multifactor dimensionality reduction (GMDR) approach was used to analyze gene–gene interactions among the 19 SNPs.

Results: Among the 2,377 subjects with high stroke risk, 1,028 subjects had carotid atherosclerosis (43.2%), of which 852 (35.8%) cases had carotid plaque, 295 (12.4%) cases had ≥15% carotid stenosis, whereas 445 (18.7%) had mean IMT>0.9mm. Multivariate logistic regression revealed that *IL1A* rs1609682 TT and *HABP2* rs7923349 TT served as independent risk factors for carotid atherosclerosis (OR, 1.45, 95% CI: 1.034–2.032, p=0.031, and OR, 1.829, 95% CI: 1.228–2.723, p=0.003). GMDR analysis indicated that there was a significant gene–gene interaction found among *IL1A* rs1609682, *ITGA2* rs1991013, and *HABP2* rs7923349. After adjusting the covariates, the high-risk interactive genotypes in the 3 variants were significantly associated with a significantly higher risk for carotid atherosclerosis (OR, 2.08, 95% CI: 1.257–5.98, p<0.001).

Conclusion: The prevalence of carotid atherosclerosis was observed to be extremely high in the high-risk stroke population in southwestern China. There were associations observed between the specific variants in inflammation and endothelial function relevant genes and carotid atherosclerosis. The high-risk interactive genotypes among *IL1A* rs1609682, *ITGA2* rs1991013, and *HABP2* rs7923349 significantly increased the risk of carotid atherosclerosis. These results are expected to provide novel strategies for the prevention of carotid

atherosclerosis. The gene–gene interactive analysis used in this study may be very helpful to elucidate complex genetic risk factors for carotid atherosclerosis.

KEYWORDS

high risk stroke population, carotid atherosclerosis, inflammation, endothelial function, genetic polymorphism

Introduction

Stroke is one of important causes of adult mortality as well as disability in the Western countries and in China (1), and is primarily caused by carotid atherosclerosis (2). The patients with carotid atherosclerosis have a significantly higher risk for stroke and other cardiovascular events as a result of luminal stenosis or plaque rupture (2–4). Carotid atherosclerosis, including carotid plaque, increased intima-media thickness (IMT) and carotid stenosis, is considered as powerful subclinical predictors of the future vascular events (4, 5). Therefore, it is important to investigate the potential etiology of carotid atherosclerosis for better prevention of stroke and other vascular events. Although the associations between carotid atherosclerosis and traditional vascular risk factors have been reported, current studies have focused on the effect of genetic factors because of their potential contributions to the vascular lesions (6, 7). However, up to date, such a genetic effect on carotid atherosclerosis is not clear.

Atherosclerosis is a chronic immune inflammatory process related to a variety of immune-inflammatory cells and mediators and causes instability of plaque or plaque rupture. The risk of atherosclerosis increases with an increase in plaque vulnerability (8). Atherosclerosis as a complex inflammatory disorder, activation and recruitment of the various inflammatory cells, endothelial injury, smooth muscle cell proliferation, and influx of the lipoproteins through vessel injury space are important mechanisms of atherosclerosis (8, 9). Thus, inflammation and endothelial injury play key roles in the pathogenesis of atherosclerosis. The variable risk for atherosclerosis reflects the variants that can effectively modulate endothelial function and inflammatory response in the arterial walls (9). A number of previous studies have demonstrated that various genes related to inflammation are associated with vulnerability of the carotid plaque (6, 10, 11). Furthermore, variants in the genes related to endothelial function and inflammation have been found to play key function in carotid plaque and carotid stenosis (7, 12, 13). A study from the Northern Manhattan population examined the association between carotid plaque and 197 single nucleotide polymorphisms (SNPs) in 43 genes implicated in inflammation and endothelial function, and found that the associations between variants in 10 genes (*TNF*, *NOS2A*, *IL6R*, *TNFSF4*, *PPARA*, *IL1A*, *TLR4*, *ITGA2*, *VCAM1*, and *HABP2*) and carotid plaque phenotypes (12). Studies from Chinese population also demonstrated that specific SNPs in inflammation and endothelial function relevant genes were associated with carotid plaque, the high-risk interactive genotype among rs7923349, rs1991013, rs1609682, and rs8081248 was independently associated with a higher risk for vulnerable plaque (7), and the high-risk interaction in *ITGA2* rs4865756 and *HABP2* rs7923349 increased the risk of carotid stenosis (13).

In general, carotid plaque, increased IMT and carotid stenosis can exist simultaneously in patients with carotid atherosclerosis. Thus, it might be inappropriate to analyze the possible association of endothelial function and inflammation relevant genetic SNPs with carotid plaque or carotid stenosis separately. Atherosclerosis is a complex disease and it does not follow Mendelian mode of Inheritance (14), which could be attributed to the effect of gene–gene interactions (6, 7). However, few studies have examined the effect of gene–gene interactions among various genes regulating inflammation and endothelial function on the carotid atherosclerosis.

According to China National Stroke Screening Survey (CNSSS) program (1), we carried out this population-based high-risk stroke population survey in Sichuan of southwestern China (15). On the basis of our survey, we performed this study to investigate: (1) the prevalence of carotid atherosclerosis in the high-risk stroke population; (2) the associations of 19 SNPs in genes relevant to endothelial function and inflammation with carotid atherosclerosis, and the influence of gene–gene interaction among the 19 SNPs on carotid atherosclerosis. Overall, the findings can be very important to identify genetic etiology of carotid atherosclerosis, and can aid in better prevention of atherosclerosis and vascular events.

Materials and methods

Study population

This multicenter community-based sectional survey was a part of CNSSS, which was approved by Stroke Screening and Prevention Commission in China (Grant No. 2011BAI08B01) (16). The study protocol was reviewed and approved by the Ethics Committee of Suining Central Hospital, the Affiliated Hospital of Southwest Medical University, and the People's Hospital of Deyang City. A written informed consents were obtained from all the participants before enrollment.

The implementation and organization of this survey can be found in the articles previously published by our group (15–17). Briefly, the 8 communities in Sichuan were randomly selected during May 2015 to September 2015. The residents aged ≥40 years who lived in the community for more than 6 months were surveyed using the structured face-to-face questionnaire. The questionnaire included details about the demographic characteristics, behavioural factors, family and personal history of stroke, history of chronic diseases (such as diabetes mellitus, hypertension, atrial fibrillation, and dyslipidemia), and physical examination. For the subjects who were identified to be as a high-risk for stroke, carotid ultrasonography was measured.

Evaluation of risk factors and definitions of high-risk stroke population

The eight different conventional risk factors were evaluated, including overweight/obesity, smoking, physical inactivity, family

history of stroke, diabetes mellitus, hypertension, atrial fibrillation, and dyslipidemia. The detailed diagnostic criteria for the eight conventional risk factors have been described in our previous study (17).

The individuals were defined as the high-risk stroke population if they had at least three of aforementioned eight conventional risk factors for stroke, or a history of stroke (15–17). The history of stroke was identified by self-reporting and the neuroimaging (magnetic resonance imaging or brain computed tomography scan) (15). Exclusion criteria included: (1) subjects declined to participate in this study; (2) severe cardiovascular, liver or renal disease; (3) hematological diseases, acute or chronic inflammation, immune system diseases, and malignant tumors; (4) history of carotid artery stenting or endarterectomy.

Data cleaning procedures

The detailed procedure has been presented in Figure 1. Briefly, 2,893 individuals were identified as the high-risk stroke population among 16,892 participants. Both DNA and carotid ultrasonography information was obtained in the 2,377 subjects among the 2,893 high-risk stroke population.

Carotid ultrasonography and definition of carotid atherosclerosis

Bilateral common and internal carotid arteries and bifurcations were evaluated using the Color duplex scan (Acuson Sequoia Apparatus, type 512, 7.5-MHz probe, Berlin, Germany) in 2377 high-risk stroke population, according to the standard scanning and reading protocols (5, 7, 13). The common markers for carotid characteristics, including IMT, plaque and extracranial carotid stenosis were measured. The detailed procedure and definition for carotid plaques, degree of carotid stenosis, and interobserver and intraobserver coefficients have been described in detail in our previous articles (7, 13). The IMT was evaluated from the intima-lumen interface to the media-adventitia interface in each carotid segment and outside the segment of plaque when the plaque was present in a given segment. The mean of IMT was evaluated at 6 carotid sites: common carotid artery (20 mm from the flow divider), bifurcation, and internal carotid artery (20 mm from the flow divider) bilaterally. Mean IMT > 0.9 mm was considered as abnormal (18). The carotid arteries were assessed by ultrasound investigators blinded to the clinical data. Carotid atherosclerosis was defined as the presence of any carotid plaque or any carotid stenosis ≥15% or Mean IMT > 0.9 mm (19) (Figure 2).

Genotyping

Nineteen SNPs in 10 genes related to endothelial function and inflammation were obtained from NCBI database[1] following the criteria: (1) the 19 variants have been assessed in the previous studies (7, 12); (2) with the minor allele frequency > 0.05 in each SNP; (3) nonsynonymous variants; (4) the variants might lead to amino acid changes; (5) Tagging SNPs across different human populations.[2]

The peripheral blood (3 ml) was drawn from an arm vein, DNA was extracted by modified phenol/chloroform method (6, 7), and genotypes of the 19 SNPs were evaluated by using matrix-assisted laser desorption/ionization time of flight mass spectrometry method, as described previously by us (7, 13). The investigators were blinded to the clinical data of participants.

Statistical analysis

Statistical analyses were carried out using the SPSS 17.0 (SPSS Inc., New York, United States). Intergroup differences in the baseline characteristics and genotype distributions of the 19 SNPs were evaluated by χ^2 test or Fisher's exact test for the categorical variables. Student *t*-test or analysis of variance was used for the continuous variables between individuals with and without carotid atherosclerosis. Hardy–Weinberg equilibrium for allele frequencies was analyzed by χ^2-test.

Gene–gene interactions among the 19 SNPs were analyzed under the various scenarios using generalized multifactor dimensionality reduction (GMDR) approach (20), as previously described by us (6, 7). In brief, the GMDR computes the maximum likelihood estimates and the scores of all individuals under the null hypothesis. The 19 SNPs were coded from number 1 to 19, a cumulative score was then calculated within each multifactor cell, which was labeled either as high-risk if the average score exceeded a pre-assigned threshold of zero or as low-risk if score was less than zero. An exhaustive search of all possible models was conducted for all SNPs. The model with minimum prediction error, maximum cross-validation consistency score and a *p*-value ≤0.05 [obtained automatically from the sign test in the GMDR software (20)] was defined as the best model. Then the model was confirmed using a permutation test implemented in the GMDR software.

The prevalence of carotid atherosclerosis between individuals with and without high risk interactive genotypes was compared using χ^2-test. Multivariate logistic regression analysis was performed to evaluate the potential risk for carotid atherosclerosis conferred by the high-risk interactive genotypes, and the odds ratio (OR) with 95% confidence interval (CI) was reported. The other variables that exhibited a significant association with carotid atherosclerosis ($p < 0.05$) in the univariate analysis were introduced into the multivariate logistic regression model. Furthermore, Hosmer and Lemeshow (H-L) test was used to evaluate the goodness of fit of multivariate logistic regression model. All the tests were two sided, and *p*-value <0.05 denoted statistical significance.

Results

Prevalence of carotid atherosclerosis in the high-risk population for stroke

Among the 2,377 participants with high risk stroke population, carotid atherosclerosis was present in 1028 subjects (43.2%), among

1 http://www.ncbi.nlm.nih.gov/SNP

2 http://pga.gs.washington.edu

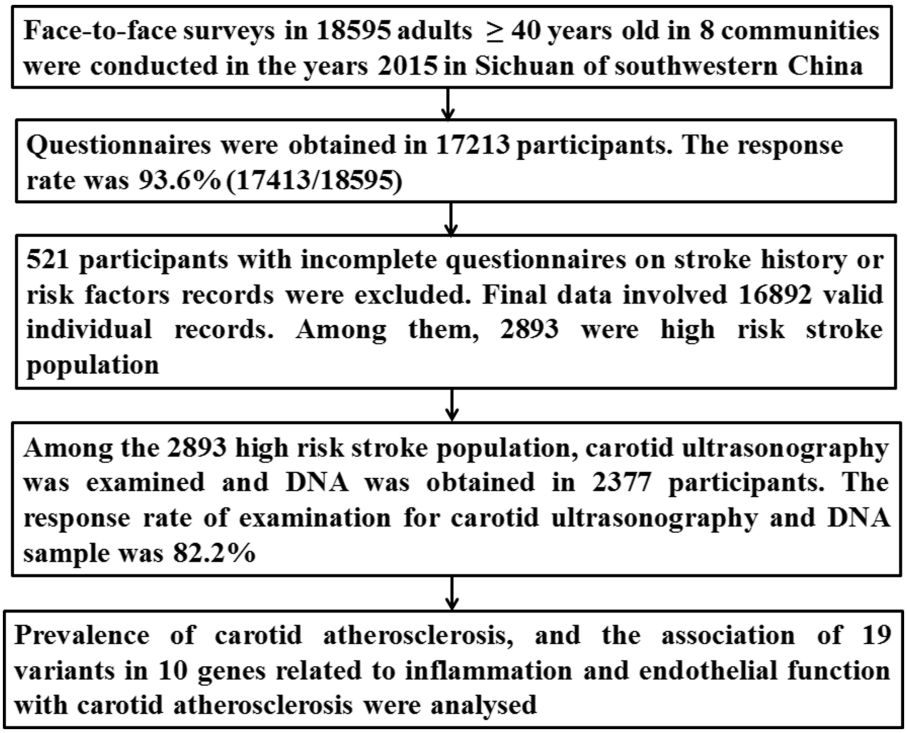

FIGURE 1
Flow chart in this study.

which 852 (35.8%) cases had carotid plaque [454 (53.3%) had stable plaque, 398 (46.7%) had vulnerable plaque], 295 (12.4%) cases had carotid stenosis [244 (82.7%) had 15–49% stenosis, 51 (17.29%) had more than 50% stenosis], whereas 445 (18.7%) had mean IMT > 0.9 mm (Table 1). It was observed that compared with individuals without carotid atherosclerosis, individuals with carotid atherosclerosis were older, had a higher proportion of males, rural residents, with junior middle school or below level of education, and had a history smoking, hypertension and dyslipidemia ($p < 0.05$, Table 1).

Distribution of genotypes in the subjects

The genotype distributions of the 19 variants analyzed in this study were in agreement with Hardy–Weinberg Equilibrium ($p > 0.05$). Moreover, univariate analyses showed that there were significant differences in genotype distributions of *IL1A* rs1609682, *PPARA* rs4253655, and *HABP2* rs7923349 between individuals with and without carotid atherosclerosis ($p < 0.05$, Table 2).

Gene–gene interactions among the 19 variants

The association of gene–gene high-order interaction in the 19 variants with carotid atherosclerosis was evaluated using the GMDR approach. A significant gene–gene interaction was found in the 19 variants, and the best interactive model for carotid atherosclerosis was interaction among *IL1A* rs1609682, *ITGA2* rs1991013 and *HABP2* rs7923349, which scored 10/10 for the cross-validation consistency and 10 for sign test ($p = 0.001$, Table 3). The p-value of prediction error was 0.016 for the GMDR based on the permutation testing.

Different genotype combinations with the risk of carotid atherosclerosis

Thereafter, the associations of different genotype combinations in the 3 three interactive variants with the risk of carotid atherosclerosis were evaluated. It was found that compared with the individuals with wild-type genotype of the three variants (i.e., rs1609682 GG, rs1991013 GG, and rs7923349 GG), the relative risk of the different genotype combinations in the three variants for carotid atherosclerosis was assessed. The results showed that the 4 genotype combinations contributed to the larger risk for carotid atherosclerosis, including those subjects carrying rs1609682 TT, rs1991013 AA and rs7923349 TT (OR = 2.62, 95% CI: 1.21–6.86, $p = 0.007$); rs1609682 TT, rs1991013 AG and rs7923349 TT (OR = 2.06, 95% CI: 1.07–4.62, $p = 0.036$); rs1609682 GT, rs1991013 AA and rs7923349 GT (OR = 1.76, 95% CI: 1.03–2.63, $p = 0.043$); rs1609682 TT, rs1991013 AA and rs7923349 GT (OR = 2.14, 95% CI: 1.18–5.37, $p = 0.012$) (Table 4), which were considered as the high-risk interactive genotypes. The other combinations among the three variants did not achieve statistical significance ($p > 0.05$) and were thus considered as the low-risk interactive genotypes.

Association of the high-risk interactions with carotid atherosclerosis

There were 523 subjects identified who were carrying the high-risk interactive genotypes in the 2,377 high risk stroke population. The

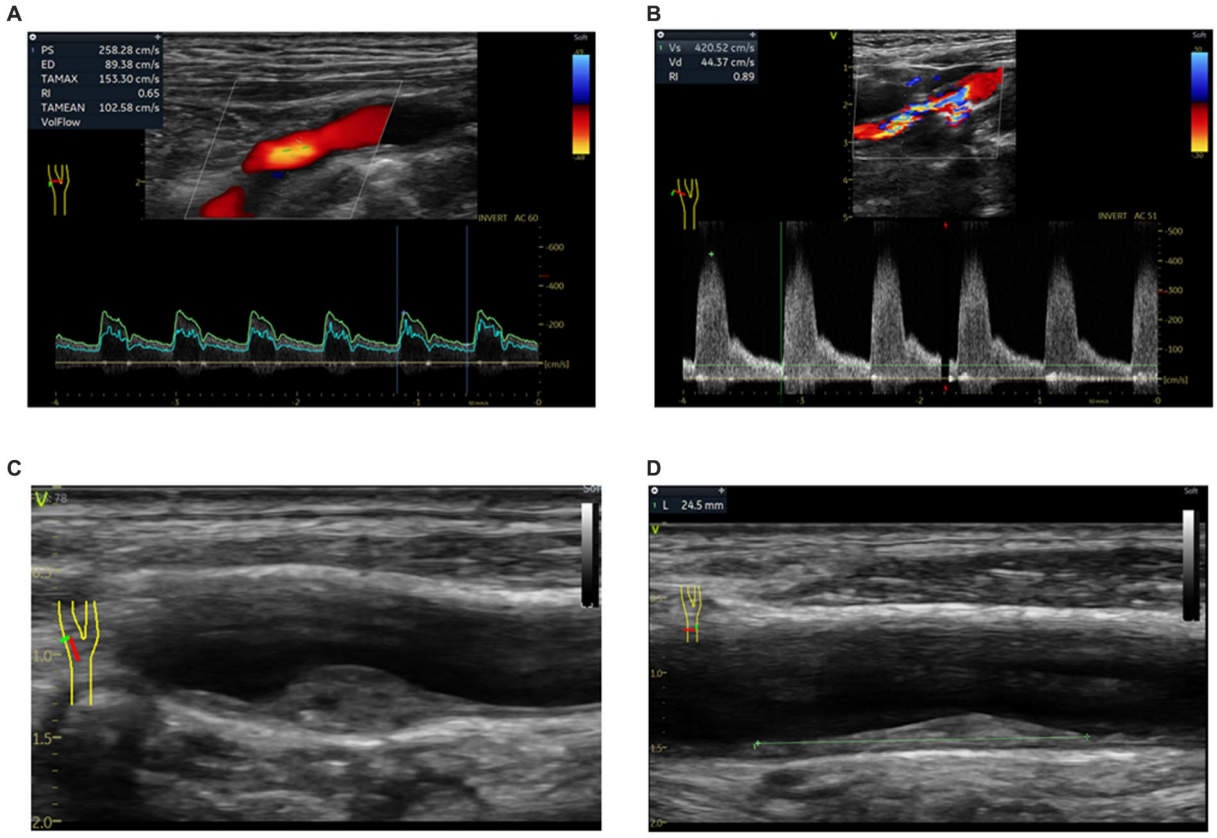

FIGURE 2
Characteristics of carotid atherosclerosis by carotid ultrasonography. **(A)** >50–69% stenosis internal carotid artery; **(B)**>70% stenosis internal carotid artery; **(C)** vulnerable plaque in bifurcation; **(D)** stable plaque in common carotid artery.

prevalence of carotid atherosclerosis was found to be significantly higher in the subjects carrying the high-risk interactive genotypes in comparison to those carrying the low-risk interactive genotypes (56.6% [296/523] vs. 39.5% [732/1854], $\chi^2 = 48.68$, $p < 0.001$).

Furthermore, multivariate logistic regression was employed to evaluate the risk of carotid atherosclerosis conferred by the high-risk interactive genotypes among *IL1A* rs1609682, *HABP2* rs7923349, and *ITGA2* rs1991013. The low-risk interactive genotypes were assigned as zero, whereas the high-risk interactive genotypes were designated as one. The other variables that showed a significant association with carotid atherosclerosis ($p < 0.05$) in the univariate analysis were entered the multivariate logistic regression model to adjust. The results exhibited that the high-risk interactive genotypes in *IL1A* rs1609682, *ITGA2* rs1991013, and *HABP2* rs7923349 were independently associated with a higher risk for carotid atherosclerosis after adjusting covariates (OR, 2.08, 95% CI: 1.257–5.980, $P < 0.001$, Table 5). Furthermore, H-L test was used to evaluate the goodness of fit of the multivariate logistic regression model, and the result showed that the goodness of fit of the model was well (χ^2 value = 4.324, $p = 0.823$).

Discussion

In the present study, we have observed a high prevalence of carotid atherosclerosis (43.2% [1,028/2377)] in the high-risk stroke population and the associations of variants in two distinct genes related to inflammation (*IL1A* rs1609682, *PPARA* rs4253655) and one gene related to endothelial function (*HABP2* rs7923349) with carotid atherosclerosis in southwestern China. Furthermore, statistical interactions were found between three SNPs (*IL1A* rs1609682, *HABP2* rs7923349 and *ITGA2* rs1991013) and carotid atherosclerosis by GMDR analysis, and the high-risk interactive genotypes in the three SNPs were significantly associated with a higher risk for carotid atherosclerosis.

Numerous studies have previously demonstrated that carotid atherosclerosis (including carotid plaque, increased IMT, and carotid stenosis) can be considered as subclinical predictors of the future vascular events (4, 5). In this study, we found that prevalence of carotid atherosclerosis was high (43.2%) in the high-risk stroke population, and old age, smoking and hypertension were identified as potential risk factors for carotid atherosclerosis. Our results were in agreement with other prior studies (5, 21). Hypertension is a very important risk factor for carotid atherosclerosis and stroke (21). However, the proportion of people whose hypertension is controlled is extremely low in China (17, 22). In this survey, only 40.0% (950/2377) of patients with hypertension were receiving optimal antihypertensive treatment. Smoking contributed to an increased risk of carotid atherosclerosis, and smoking prevalence has consistently increased in the past three decades in China (23). Thus, behavioral interventions for smoking and clinical control of hypertension could be useful for preventing carotid atherosclerosis.

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TABLE 1 Demographic characteristics of the high-risk population for stroke with and without carotid atherosclerosis [*n*(%)].

Variables	Carotid atherosclerosis (*n* =1,028)	Non-carotid atherosclerosis (*n* =1,349)	*p*-Value
Sex			0.004
Male	495 (48.2)	570 (42.3)	
Female	533 (51.8)	779 (57.7)	
Age, y			<0.001
40–49	42 (4.1)	176 (13.0)	
50–59	182 (17.7)	367 (27.2)	
60–69	415 (40.4)	545 (40.4)	
70–79	325 (31.6)	219 (16.2)	
≥80	64 (6.2)	42 (3.1)	
Residence			<0.001
Urban	415 (40.4)	649 (48.1)	
Rural	613 (59.6)	700 (51.9)	
Education			0.001
Junior middle school or below	958 (93.2)	1,205 (89.3)	
Senior middle school or above	70 (6.8)	144 (10.7)	
Overweight/obesity			0.155
Yes	546 (53.1)	756 (56.0)	
No	482 (46.9)	593 (44.0)	
Smoking			<0.001
Yes	413 (40.2)	403 (29.9)	
No	615 (59.8)	946 (70.1)	
Physical inactivity			0.318
Yes	641 (62.4)	868 (64.3)	
No	387 (37.6)	481 (35.7)	
Hypertension			<0.001
Yes	820 (79.8)	983 (72.9)	
No	208 (20.2)	366 (27.1)	
Diabetes			0.739
Yes	286 (27.8)	367 (27.2)	
No	742 (72.2)	982 (72.8)	
Dyslipidemia			
Yes	319 (31.0)	456 (33.8)	0.153
No	709 (69.0)	893 (66.2)	
Atrial fibrillation			0.296
Yes	18 (1.8)	32 (2.4)	
No	1,010 (98.2)	1,317 (97.6)	
Family history			0.192
Yes	173 (16.8)	255 (18.9)	
No	855 (83.2)	1,094 (81.1)	
History of stroke			0.522
Yes	186 (18.1)	258 (19.1)	
No	842 (81.9)	1,091 (80.9)	
Carotid plaque	852 (35.8)	--	

(Continued)

TABLE 1 (Continued)

Variables	Carotid atherosclerosis (*n* =1,028)	Non-carotid atherosclerosis (*n* =1,349)	*p*-Value
Stable plaque	454 (19.1)	--	
Vulnerable plaque	398 (16.7)	--	
Carotid stenosis		--	
15–49% stenosis	244 (10.3)	--	
≥50% stenosis	51 (2.1)	--	
Mean IMT ≥1.0 mm	445 (18.7)	--	

A number of previous studies have also explored the associations of inflammation and endothelial function relevant genetic SNPs with stroke (24, 25), but only few studies have primarily focused on the subclinical carotid atherosclerosis. For instance, Gardener et al. (12) was the first to evaluated the associations of variants in the genes related to endothelial function and inflammation with carotid plaque in Hispanics from Northern Manhattan, and they demonstrated that variants in 10 different genes linked with inflammation and endothelial function (*NOS2A*, *TNF*, *IL6R*, *PPARA*, *TNFSF4*, *TLR4*, *IL1A*, *ITGA2*, *HABP2,* and *VCAM1*) were associated the carotid plaque phenotypes. Our previous studies have also revealed significant associations of variants in genes related to endothelial function and inflammation with vulnerable carotid plaque (7) and carotid stenosis (13) in the Chinese population. However, carotid plaque, increased IMT, and carotid stenosis were present simultaneously in patients with carotid atherosclerosis. Thus, it may be inappropriate to analyze the associations of the genetic variants with carotid plaque, increased IMT or carotid stenosis separately. According to findings of the previous studies (18, 21), carotid atherosclerosis was defined as presence of any carotid plaque or any carotid stenosis ≥15% or mean IMT > 0.9 mm in this study, and we found that there were significant associations between the polymorphisms of *IL1A* rs1609682, *PPARA* rs4253655, and *HABP2* rs7923349 and carotid atherosclerosis.

Interleukin-1 (IL-1) as a cytokine play a key role in "response to injury" model of atherosclerosis and stroke (26). In animal models, IL-1a was found to be up-regulated after acute middle cerebral artery occlusion, inducing migration, proliferation and angiogenesis in brain endothelial cells (27). After cerebral ischemia, IL-1a express in microglia, astrocytes, and endothelial cells, inducing activation of astrocytes and endothelial cells and promoting formation of tube-like structure that is an important hallmark of angiogenesis, knockout IL-1a in mice can reduce ischemic damage (27, 28). Polymorphisms in *IL1A* gene may increase the risk of ischemic stroke (29). In this study, we also revealed polymorphisms in *IL1A* were associated with carotid atherosclerosis. SNPs in inflammatory genes can interact with the conventional risk factors directly or indirectly to influence the development of atherosclerosis. IL-1α in macrophage is an important cytokine regulating the development of atherosclerosis (30), over-representation of *IL1A* gene was associated with the coronary artery disease (31). In addition, prior studies also support the association between variant in *IL1A* gene and carotid atherosclerosis (7, 12, 32). Polymorphisms in *IL1A* can significantly increase the susceptibility for carotid atherosclerosis, and the *IL1A* allele 2 might influence the inflammatory environment in the vascular endothelium (33). Peroxisome proliferator-activated receptor alpha (PPARα) as a nuclear receptor when activated, can effectively trigger the acyl-CoA oxidase transcription by catalyzing the fatty acid *β*-oxidation pathway. Polymorphisms in *PPARA* gene have been demonstrated to substantially affect the oxidative stress, lipid metabolism, progression of coronary atherosclerosis, and the risk of myocardial infarction (34, 35). However, studies on the potential relationship between *PPARA* SNPs and carotid atherosclerosis are lacking in the literature. *PPARA* rs4253655 SNPs have been associated with carotid plaque and vulnerable plaque in a cohort of Northern Manhattan (12) and a community-based study of China (7). In present study, we found that *PPARA* rs4253655 was also associated with carotid atherosclerosis, thereby indicating its key role in the different stages of carotid atherosclerosis.

The endothelial function maintains the vascular barrier by controlling platelet adhesion and aggregation, platelet and immune cell interactions, capillary tone and interendothelial cell adherence. Endothelial dysfunction may damage vascular integrity, is associated with various human diseases such as stroke, atherosclerosis, and coronary artery disease (36). Vascular integrity is regulated by hyaluronan-binding protein 2 *(HABP2)* gene, which encodes a cell adhesion protein (hyaluronan-binding protein 2). *HABP2* gene may be a genetic susceptibility locus in stroke (25). HABP2 has been shown to effect the vascular smooth muscle cell proliferation and modulate the vulnerability of atherosclerotic plaque (37). Our previous studies as well as other prior reports have demonstrated that *HABP2* rs7923349 variants were associated with the carotid stenosis (13, 38), and carotid plaque (7, 12). Here, we found that *HABP2* rs7923349 was also associated with carotid atherosclerosis. Gardener et al. (12) reported the associations between variants in *NOS2A, TNF, IL6R, TLR4, TNFSF4,* and *VCAM1* genes and carotid atherosclerosis. However, in this study we found that the genotypes of these genes were irrelevant to carotid atherosclerosis. The differences in the findings could be attributed to the different study population, as gene SNPs can vary greatly among the different ethnic population.

Atherosclerosis is a complex disease, as it does not follow the Mendelian mode of inheritance, which may be the result of gene–gene interactions (6, 7). Single gene approach may not be effective to find the genetic etiology of the complex disease, and it has been emphasized that assessment of gene–gene interactions is necessary to investigate the genetic mechanisms for the complex diseases, such as carotid atherosclerosis. Interestingly, in a previous study Gardener et al. (12) revealed there were interactions among the haplotypes in *IL6R, TNFSF4, NOS2A* and *PPARA* for thick plaque, and interactions between the haplotypes in *PPARA* and *IL1A* for irregular plaque. Our previous studies have also found that the high-risk interactions among

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TABLE 2 Genotype distribution in individuals with and without carotid atherosclerosis (%).

	Carotid atherosclerosis (*n* =1,028)	Non- carotid atherosclerosis (*n* =1,349)	Wald $\chi 2$ value	*P*-value
IL6R (rs4845625)			3.052	0.217
TT	297 (28.9)	358 (26.5)		
CC	222 (21.2)	328 (24.3)		
CT	509 (49.4)	663 (49.1)		
IL6R (rs1386821)			2.158	0.394
GT	69 (6.7)	112 (8.3)		
GG	3 (0.3)	4 (0.3)		
TT	956 (93.0)	1,233 (91.4)		
IL1A (rs1800587)			1.963	0.370
AG	141 (13.7)	173 (12.8)		
GG	883 (85.9)	1,165 (86.4)		
AA	4 (0.4)	11 (0.8)		
IL1A (rs1609682)			9.072	0.011
GG	457 (44.5)	576 (42.7)		
GT	479 (46.6)	690 (51.1)		
TT	92 (8.9)	83 (6.2)		
PPARA (rs4253778)			0.006	0.938
CG	2 (0.2)	4 (0.3)		
GG	1,026 (99.8)	1,345 (99.7)		
PPARA (rs4253655)			5.258	0.035
AG	4 (0.4)	0 (0.0)		
GG	1,024 (99.6)	1,349 (100.0)		
TLR4 (rs752998)			2.589	0.274
TT	19 (1.8)	36 (2.7)		
GG	733 (71.3)	931 (69.0)		
GT	276 (26.8)	382 (28.3)		
TLR4 (rs1927911)			1.203	0.58
AG	509 (49.5)	650 (48.2)		
AA	163 (15.9)	203 (15.0)		
GG	356 (34.4)	496 (36.8)		
TNFSF4 (rs1234313)			4.691	0.096
AG	487 (47.4)	579 (42.9)		
GG	116 (11.3)	163 (12.1)		
AA	425 (41.3)	607 (45.0)		
TNFSF4 (rs11811788)			0.200	0.905
CG	158 (15.4)	215 (15.9)		
GG	11 (1.1)	13 (1.0)		
CC	859 (83.6)	1,121 (83.1)		
NOS2A (rs8081248)			0.447	0.800
AG	459 (44.6)	591 (43.8)		
AA	106 (10.3)	150 (11.1)		
GG	463 (45.0)	608(45.1)		

(Continued)

TABLE 2 (Continued)

	Carotid atherosclerosis (*n* =1,028)	Non- carotid atherosclerosis (*n* =1,349)	Wald $\chi 2$ value	*P*-value
NOS2A (rs2297518)			0.151	0.927
AG	277 (26.9)	373 (27.7)		
AA	22 (2.1)	28 (2.1)		
GG	729 (70.9)	948 (70.3)		
TNF (rs3093662)			0.485	0.486
AG	52 (5.1)	60 (4.4)		
AA	976 (94.9)	1,289 (95.6)		
VCAM1(rs2392221)			3.407	0.182
CT	252 (24.5)	293 (21.7)		
CC	756 (73.5)	1,021 (75.7)		
TT	20 (1.9)	35 (2.6)		
VCAM1 (rs3783615)				Na
AA	1,028 (100.0)	1,349 (100.0)		
HABP2 (rs7923349)			12.141	0.002
TT	68 (6.6)	49 (3.6)		
GT	389 (37.8)	499 (37.0)		
GG	571 (55.5)	801 (59.4)		
HABP2 (rs932650)			1.588	0.452
CT	452 (44.0)	578 (42.8)		
CC	91 (8.9)	140 (10.4)		
TT	485 (47.2)	631 (46.8)		
ITGA2 (rs1991013)			2.056	0.358
GG	90 (8.8)	141 (10.5)		
AA	480 (46.7)	628 (46.6)		
AG	458 (44.6)	580 (43.0)		
ITGA2 (rs4865756)			2.531	0.282
AG	401 (39.0)	488 (36.2)		
GG	557 (54.2)	775 (57.4)		
AA	70 (6.8)	86 (6.4)		

HABP2 rs7923349, *IL1A* rs1609682 *ITGA2* rs1991013 and *NOS2A* rs8081248 increased the risk for the carotid vulnerable plaque (7), and potential interactions between *ITGA2* rs4865756 and *HABP2* rs7923349 were considered as the risk for carotid stenosis (13). The noteworthy finding in the present study was that there was a significant gene–gene interaction observed in *IL1A* rs1609682, *ITGA2* rs1991013, and *HABP2* rs7923349 using the GMDR approach, and the high-risk interactive genotypes in the three variants were independently risk factors of carotid atherosclerosis. However, the molecular mechanisms of interactions in the three variants are unclear. Integrin alpha 2 (ITGA2) can regulate the cell adhesion and cell-surface-mediated signaling. SNPs of *ITGA2* C807T were associated with carotid IMT, plaque, and the risk of ischemic stroke in patients with type 2 diabetes (10, 39). *ITGA2* rs1991013 was associated with carotid calcified plaque and increased risk of general atherosclerosis (12). A number of previous studies have revealed that the associations of SNPs in *ITGA2*, *IL1A, HABP2* and *NOS2A* genes with inflammation and endothelial function (7, 10, 12, 13, 39). Therefore, one possible explanation is that the three variants can encode and regulate endothelial function and inflammation relevant enzymes, which can participate in the important pathogenic mechanisms for atherosclerosis. However, further studies are needed to explore the molecular mechanisms of interaction among the three variants are necessary in future.

The major strengths of this study include: (1) systematic examination of 19 variants in 10 different genes involved in endothelial function and inflammation; (2) multicenter population-based cross-sectional survey and focus on the high-risk population for stroke; (3) use of the GMDR approach to analyze gene–gene interactions among the 19 SNPs. However, there are also several limitations associated with this this study. First, this was a population-based cross-sectional survey with self-reported questionnaire, and thus, there may be significant recall bias. Second, carotid arteries were only evaluated

TABLE 3 GMDR analysis of the best models, prediction accuracies, cross-validation consistencies, and *p*-values for carotid atherosclerosis.

Best model*	Training balanced accuracy	Testing balanced accuracy	Cross- validation consistency	Sign test (*P*-value)
1	0.562	0.531	8/10	5 (0.214)
1, 2	0.543	0.527	7/10	7 (0.053)
1, 2, 3	0.572	0.526	10/10	10 (0.001)
1, 2, 3, 4	0.593	0.576	7/10	9 (0.056)
1, 2, 3, 4, 5	0.592	0.586	8/10	5 (0.367)
1, 2, 3, 4, 5, 6	0.684	0.633	6/10	8 (0.339)
1, 2, 3, 4, 5, 6, 7	0.635	0.612	9/10	6 (0.136)
1, 2, 3, 4, 5, 6, 7, 8	0.632	0.529	7/10	7 (0.292)
1, 2, 3, 4, 5, 6, 7, 8, 9	0.723	0.712	5/10	8 (0.623)
1, 2, 3, 4, 5, 6, 7, 8, 9, 10 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	0.598 0.537	0.562 0.387	10/10 6/10	10 (0.552) 9 (0.182)
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12	0.586	0.575	7/10	5 (0.372)
1, 2,3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13	0.637	0.625	7/10	7 (0.089)
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14	0.588	0.523	6/10	8 (0.562)
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15	0.629	0.627	7/10	8 (0.394)
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16	0.625	0.608	8/10	9 (0.288)
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17	0.514	0.497	6/10	10 (0.593)
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18	0.553	0.512	10/10	6 (0.264)
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19	0.645	0.623	8/10	7 (0.396)

GMDR, generalized multifactor dimensionality reduction. *Numbers 1–19 represent rs1609682, rs7923349, rs1991013, rs8081248, rs4253778, rs2297518, rs4253655，rs3093662, rs4845625, rs1386821, rs1234313, rs1800587, rs3783615, rs2392221, rs11811788, rs752998, rs1927911, rs4865756, and rs932650, respectively.

TABLE 4 Associations between genotype combinations and the risk of carotid atherosclerosis.

rs1609682	GG	TT	TT	TT	GT	TT, GT	TT	TT, GT
rs7923349	GG	TT	GT	TT	GT	TT	TT, GT	TT, GT
rs1991013	GG	AA	AA	AG	AA	AA, AG	AA	AA, AG
OR	1*	2.62	2.14	2.06	1.76	1.27	1.45	1.12
95% CI	–	1.21–6.86	1.18–5.37	1.07–4.62	1.03–2.63	0.92–1.69	0.82–2.23	0.78–1.69
P-value	–	0.007	0.012	0.036	0.043	0.224	0.621	0.579

*The wild-type genotype for each genetic factor was used as the reference OR. OR, odds ratio; CI, confidence interval.

by ultrasound analysis in this study. Computed tomography angiography and high-resolution magnetic resonance imaging might provide additional information on carotid atherosclerosis. Third, the main aim of present study was to investigate the associations of the 19 SNPs with carotid atherosclerosis, but analysis of the associations of these SNPs was not stratified based on the carotid plaque, carotid stenosis and IMT. Fourth, we investigated the role of several known genes related to inflammation and endothelial function, but the possible involvement of other relevant genes was not assessed. In addition, although we found that the high-risk interactions among *IL1A* rs1609682, *ITGA2* rs1991013 and *HABP2* rs7923349 increased the risk of carotid atherosclerosis, the detailed molecular mechanisms were not investigated. Furthermore, statins, antiplatelet drugs and antihypertensives may affect carotid atherosclerosis, but the effect of these drugs was not examined on carotid atherosclerosis. Finally, as is known to all, intracranial stenosis is more prevalent than extra cranial stenosis in Asian population. However, this multicenter community-based sectional survey was a part of CNSSS program, intracranial stenosis was not evaluated. Thus, we did not know the prevalence of intracranial atherosclerosis in the high-risk stroke population in China.

Conclusion

In the present study, we found a high prevalence of carotid atherosclerosis in the high-risk stroke population in China and also identified the associations of variants in *IL1A* rs1609682, *PPARA*

TABLE 5 Multivariate analysis of the major risk factors for carotid atherosclerosis.

Risk factor	OR*	95% CI	*P*-value
Age	1.053	1.043–1.063	<0.001
Male	1.093	0.880–1.358	0.421
Rural	1.274	1.071–1.515	0.006
Junior middle school or below	1.118	0.810–1.543	0.498
Smoking	1.544	1.233–1.933	<0.001
Hypertension	1.252	1.018–1.539	0.033
IL1A rs1609682 TT	1.450	1.034–2.032	0.031
PPARA rs4253655 AG	1.122	0.892–1.686	0.253
HABP2 rs7923349 TT	1.829	1.228–2.723	0.003
High-risk interactive genotypes	2.08	1.257–5.980	<0.001

OR, odds ratios; CI, confidence interval.

rs4253655, and *HABP2* rs7923349 with carotid atherosclerosis. There was a significant gene–gene interaction observed in *IL1A* rs1609682, *ITGA2* rs1991013, and *HABP2* rs7923349, the high-risk interactive genotypes in the three variants served as independent risk factors of carotid atherosclerosis. These results are expected to provide novel strategies for prevention of carotid atherosclerosis in Chines population. Based on our findings, active intervention of conventional risk factors, such as hypertension and smoking, may be very important in reducing the risk for stroke in the high-risk stroke population carrying the high-risk interactive genotypes. Furthermore, our findings are expected to identify new gene targets for prevention and treatment of carotid atherosclerosis and stroke, and provide a theoretical basis for drug development and gene therapy against new gene targets in the future. The gene–gene interactive analysis used in present study may be very helpful to elucidate complex genetic risk factors for carotid atherosclerosis.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committees of Suining Central Hospital, the Affiliated Hospital of Southwest Medical University and the People's Hospital of Deyang City. Written informed consent to participate in this study was provided by the patients/participants or patients/participants' legal guardian/next of kin.

Author contributions

YX, XY, and HL designed this study and acquired the funding. HL, MY, TQ, and WW performed the face to face survey and follow up. YX, TQ, and MS drafted the figures and analyzed the results. YX, XY, and MS drafted the manuscript and the tables. XY, HL, and MY supervised this project. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Publisher's note

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"Time lost is clot resolution lost": the neglected perspective of the therapeutic time window for ischemic stroke

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"Time is brain," a mantra adapted from the cardiological "time is muscle," was first proposed 30 years ago (1), and it is still a valid concept, stressing the need for urgent intervention in acute ischemic stroke (AIS). The suffering but still viable neurons residing in the ischemic penumbra are at high risk of being included in the necrotic core over time. Hence, "time is brain" was also translated into the statement "time lost is penumbra lost," highlighting even better the concept of the penumbral tissue lost during the therapeutic time window. In fact, it is well established that the efficacy of both intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) gradually declines and the chance of recanalization and of reaching a good outcome is much higher during the 1st h after stroke onset, the so-called "golden hour" (2). More recently, the wider use of advanced neuroimaging made it clear that this evolution takes place at different paces, depending on the collateral circulation status (3).

Another issue to that rates of near-complete or complete recanalization of LVO in the AIS amount to a maximum of 32% with IVT (10–15 and 25–50% for internal carotid artery and proximal middle cerebral artery occlusion, respectively) (4, 5) and of 56–59.9% with MT (6). Therefore, for patients with LVO, bridging therapy is recommended (7).

Reasons for this recanalization "resistance" are not completely known. Clot burden, good collaterals (that can deliver more rTPA in the clot via backflow), timing from stroke onset, and thrombus composition have been advocated (8). In case of recanalization failure after MT, other important determinants are the pressure gradient across the thrombus and the stickiness of the thrombus itself (due to the combined force of friction and adhesion on the vessel wall) (9). Notably, it has been observed that the achievement of recanalization with a single thrombectomy device pass, the "first-pass effect," is associated with a better outcome (6).

In 2014, in a single-center prospective study, Muchada et al. (10) showed that the effect of IVT on early recanalization detected by transcranial doppler sonography declined over time. Treatment initiation after 270 min was an independent predictor of lack of recanalization in distal MCA occlusion, whereas there was a trend toward lower recanalization in proximal MCA occlusion treated after 90 min. In the related editorial comment, Tsivgoulis and Alexandros (11) proposed the motto "time is clot" for thrombolytic therapy. After 1 year, Kim et al. (12) reported a linear inverse relationship between time from symptom onset to treatment and the degree of thrombus resolution after rtPA administration, assessed by a thin section non-contrast computed tomography scan performed at 1 h after IVT. In the

same study, it was observed, by using an animal model of stroke, that the effect of rTPA depended on the thrombus age (12). The authors concluded their study by reviving the sentence "time is clot" for thrombolytic treatment but it did not gain a foothold and was early neglected. Afterward, growing evidence from research on retrieved thrombi during MT has been brought back into the spotlight, with the occluding clot as one of the main actors of the acute phase of IS.

It is now clear that, whether it has an atherothrombotic or an embolic origin, the clot is a tissue with specific characteristics evolving over time, whose probability to be resolved by thrombolytic therapy or removed by MT quickly declines pari passu (12). In this perspective, two variables are particularly relevant: length of thrombus and its composition.

Thrombi exceeding the length of 8 mm seem to have almost no chance to be recanalized by IVT (13).

Recent data on the composition of retrieved thrombi suggest that stroke clots can be categorized into platelet-rich thrombi and red blood cells (RBC)-rich thrombi with, in the middle, a wide range of more heterogeneous thrombi having a mixed coexisting platelet-rich and RBC-rich areas (14, 15).

RBC-rich clots and areas consist of densely packed RBC surrounded by a thin fibrin network, while platelet-rich clots and areas are much more complex and organized with dense fibrin strings, von Willebrand factor (VWF), platelets, DNA from neutrophil extracellular traps (NETs), and sparse leukocytes. Interestingly, networks of extracellular DNA and leukocytes have been more frequently found within the platelet-rich areas and at the interface between the platelet-rich and the RBC-rich areas but not within the RBC-rich areas (15).

Although it is not possible to analyze the histological characteristics of clots lysed and dissolved by rTPA, RBC-rich thrombi appear more susceptible to be lysed and more easily to be retrieved by thrombectomy devices compared to the other types of thrombi (16, 17). RBC-rich clots are also associated with non-cardioembolic stroke and with hyperdense MCA sign on non-contrast CT scan or blooming artifact on brain MRI (14, 18). In 2021, Gunning et al. demonstrated that fibrin-rich thrombi had a significantly higher coefficient of friction between the clot and the vessel wall than RBC-rich thrombi, thus contributing to the difficulty in retrieval by MT (19). In this regard, it has been observed that clots retrieved in earlier passes have higher RBC content in comparison with clots retrieved in later passes that are conversely, rich of fibrin, platelets, and other components (20). Interestingly, in this study, the extracted clot area was larger in the earlier than in later passes (20), supporting the fact that RBC-rich thrombi and RBC-rich areas inside the same thrombus are less sticky and more easily retrievable compared to fibrin-rich thrombi and fibrin-rich areas. However, it is not possible to rule out a direct effect of passes on the clot itself.

By using scanning electron microscopy (SEM), it is possible to identify two different time-related structural thrombotic patterns, one formed by dense fibrin mesh with sparse cellular elements suggesting a matured clot and another one characterized by looser fibrin strands and intact RBC suggesting a fresh and evolving clot (21). Figure 1 clearly shows these two patterns from the same thrombus retrieved by the proximal MCA of an adult patient treated in our center with bridging therapy 3 h after symptoms onset and analyzed by SEM.

Interestingly, SEM and immunohistological analysis of retrieved large vessel occluding thrombi have shown a common outer shell formed by densely compacted fibrin network, VWF, and aggregated platelets resistant to rTPA-mediated thrombolysis as compared to the inner core mainly formed by looser fibrin mesh and RBC (22). The fibrin shell thickness seems not to be dependent on patients' characteristics, pre-thrombectomy treatment, and stroke pathophysiology; the outer shell is more resistant to rTPA not only for its compaction and particular structure but also because platelet-derived direct inhibitors of tPA accumulate in it. Platelets play a fundamental role in the outer shell formation (22).

Although most of the available data on the evolution of thrombus composition come from venous and pulmonary embolism and *in vitro* studies, it is well recognized that arterial thrombus composition changes over time (14, 23).

Mechanisms of thrombosis are the result of an extremely complex interplay between endothelial cells, platelets, leukocytes- and platelet-derived microparticles, VWF, and coagulation factors (24, 25). High shear rate of blood is also an important contributor to arterial thrombus formation and propagation (24). Being such a highly dynamic process, clot formation in humans is difficult to study *in vivo*. However, studies on thrombus formation in live animals by using intravital microscopy and genetically altered mice (i.e., VWF null mouse) (25) confirmed data from *in vitro* experiments and shed light on the role of platelets and fibrin that strictly cooperate with the developing thrombus in the first 60 min of vessel occlusion (25, 26).

In the initial phases of thrombosis, platelets become activated due to contact with an altered endothelium surface, tissue factor, binding Factor VIIa, and active Factor IX and X that bind to Factor II to form thrombin. Thrombin transforms fibrinogen in fibrin and polymerizes fibrin monomers in fibers that entrap activated platelets and RBC (24). At this stage, the fresh thrombus presents a porous fibrin scaffold that rTPA can easily dissolve, especially because thrombin has not yet activated Factor XIII which catalyzes the formation of covalent bonds between adjacent fibrin subunits and the cross-links of alpha2-antiplasmin (an enzyme that participates to endogenous fibrinolysis) to fibrin, resulting in new fibers more resistant to lysis (27). Interestingly, it has been demonstrated *in vitro* that the scaffold and the fibrin network take less than 5 min in average to form (28), but the lateral aggregation of the protofibrils forming fibrin fibers reaches a plateau after 50 min (29). Clot contraction due to platelet–platelet, platelet–fibrin(ogen), and RBC–fibrinogen interaction stabilizes the clot by forcing platelets and fibrin on the external surface of the thrombus and by inducing the deformation of RBC into densely packed polyhedrocytes (30). At the same time, the crosstalk between activated platelets and leukocytes promotes further stability of the thrombus through the release of NETs by activated neutrophils (31). NETs promote fibrin deposition, bind VWF, favor platelet adhesion, and contain some factors (i.e., tissue factor) that make them procoagulants. As a result, over time, the thrombus quickly becomes a dense and compact structure adherent to the endothelial wall and is difficult to be lysed by rTPA and to be retrieved by thrombectomy devices (14).

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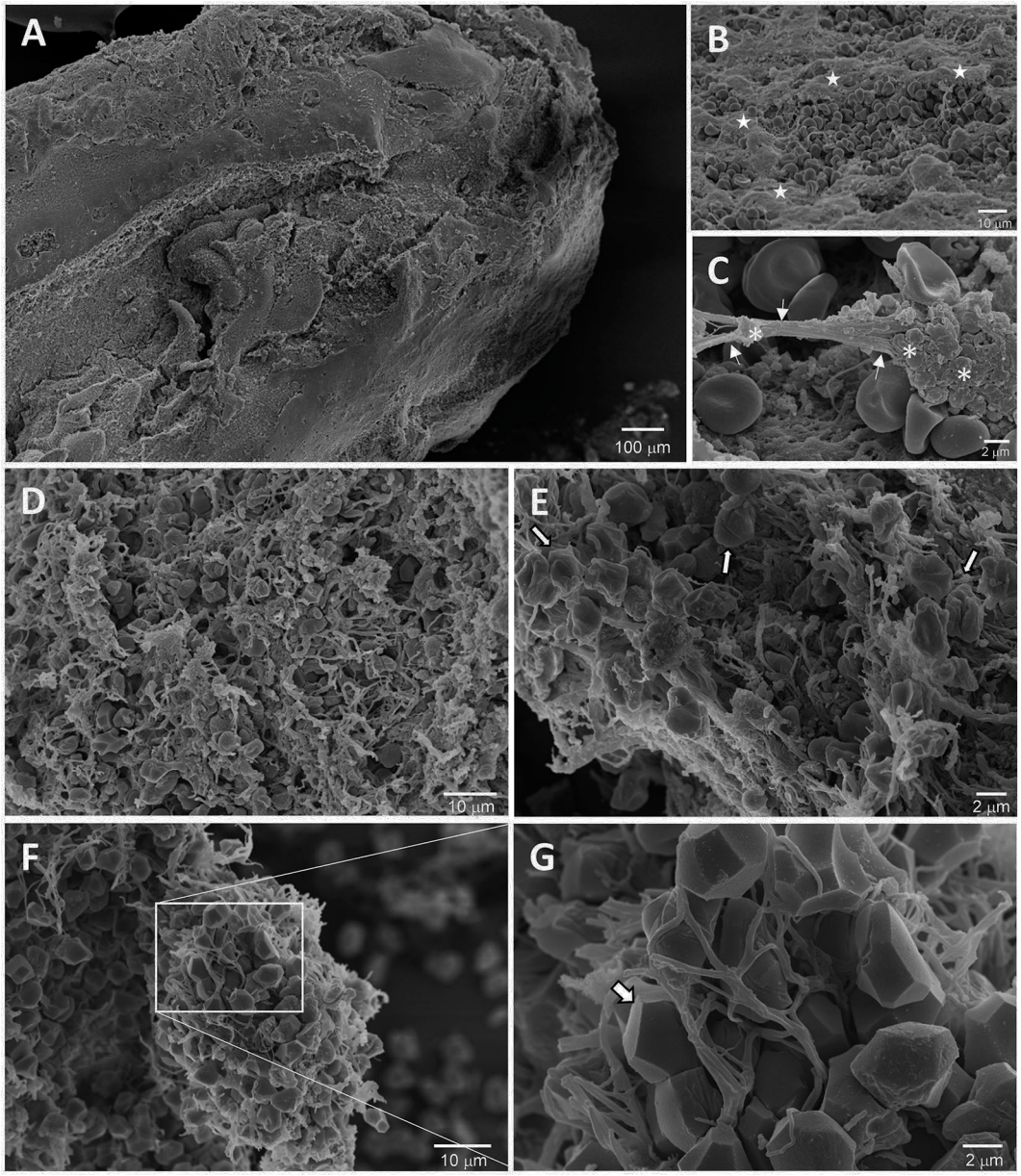

FIGURE 1
SEM micrographs of an arterial thrombus retrieved from a stroke patient. **(A, B)** Clot shell was characterized by a very thick meshwork of fibrin and platelet aggregates (**B**, white stars) that envelope erythrocytes with the typical biconcave shape. **(C)** High magnification of bundles of fibrin fibers (arrows) that protrude from strongly amassed platelets (*). **(D–G)** Inside portion of the thrombus displaying phases of the progressive clot contraction. **(D)** An area rich in partially compressed erythrocytes and platelet aggregates from which fibrin bundles protruded. **(E)** A partially compressed zone in which are clearly visible different intermediate shapes of erythrocytes scratched by the fibrin fibers compression (white arrows) (initial contraction of the clot). **(F)** A more compressed area of the clot in a more advanced phase of compression in which the erythrocytes have the typical polyedrocyte shape. **(G)** High magnification of the squared areas in **F** (arrow: polyedrocyte). SEM, Scanning Electron Microscopy.

The development of adjuvant treatment strategies targeting other clot components are actively under investigation and will likely improve the chance to lyse large vessel occluding clots (8).

Conclusion

Stroke physicians and neurointerventionists should keep in mind that a clot is a vital and rapidly changing tissue. The sooner IV rt-PA is administered and endovascular thrombectomy is performed after stroke onset, the higher is the chance to dissolve the large vessel occluding thrombus and the better will be the outcome. That is a non-"neuro-centric" but "clot-centric" view of the ischemic stroke therapeutic time window. Indeed, time is not only brain but it is also clot: *time lost is clot resolution lost*.

Author contributions

MD conceived the idea for the editorial and drafted the article. SL and DT critically revised the article. LB and FI analyzed the thrombus by using scanning electron microscopy and conceived

the Figure 1. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Global trends in perioperative stroke research from 2003 to 2022: a web of science-based bibliometric and visual analysis

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Background: Perioperative stroke is a potentially devastating complication in surgical patients, which has attracted global attention. This retrospective bibliometric and visual analysis evaluates the status and global trends in perioperative stroke research.

Methods: Papers published between 2003 and 2022 were retrieved from the Web of Science core collection. Extracted data were summarized and analyzed using Microsoft Excel and further bibliometric and co-occurrence analyses were conducted using VOSviewer and CiteSpace software.

Results: Publications on perioperative stroke have increased over the years. The USA topped the list of countries with the highest number of publications and citations, while Canada had the highest mean citation frequency. The Journal of Vascular Surgery and Annals of Thoracic Surgery had the highest number of publications and citation frequency for perioperative stroke. Regarding authors, Malas, Mahmoud B. contributed the most publications to the field, and Harvard University had the highest number of publications (409 papers). Based on an overlay visualization map, timeline view, and the strongest strength burst of keywords, "antiplatelet therapy," "antithrombotic therapy," "carotid revascularization," "bleeding complications," "postoperative cognitive dysfunction," "intraoperative hypotension," "thrombectomy," "cerebral revascularization," "valve surgery," "tranexamic acid," and "frozen elephant trunk" were trending topics in perioperative stroke research.

Conclusion: Publications regarding perioperative stroke have experienced rapid growth in the past 20 years and are likely to continuously increase. Research on perioperative antiplatelet and antithrombotic, cardiovascular surgery, postoperative cognitive dysfunction, thrombectomy, tranexamic acid, and frozen elephant trunk has attracted increasing attention, and these topics are emerging hotspots of present research and possible candidates for future research.

KEYWORDS

anesthesia, bibliometric, perioperative period, stroke, surgery, visualized study

1. Introduction

Stroke is characterized by brain cell death due to ischemia with indications of irreversible damage. Its diagnosis is established by neuropathology, neuroimaging, or clinical evidence (1). Although such lesions may result in critical functional impairments, a small infarct may fail to manifest clinically (i.e., covert stroke). Perioperative stroke is defined as the onset of cerebral infarction within 30 days after surgery (2). The prevalence of overt perioperative stroke ranges from approximately 0.1 to 2% and is determined by various risk factors (3). A covert stroke occurs in approximately 7% of non-cardiac surgical patients, aged >65 years (4). An epidemiological database demonstrated that the prevalence of perioperative stroke is increasing (5). In addition, a high risk of long-term cognitive impairment, visible in patients with covert stroke, has been observed in patients with a clinical diagnosis of stroke who presented with symptoms such as delirium and postoperative cognitive dysfunction (4, 6). Owing to delayed recognition of perioperative stroke which results in a lack of appropriate and timely intervention, non-cardiac surgical patients with postoperative stroke have >80% risk of death or severe disability upon their discharge from prolonged medical care (7). Hence, perioperative stroke is a serious medical condition that should be actively addressed by public health practitioners.

Publications are essential for research trend examination. Consequently, bibliometrics provides a valuable statistical and analytical tool that can be used to perform a qualitative and quantitative evaluation of research trends based on the bibliometric characteristics of publications databases (8). This approach analyzes the evolution of a specific field and appraises relevant contributions made to it by countries, institutions, authors, and journals. CiteSpace and VOSviewer are recently popular Java applications for visualizing and analyzing trends and patterns in scientific literature. These tools provide various functions to facilitate the understanding and interpretation of network patterns and historical patterns, including identifying the fast-growth topical areas, finding citation hotspots in the land of publications, decomposing a network into clusters, geospatial patterns of collaboration, and unique areas of international collaboration.

This study aimed to conduct a comprehensive and systematic literature-based metric data analysis of perioperative stroke-related studies. To clarify the direction of perioperative stroke research and provide a basis for the prevention and treatment of related complications, this study summarized and highlighted the state of worldwide research on the condition over the past 20 years.

2. Methods

2.1. Data sources and search strategy

The initial search was performed on 10 January 2023 and updated on 4 February 2023, from the Science Citation Index Expanded database of Web of Science (WoS) by entering the following keywords: (perioperative OR postoperative OR intraoperative OR perisurgical OR postsurgical OR intrasurgical) AND "stroke"—in the topic field. A total of 11,772 publications were initially retrieved. After restricting the timespan to 2003–2022, 10,844 publications remained. Only reviews and articles were included, leaving 10,432 publications after the screening. Finally, the English language restriction was applied for a final total of 10,172 publications (Figure 1).

2.2. Data extraction and visualization

The retrieved publications were compiled and exported into "plain text" files. The exported records comprised "full records and references cited" and the extracted data included authors, publication year, journals, H-index, institutions, and countries. The data were analyzed using Microsoft Excel 2019 (Microsoft Corporation, Santa Rosa, CA, USA), VOSviewer (version 1.6.18; Leiden University), and CiteSpace (6.1.R6).

Microsoft Excel 2019 was used to assemble and sequence every publication feature. As popular knowledge mapping tools, the VOSviewer and CiteSpace—operated using a Java program—provided strong data visualization capabilities. Every record in the WoS database was imported into VOSviewer by using co-authorship, co-citation, and co-occurrence analysis. Burst detection and timeline view were performed on the keywords and the strongest keywords were extracted by CiteSpace.

Co-authorship analysis was used to connect two elements who co-authored an article to reveal a specific condition of the collaboration network (9). Co-citation analysis was used to examine the relationship between the two documents by determining the frequency of simultaneous citations of other documents (10). Co-occurrence analysis was used to calculate every keyword to identify high-frequency terms and research directions. Visualization of links across countries, institutions, and authors was accomplished by using weighted total link strength (TLS) lines. TLS signified the strength of linkages between objects; the higher the TLS, the greater the weight given to the linkage drawing in the visual analysis.

3. Results

3.1. Number of publications and their trend

The number of publications on perioperative stroke increased annually from 2003 to 2022. They peaked in 2021 with 948 (9.32%) studies (Figure 2A). Despite slight fluctuations over the past two decades, the general publication trend has been on the rise. Based on the growth model equation in Microsoft Excel ($Y = 38.905X + 100.05$), approximately 1,267 papers are projected to be published by 2032. Overall, these data indicate that research on perioperative stroke has been a focus area and the value of mining is increasing.

3.2. Country analysis

Over the past two decades, 42 countries have published over 20 articles on perioperative stroke. Figure 2C presents the geographical distribution of these publications. The prolific countries include North America, Europe, and some Asian

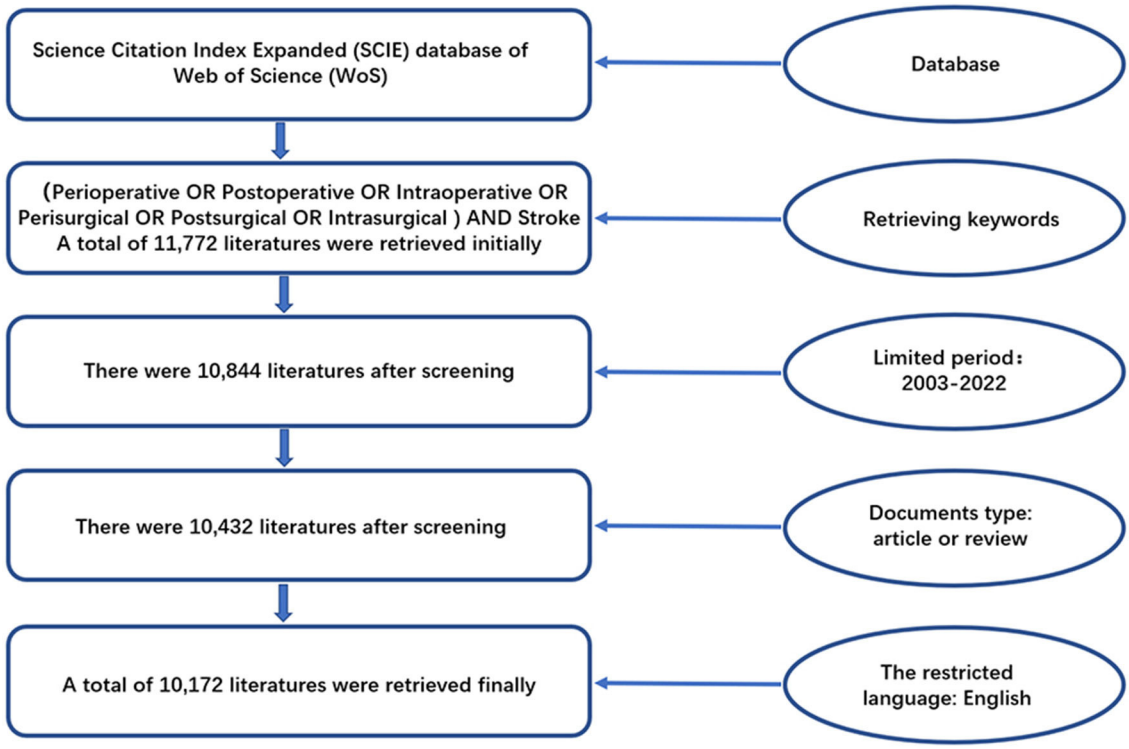

FIGURE 1
Flow chart of literature search, filtering, and selection of included publications.

countries, mainly concentrated in the Northern Hemisphere. Notably, the USA was responsible for the highest number of publications (n = 3,958), followed by China (n = 1,201) and Germany (n = 918). A list of 10 countries credited with the highest number of publications on perioperative stroke is presented in Table 1. The USA had the highest H-index (132), followed by Canada (84), England (78), and Germany (77). In addition, it had the highest number of citations (n = 114,598), followed by Canada (n = 31,525), Germany (n = 28,143), and China (n = 12,939). Publications from Canada had the highest mean number of citations (n = 52.54), followed by those from England (n = 46.40), the Netherlands (n = 34.09), and Germany (n = 30.66).

For an in-depth overview of the collaboration between countries, we used VOSviewer software to visualize the co-authorship analysis. A total of 63 countries had at least five publications. Each node in the VOSviewer represented a country, and the node radius increased with the number of publications. The connections between nodes represented the collaborative relationships between individual countries, and the link thickness was positively associated with the collaboration strength. The five countries with the highest TLS were the USA (1,465), Germany (877), England (846), Italy (769), and Canada (736) (Figures 3A, B). Remarkably, the USA had the highest interpersonal collaboration with different countries as evidenced by its location at the center of the network.

3.3. Institution analysis

Between 2003 and 2022, 40 institutions published over 100 articles on perioperative stroke. The 10 centers with the highest number of publications are presented in Table 2. They included eight research institutions from the USA and one each from Canada and China. Harvard University had the highest number of publications (n = 409), followed by the University of California System (n = 295) and Mayo Clinic (n = 284). The three institutions also had the highest H-indices—60 (Harvard University), 49 (the University of California System), and 49 (Mayo Clinic).

We selected 923 institutions for a visualization based on a minimum of five publications and constructed a co-authorship network based on the number of publications and relationships at each institution. The five centers with the highest TLS were the University of Toronto (606), McMaster University (463), Cleveland Clinic (396), Harvard Medical School (377), and Duke University (365) (Figure 4A). The connection density in the collaboration network diagram demonstrated that institutions from North America and Europe often collaborated closely.

3.4. Author analysis

A list of the 10 most prolific authors is presented in Table 3. These authors published 443 publications, accounting for 4.35% of

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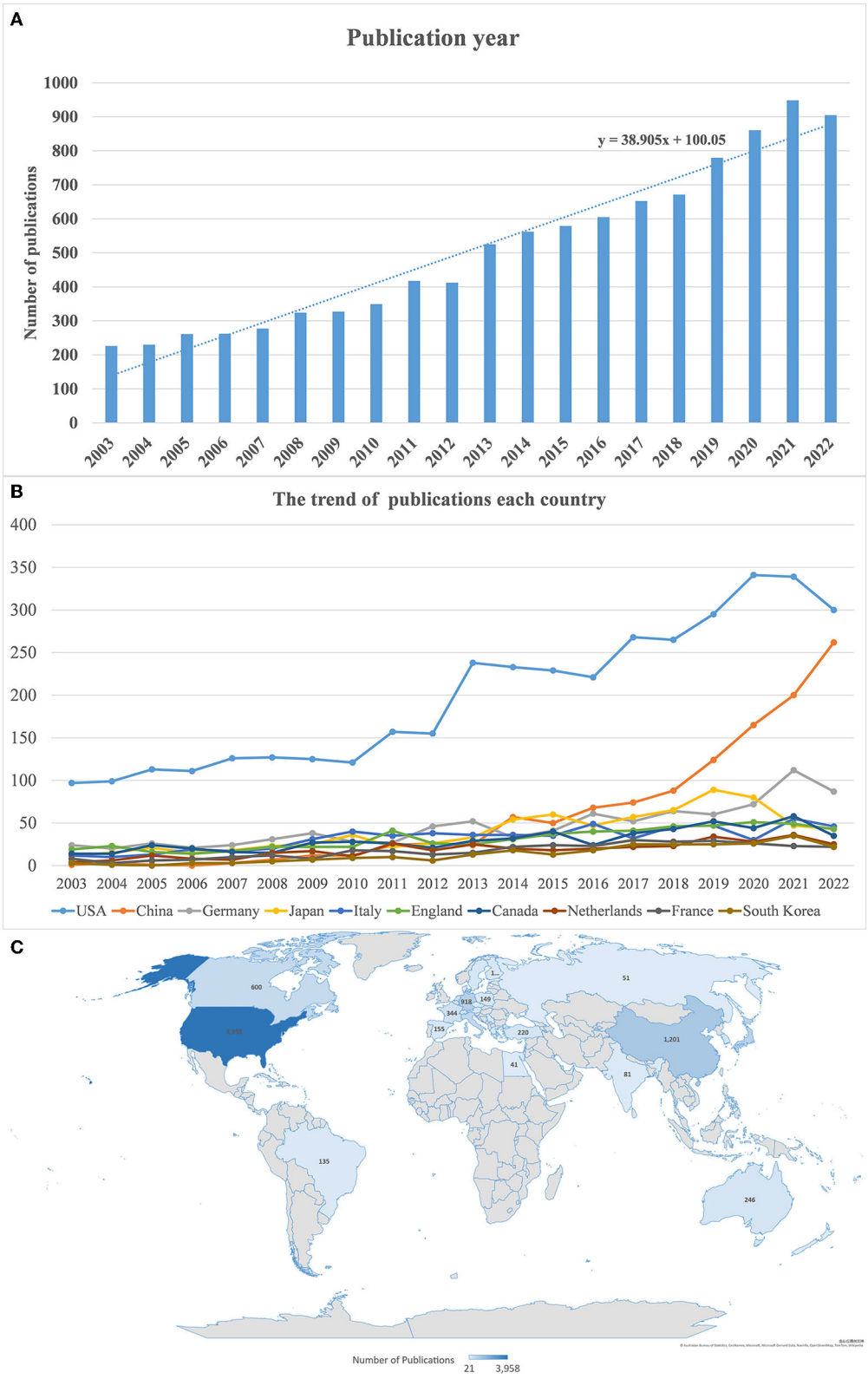

FIGURE 2
(A) Annual number of publications. **(B)** Annual publication trend in every country. **(C)** Distribution of perioperative stroke research by country from 2003 to 2022.

TABLE 1 Ten most prolific countries.

Country	Number (%)	H-index	Total times cited	Average per term
USA	3,958 (38.9%)	132	114,598	28.95
China	1,201 (11.8%)	48	12,939	10.77
Germany	918 (9.0%)	77	28,143	30.66
Japan	788 (7.7%)	45	11,228	14.25
Italy	647 (6.4%)	62	15,834	24.47
England	632 (6.2%)	78	29,327	46.40
Canada	600 (5.9%)	84	31,525	52.54
Netherlands	375 (3.7%)	51	12,782	34.09
France	344 (3.4%)	46	7,974	23.18
South Korea	267 (2.6%)	27	3,118	11.68

the total. Malas, Mahmoud B. from the University of California, San Diego (USA) contributed the highest number of publications ($n = 72$), followed by Biancari, Fausto ($n = 68$), Schermerhorn, Marc L. ($n = 51$), De Borst, Gert J ($n = 43$), and Gaudino, Mario F.L. ($n = 39$). Among the 10 authors, Joseph E. Bavaria had the highest H-index (24) and a mean number of citations ($n = 56.49$). Furthermore, most of the top 10 authors were from the USA. This suggests that there are more researchers in the USA who focus on perioperative stroke.

A co-authorship map was drawn to indicate the authors who had collaborated on perioperative stroke research. The size of the circle refers to the number of articles published by the author. The connection between the nodes reveals a collaborative relationship between them. A total of 326 authors had published at least 10 articles. The five authors with the highest TLS were Malas, Mahmoud B. (156), Gaudino, Mario F.L. (135), Biancari, Fausto (134), Santarpino, Giuseppe (127), and Mariscalco, Giovanni (116) (Figure 4B). There are multiple potential cooperation teams in the author's cooperation network. Nevertheless, the collaborative network of authors is scattered, and cross-border cooperation needs to be strengthened.

3.5. Journal analysis

A list of the 10 most prolific journals with the highest number of publications on perioperative stroke is presented in Table 4. The Journal of Vascular Surgery had the highest number of articles on the condition ($n = 626$), followed by the Annals of Thoracic Surgery ($n = 517$), the Journal of Thoracic and Cardiovascular Surgery ($n = 336$), and the Annals of Vascular Surgery ($n = 320$). The Journal of Vascular Surgery had the highest number of citations ($n = 17,872$), followed by the Annals of Thoracic Surgery ($n = 17,529$), the Journal of Thoracic and Cardiovascular Surgery ($n = 14,437$), and the European Journal of Cardio-thoracic Surgery ($n = 7,654$). According to the 2021 Journal Citation Reports, Stroke had the highest impact factor (10.17), followed by the Annals of Thoracic Surgery (5.11) and the Journal of Vascular Surgery (4.86) (Table 4).

The articles cited by every publication were represented as nodes in a co-citation visualization network. Co-cited journals were cited by other researchers. Clusters symbolized by different colors were generated based on citation links. The size of the circle indicates the co-citation frequency. The line between the circles represents the co-citation relationship. Thickness and the number of connections with the nodes indicate the link strength between the journals. A total of 623 journals were cited at least 50 times. The five journals with the highest TLS were Stroke (546,381), New England Journal of Medicine (468,018), Annals of Thoracic Surgery (456,554), Circulation (439,048), and Journal of Vascular Surgery (413,991) (Figure 4C).

3.6. Keyword analysis

A list of the 20 most common keywords mentioned by perioperative stroke publications is presented in Table 5. The top five co-occurring keywords were stroke ($n = 2,825$), surgery ($n = 1,853$), outcome ($n = 1,636$), mortality ($n = 1,436$), and risk ($n = 1,375$). To visualize the global trends in perioperative stroke research over the last two decades, a visual network map of co-occurrence analysis was created. An overlay visualization map (Figure 5A) was colored using the VOSviewer according to the mean year in which the keywords appeared in a publication. The overlay visualization of the keywords, which appeared in the most recent years, included "TAVI," "mean arterial-pressure," "TCAR," "predictive factors," "thrombectomy," "intraoperative hypotension," "biomarker," and "transcarotid artery revascular."

Burst keywords were performed to predict cutting-edge research. The green line represented the timeline, and the red line represented the outbreak period. As presented in Figure 5B, the keywords with the strongest burst strength were cardiopulmonary bypass (45.68), operation (28.28), angioplasty (16.66), and mechanical thrombectomy (16.47). The burst keywords that continued until 2022 included "long-term outcome," "thrombectomy," "intraoperative hypotension," "epidemiology," "dementia," "carotid revascularization," "guideline," and "flow reversal."

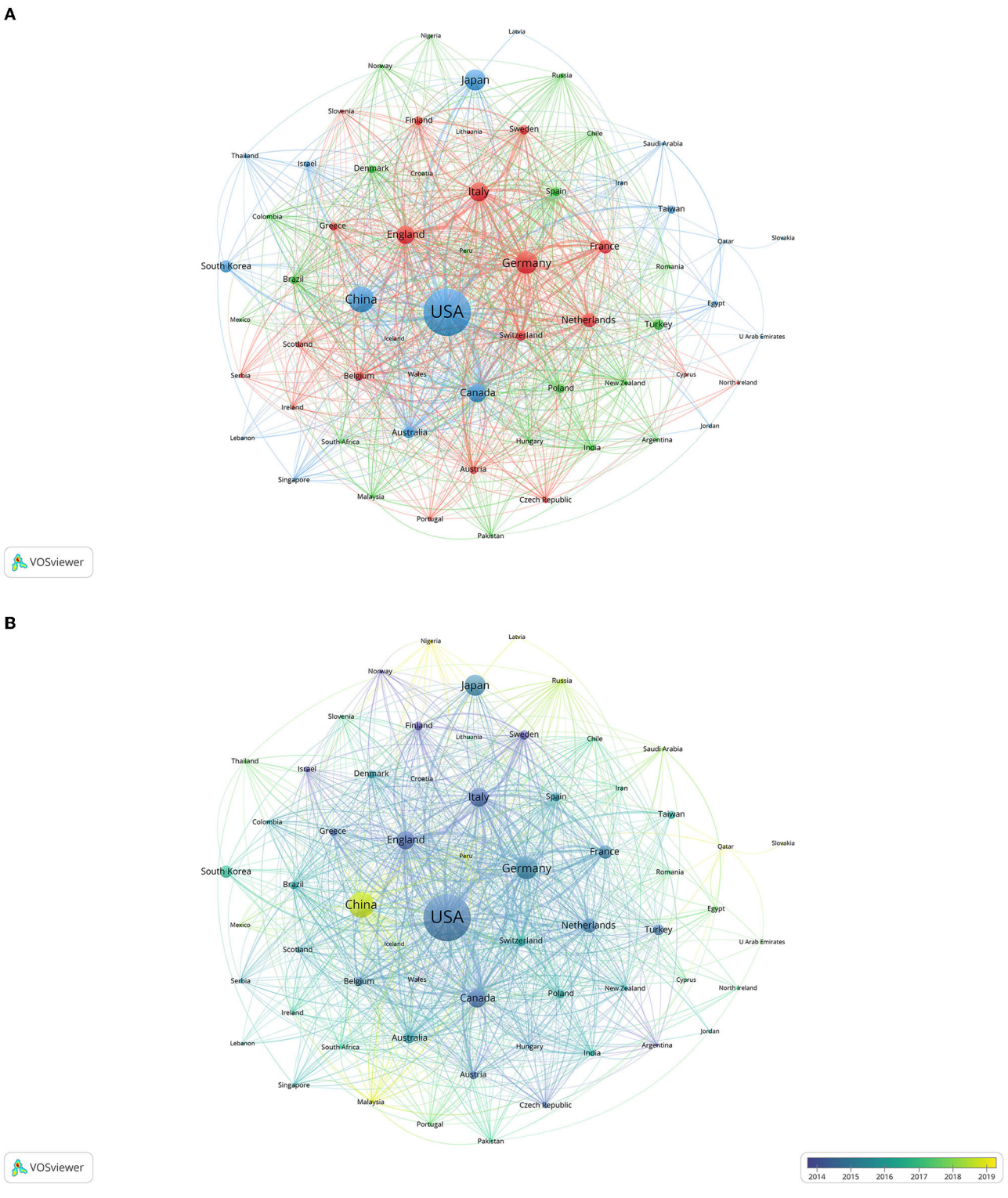

FIGURE 3
Co-authorship analysis of countries. Link thickness indicates collaboration strength and node size denotes the number of publications by every country. **(A)** Network visualization; **(B)** Overlay visualization.

A timeline view of the keywords' co-occurrence network analysis was performed with CiteSpace. The most frequent keywords for each cluster over time were visualized (Figure 5C). Each horizontal line represented a keyword cluster, which was sorted by the total number of keywords in descending order. The timeline from left to right represents 2003 to 2022. The

TABLE 2 Ten most prolific institutions.

Institutions	Record count (%)	Country	H-index	Sum of times cited	Average per item
Harvard University	409 (4.0%)	USA	60	16,483	40.3
University of California System	295 (2.9%)	USA	49	8,579	29.08
Mayo Clinic	284 (2.8%)	USA	49	9,480	33.38
Harvard Medical School	244 (2.4%)	USA	42	9,321	38.2
Cleveland Clinic Foundation	225 (2.2%)	USA	48	9,439	41.95
University of Toronto	216 (2.1%)	Canada	49	9,563	44.27
Johns Hopkins University	206 (2.0%)	USA	39	8,272	40.16
Pennsylvania Commonwealth System of Higher Education Pcshe	206 (2.0%)	USA	35	7,167	34.79
Capital Medical University	196 (1.9%)	China	20	1,475	7.53
University of Pennsylvania	188 (1.8%)	USA	49	8,459	44.99

corresponding year in which the node appears in the horizontal line represents its first appearance. The red circle refers to the keywords which appeared more recently, and the gray and blue ones represented keywords appearing in the early period.

Clusters #0 (morbidity) and #1(postoperative complications) are the two largest clusters. The keywords of "antithrombotic therapy," "thromboembolism," "oral anticoagulation," "molecular weight heparin," "metoprolol," "renal failure," and "diabetes mellitus" appeared only in the early period. In contrast, the keywords of "aspirin," "antiplatelet therapy," "clopidogrel," "warfarin," "bleeding complications," "near infrared spectroscopy," "postoperative atrial fibrillation," and "predictor" appeared throughout the entire period. "Acute coronary syndrome" was the new emerging keyword. This result indicates that antiplatelet and antithrombosis have been hot research topics in the past 20 years. Monitoring technique with near-infrared spectroscopy has received increasing attention.

Clusters #2 (acute ischemic stroke) and #8 (ischemic stroke) refer to a similar theme. The keywords of "cerebral perfusion pressure," "ultrasound," "magnetic resonance," "cognitive impairment," and "focal cerebral ischemia" appeared only in the early period. Red nodes represented the keywords of "recurrence," "mechanical thrombectomy," "resection," "MRI," "intracranial pressure," "postoperative cognitive dysfunction," and "decompressive craniectomy." The distribution of keywords indicates the shift of research focus, with mechanical thrombectomy being established as a popular treatment more recently. The association between postoperative stroke and postoperative cognitive dysfunction has always been the research hotspot in this field.

Clusters #3 (cardiopulmonary bypass), #4 (aortic valve replacement), #9 (coronary artery bypass), and #11 (thoracic endovascular aortic repair) are related to cardiovascular surgery. The keywords of "intraoperative transesophageal echocardiography", "open surgical repair", "stent grafts", "inflammatory response", and "serum creatinine" appeared in the early period. More recent studies have focused on minimally invasive and interventional cardiac procedures as evidenced by the emerging keywords of "carotid artery stenosis," "transcatheter aortic valve replacement," "transient ischemic attack," "percutaneous coronary intervention," and "thoracic endovascular aortic repair."

In clusters #5 (fluid therapy) and #6 (management), the keywords included "risk assessment," "goal directed therapy," "controlled trial," and "major surgery" appeared in the earlier period. New emerging keywords included "central venous pressure," "stroke volume variation," "multicenter," "hip fracture," and "tranexamic acid." Hip fracture and tranexamic acid have been shown to be associated with an increased risk of postoperative stroke in surgical patients, these terms might represent current hot research topics.

In cluster #7 (moyamoya disease), early keywords included "cerebral aneurysms," and "endarterectomy carotid." The keywords "postoperative stroke" and "cerebral revascularization" appeared in more recent periods. In cluster #10 (aortic dissection), "frozen elephant trunk" is the new emerging keyword.

4. Discussion

4.1. Global trends

The bibliometric properties of 10,172 documents—which were retrieved from the WoS database by this study—in the citation indices were scrutinized. Over the past two decades, the number of perioperative stroke papers had almost tripled from 226 to

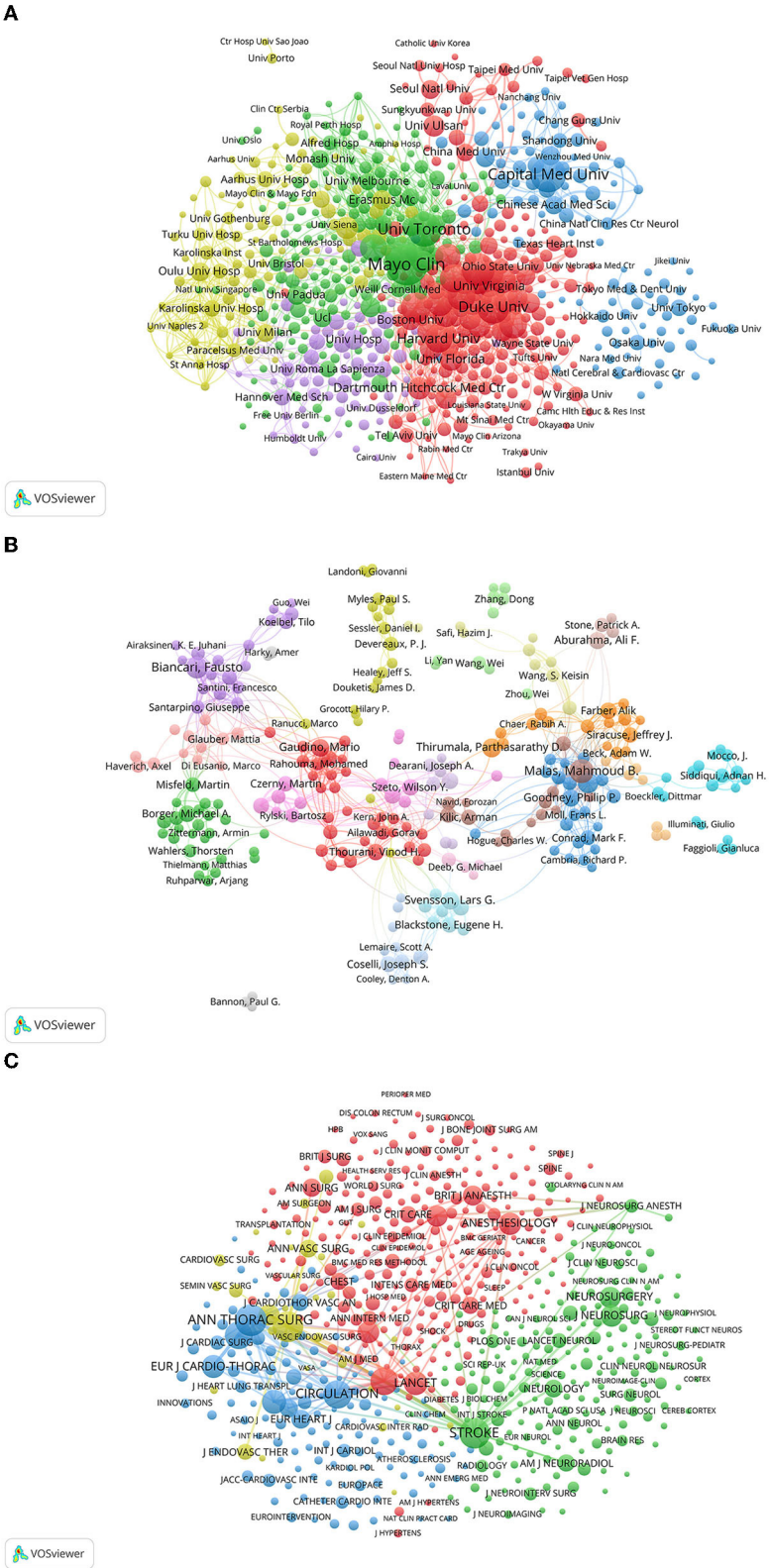

FIGURE 4
(A) Co-authorship analysis of institutions. The nodes of the circle represent the institutions and the links denote collaborations between them. The node size relates to the number of published articles and collaboration strength is indicated by link thickness. **(B)** Co-authorship analysis of authors. **(C)** Co-citation analysis of journals. The links between nodes indicate the citation frequency of the articles. Journals with higher co-citation frequency have larger nodes.

TABLE 3 Ten most prolific authors.

Author	Country	Number of publications	H-index	Average citation	Total times cited	Institution
Malas, Mahmoud B.	USA	72	18	13.49	971	University of California San Diego
Biancari, Fausto	Italy	68	23	24.99	1,699	Helsinki University Hospital
Schermerhorn, Marc L.	USA	51	17	18.06	921	Beth Israel Deaconess Medical Center
De Borst, Gert J.	Netherlands	43	17	20.07	863	Utrecht University Medical Center
Gaudino, Mario F. L.	USA	39	15	13.46	525	Cornell University
Goodney, Philip P.	USA	39	19	20.92	816	White River Junct VA Med Ctr
Joseph E. Bavaria	USA	37	24	56.49	2,090	University of Pennsylvania
Pochettino, Alberto	USA	34	22	46.29	1,574	Mayo Clinic
Borger, Michael A.	USA	30	21	71.1	2,133	Heart Center Leipzig GMBH
Farber, Alik	USA	30	10	8.63	259	Boston University

TABLE 4 Ten most prolific journals.

Journal	Total publications	Times Cited	H-Index	Average per item	IF (2021)
Journal of vascular surgery	626	17,872	60	28.55	4.86
Annals of thoracic surgery	517	17,529	65	33.91	5.11
Journal of thoracic and cardiovascular surgery	336	14,437	64	42.97	4.53
Annals of vascular surgery	320	3,144	27	9.83	1.60
European journal of cardio-thoracic surgery	293	7,654	47	26.12	4.53
World neurosurgery	234	2,036	23	8.7	2.21
Journal of cardiac surgery	186	1,634	21	8.78	1.78
Journal of cardiothoracic and vascular anesthesia	179	2,478	28	13.84	2.89
Interactive cardiovascular and thoracic surgery	149	1,663	23	11.16	1.98
Stroke	142	7,780	49	54.79	10.17

905. After 2018, a sharp increase was observed, and the number is projected to increase to 1,267 by 2032, indicating that the condition was a popular research topic. An increase in the number of publications could be associated with the growing medical and economic burden attributed to perioperative neurological complications, which predicts a continuation of comprehensive and in-depth research into perioperative stroke.

4.2. Countries

The H-index and the total number of citations are essential metrics to measure the academic impact and quality of publications (11). According to the network visualization map, the 10 countries with the highest number of publications included five European countries (Germany, Italy, England, Netherlands, and France), three Asian countries (China, Japan, and South Korea), and two North American countries (the USA and Canada). The USA led the field with the highest number of citations ($n = 114,598$) and H-index (132). Although Canada contributed only 5.9% to the total number of publications, it had the highest mean number of citations per term with an outstanding H-index of 84.

According to the publication trend in every country (Figure 2B) and the overlay visualization of co-authorship analysis of countries (Figure 3B), China had the fastest-growing number of publications and had strengthened its academic collaboration with other countries. This may be attributed to Chinese extensive population base, the progress of population aging, and increasing funding in scientific research, which drive in-depth research in this field. However, its relatively low H-index (48) and mean citation figure

TABLE 5 Top 20 keywords.

Keywords	Number of occurrences
Stroke	2,825
Surgery	1,853
Outcomes	1,636
Mortality	1,436
Risk	1,375
Management	1,181
Cardiac-surgery	769
Complications	756
Disease	740
Stenosis	733
Risk-factors	711
Endarterectomy	606
Impact	571
Carotid endarterectomy	511
Revascularization	506
Cardiopulmonary bypass	506
Experience	503
Meta-analysis	471
Trial	463
Therapy	425

(n = 10.77) indicate that its research quality can be further improved. African and Southeast Asian countries contributed minimal research to the field, which may be attributed to their lower economic growth and international academic collaborations.

4.3. Institutions and authors

Harvard University, the University of California System, and the Mayo Clinic were the three most prolific institutions. Eight of the 10 most prolific institutions were from the USA. Based on the co-authorship analysis, we observed that institutions from the USA were at the center of the collaborative network. Institutions in North America and Europe had close collaborations; however, there was only internal collaboration in most institutions in Asian countries (Figure 4A).

Malas, Mahmoud B., Biancari, Fausto, Schermerhorn, Marc L., and De Borst, Gert J. were the most prolific contributors to perioperative stroke research. Eight of the 10 most prolific authors were from the USA. According to the co-authorship analysis, authors from the same country had frequent close collaborations; however, the connection among authors from different countries remained low (Figure 4B). Therefore, it is recommended that scholars in different countries should overcome academic barriers and enhance cooperation to promote the development of perioperative research.

4.4. Journals

Journal and co-citation analysis provide important insights for researchers to guide their selection of appropriate journals for publication consideration. The co-citation network demonstrated that Stroke (IF = 10.17, 2021) had the highest recognition and authority in perioperative stroke research. It was followed by the Annals of Thoracic Surgery (IF = 5.11, 2021) and the Journal of Vascular Surgery (IF = 4.86, 2021), both of which had the highest number of publications and a fairly high TLS in the co-citation visualization network.

Based on the co-citation frequency, these journals were classified into four clusters with similar research directions (Figure 4C). The yellow cluster represented journals that dealt with vascular surgery; the blue cluster represented journals that focused on cardiac and thoracic surgery; the red cluster referred to journals that featured anesthesia and critical care; and the green cluster represented journals that focused on neurosurgery and stroke. In addition, the proportion of publications in the 10 most prolific journals was as high as 29%, indicating a dense distribution of publications across journals. This finding may be attributed to a spike in surgical, vascular, thoracic, and stroke research. Among the 10 journals, only two had an impact factor above five. These findings suggest that most studies were published by specialist journals, and greater recognition by high-impact medical journals is required.

4.5. Current knowledge and trending topics

4.5.1. Preoperative risks and prevention strategies

Several studies have identified advanced age, renal disease, and prior episodes of transient ischemic attack or stroke as the main risk factors in perioperative stroke (3, 12, 13). Other risk factors were established by recent studies and include myocardial infarction in the last 6 months, previous history of stroke, atrial fibrillation, hypertension, chronic obstructive pulmonary disease, smoking habit, patent foramen ovale (14), female sex, and diabetes (3, 12, 15).

In addition to the identification and elucidation of the risk factors, prediction models have been used to assess perioperative stroke risk. A recent observational study found that American College of Surgeons (Chicago, Illinois) surgical risk calculator and Myocardial Infarction or Cardiac Arrest risk score, showed the highest discriminatory ability for predicting a likelihood of perioperative strokes (16). However, most prediction tools failed to account for stroke risk associated with specific scores or thresholds. Consequently, a prediction model must be developed, which comprehensively integrates every relevant risk factor and provides quantitative data for stroke risk stratification.

Preoperative medication optimization is essential for reducing adverse perioperative outcomes. Although some studies have demonstrated that beta-blockers—such as metoprolol—do not reduce the risk of perioperative stroke (17, 18), there does not appear to be an association between chronic beta-blockers and perioperative stroke in patients with multiple cardiovascular risk factors, such as hypertension (19), previous coronary

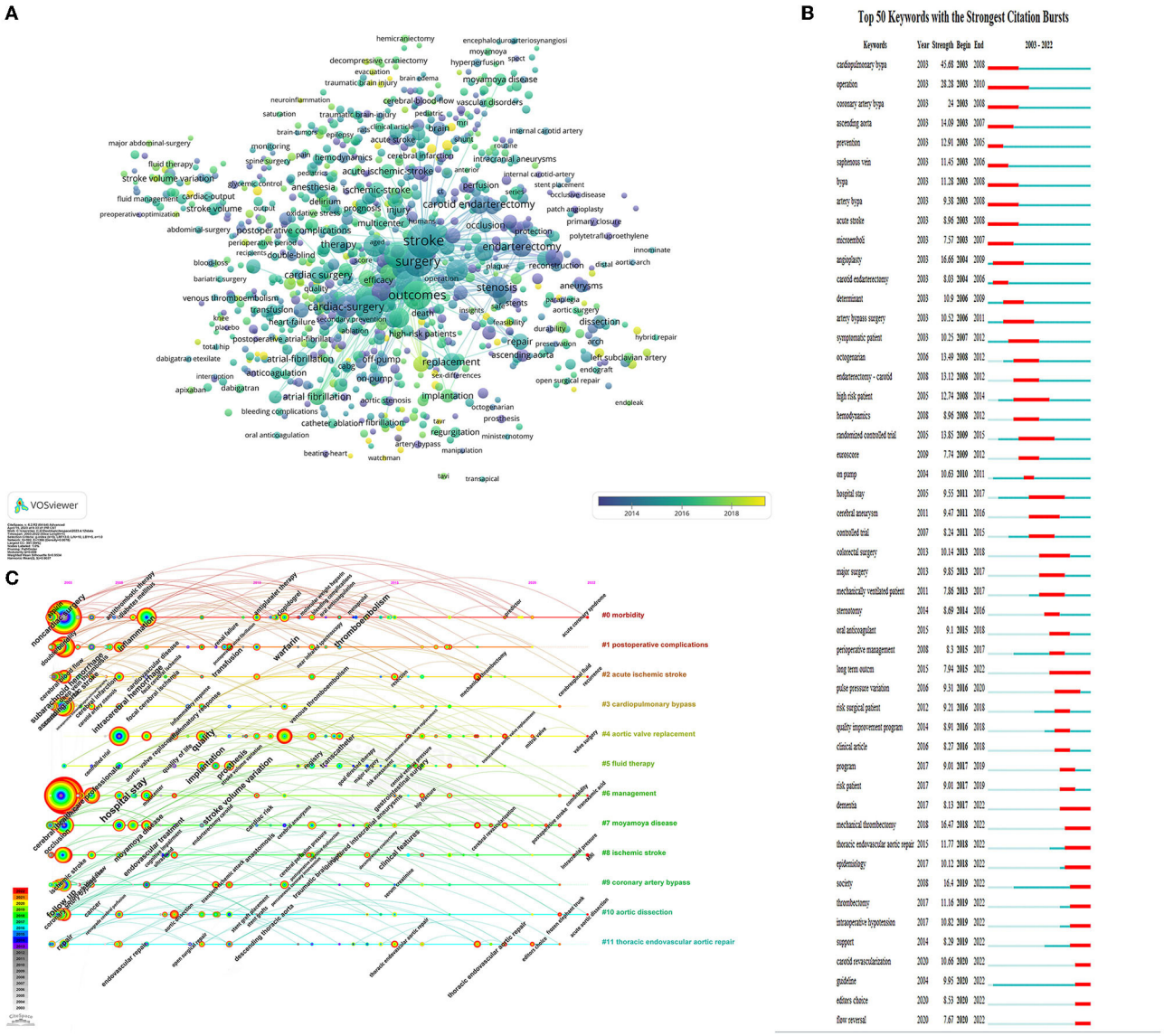

FIGURE 5
Keywords analysis **(A)** Overlay visualization of the keywords co-occurrence. The circle size indicates occurrence frequency, and a line between the circles indicates their co-occurrence in the same publication. **(B)** Top 50 keywords with the strongest citation bursts on perioperative stroke research between 2003 and 2022. The red segment of the blue line denotes the burst duration of a keyword. **(C)** CiteSpace visualization map of timeline viewer. Each node represents a keyword, and the annual ring of the node indicates the appearance time of keyword.

revascularization (20), and diabetes mellitus (21). For patients on statins before undergoing non-cardiac surgery, it is recommended that they continue to use the drugs to reduce adverse cardiovascular events; however, the relationship between statins and stroke risk is not clearly defined (22, 23).

Anti-coagulation strategies for surgical patients should balance the risk of thromboembolic prevention and the increased risk of surgical bleeding. Perioperative anticoagulation bridging therapy is only indicated in high-risk thromboembolic patients who are on vitamin K antagonists, such as warfarin (24). For oral anticoagulants, it is recommended to discontinue these drugs 2–3 days before surgery and resume them 1–3 days post-operation, based on the risk of thromboembolism and bleeding. In patients who have not undergone percutaneous coronary intervention, the use of low-dose aspirin must be discontinued as it can lead to an increased risk of perioperative bleeding (25).

In addition, preoperative functional magnetic resonance imaging can be performed in high-risk patients with previous cerebrovascular disease to determine cerebrovascular reserve (26). This preoperative strategy helps identify individualized intraoperative management goals for blood pressure and end-tidal carbon dioxide to optimize cerebrovascular perfusion.

4.5.2. Intraoperative management

Current research suggests that general or regional anesthesia does not affect perioperative stroke risk (27). The choice of anesthesia must be based on other clinical indications rather than

the perioperative stroke risk. With the possible exception of patients undergoing hip surgery, neuraxial anesthesia appears to reduce stroke risk compared to general anesthesia (28).

Although the literature findings are inconclusive, arterial blood pressure may play an important role in perioperative stroke (29). Nevertheless, the lack of a well-defined threshold for intraoperative blood pressure indicates an increased risk of perioperative stroke in patients undergoing non-cardiac surgery. Until a specific threshold is clarified, mean arterial pressure should be maintained above 70 mmHg to reduce the risk of perioperative stroke, particularly in high-risk patients (30). Intraoperative strategies based on near-infrared spectroscopy and bioimpedance can be used to determine critical thresholds for cerebral blood flow (31, 32).

Although the FEDORA trial (clinical trial registration: ISRCTN93543537) found a reduction of almost 50% in moderate or severe postoperative complications in patients who were randomly assigned to intraoperative goal-directed therapy, it did not describe a significant reduction in stroke, which was attributed to its low incidence (33). In addition, both hypoventilation and hyperventilation may lead to a reduction in cerebral blood flow that reaches the threshold of hypoxic-ischemic injury (34). An optimization of ventilation strategies is another means to improve outcomes. Despite the absence of data that support goal-directed therapy and lung-protective ventilation in stroke prevention, these methods seem reasonable as part of an overall strategy to improve perioperative outcomes.

4.5.3. Postoperative recognition and stroke treatment

In the perioperative period, stroke diagnosis is challenging owing to the use of opioids and sedatives, pain, and delayed neurocognitive recovery. Although various clinical screening tools are available to detect stroke (35), the postoperative scores obtained by these scales—such as the modified National Institutes of Health (Bethesda, MD, USA) stroke scale—are usually altered compared with the baseline (36). In the absence of reliable clinical screening tools, serum biomarkers can be used to assist in the assessment and diagnosis of perioperative stroke. However, to date, no reliable biomarkers have been clinically validated for the identification of cerebral ischemia and infarction (36). Based on postoperative signs and symptoms of large-vessel occlusion, targeted monitoring that uses computed tomography or magnetic resonance imaging can improve stroke diagnosis.

When a perioperative stroke is suspected, non-contrast computed tomography or magnetic resonance imaging must be performed to determine whether its etiology is hemorrhagic or ischemic (2). When these criteria are met, the recommended guidelines of intravenous alteplase for thrombolytic therapy must be instituted within 4.5 h from symptom onset. Thereafter, dosing may be used in certain patients (37). However, owing to the potential adverse effects of thrombolytic therapy, the time window and treatment indications must be strictly controlled. As mechanical thrombectomy is superior to intravenous thrombolysis (38), its use as a treatment option must be prioritized. Current guidelines support its intervention in patients experiencing symptom onset within 6–24 h (37).

4.5.4. Future directions and research gap

Despite steady progress that has been achieved in the research of perioperative stroke in the past two decades, the research gaps remain to be explored in this specific field. The pathophysiology of perioperative stroke needs to be further clarified elaborately, which appears to be distinct from a non-surgical stroke. In addition, balancing the risk of embolism formation and postoperative bleeding in surgical patients can be challenging. Refinement of the patients at high risk of perioperative embolization or bleeding was required before the prescription of bridging treatment. Furthermore, the biomarker-based diagnosis of a perioperative stroke may greatly improve diagnostic efficiency; however, no reliable biomarkers are currently available. More specific and refined prediction models including the relevant risk factors should be developed in predicting the likelihood of perioperative stroke. As intraoperative blood pressure reduction and hyperventilation can decrease the cerebral blood flow to the hypoxic threshold, an analysis of the intraoperative physiological data, provided by a multicenter database, can be used to determine an association between hypotension and end-tidal carbon dioxide with stroke. In addition, the role of intraoperative management strategies—such as the optimization of blood pressure and glucose—in stroke patients deserves further study. Finally, the potential outcomes of perioperative stroke on postoperative delirium and cognitive dysfunction and the association between ischemic lesions with the perioperative neurocognitive disorder are yet to be clarified.

4.6. Limitations

This study has several limitations. First, the bibliometric analysis was based on the data retrieved from the WoS database, and only English publications were included. Both factors led to selection bias, and several important publications may have been omitted in the process. Second, owing to a lack of author and address details in the publications, a count of the author collaborations may lack accuracy. Finally, although the number of citations is often used as an indicator of publication quality, this index is likely to be affected by self-citation and publication date. As recent publications tend to have a lower number of citations, their impact may have been underestimated.

4.7. Conclusion

In this study, a summary and a visual map of perioperative stroke research over the past two decades were provided to illustrate the current status, hotspots, and development of this field. Research on perioperative antiplatelet and antithrombotic, cardiovascular surgery, postoperative cognitive dysfunction, thrombectomy, tranexamic acid, and frozen elephant trunk has

attracted increasing attention, and these topics are emerging hotspots of present research and possible candidates for future research.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

BY and TT: conception and design of the study. SJ: literature search and paper writing. YS: VOSviewer and CiteSpace analysis. XF and TJ: figure and table drawing. XY: manuscript review and editing. All authors contributed to the manuscript and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Diagnostic accuracy of telestroke consultation: a Louisiana based tele-network experience

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Background and purpose: Telestroke has grown significantly since its implementation. Despite growing utilization, there is a paucity of data regarding the diagnostic accuracy of telestroke to distinguish between stroke and its mimics. We aimed to evaluate diagnostic accuracy of telestroke consultations and explore the characteristics of misdiagnosed patients with a focus on stroke mimics.

Methods: We conducted a retrospective study of all the consultations in our Ochsner Health's TeleStroke program seen between April 2015 and April 2016. Consultations were classified into one of three diagnostic categories: stroke/transient ischemic attack, mimic, and uncertain. Initial telestroke diagnosis was compared with the final diagnosis post review of all emergency department and hospital data. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR–) for diagnosis of stroke/TIA versus mimic were calculated. Area under receiver-operating characteristic curve (AUC) analysis to predict true stroke was performed. Bivariate analysis based on the diagnostic categories examined association with sex, age, NIHSS, stroke risk factors, tPA given, bleeding after tPA, symptom onset to last known normal, symptom onset to consult, timing in the day, and consult duration. Logistic regression was performed as indicated by bivariate analysis.

Results: Eight hundred and seventy-four telestroke evaluations were included in our analysis. Accurate diagnosis through teleneurological consultation was seen in 85% of which 532 were strokes (true positives) and 170 were mimics (true negatives). Sensitivity, specificity, PPV, NPV were 97.8, 82.5, 93.7 and 93.4%, respectively. LR+ and LR– were 5.6 and 0.03. AUC (95% CI) was 0.9016 (0.8749–0.9283). Stroke mimics were more common with younger age and female gender and in those with less vascular risk factors. LR revealed OR (95% CI) of misdiagnosis for female gender of 1.9 (1.3–2.9). Lower age and lower NIHSS score were other predictors of misdiagnosis.

Conclusion: We report high diagnostic accuracy of the Ochsner Telestroke Program in discriminating stroke/TIA and stroke mimics, with slight tendency towards over diagnosis of stroke. Female gender, younger age and lower NIHSS score were associated with misdiagnosis.

KEYWORDS

telestroke, telemedicine, teleneurology, accuracy, MIMICS

Introduction

Stroke is the fifth leading cause of death in the United States, and the leading cause of serious long-term disability (1). Approximately 795,000 people in the United States experience stroke every year and Louisiana is among the top three states in stroke prevalence (5.1%) with reported age-adjusted death rates as high as 88.9 deaths per 100,000 total population (2). Rural communities make up to 25% of Louisiana's population, with a greater percentage residing outside of areas with accessibility to a primary stroke center, highlighting the need for improved access and quality of healthcare in rural areas (3, 4).

Telemedicine has grown significantly since its implementation in the 1960s and, over the last decade, telestroke has been widely adopted in the care of patients with acute stroke, providing timely access to neurological expertise in rural and other underserved areas (5).

Since the US Food and Drug Administration approval of tissue plasminogen activator (tPA) for acute stroke in 1996, stroke centers have strived to increase the proportion of eligible patients treated with tPA, to improve outcomes for patients presenting within 3 h of symptom onset (6–8). With increasing evidence supporting an improved chain of care enabling rapid triage/diagnosis and increased tPA administration rates among patients presenting to community hospitals, approximately a quarter of US hospitals have implemented telestroke for patients in their emergency departments (9, 10). With expansion of the therapeutic window for patients with large vessel occlusion (LVO) through endovascular thrombectomy (EVT) from 6 to 24 h, there has been an increased focus on triage systems to minimize time to reperfusion and improve outcomes (11, 12).

Despite growing utilization, there is a paucity of data regarding the diagnostic accuracy of telestroke to distinguish between stroke and its mimics as well as specific mimic diagnoses. Due to inherent limitations including lack of physical contact between neurologist and patient, accurate determination of stroke and mimics can, at times, be challenging leading to delayed or missed neurological diagnosis, unnecessary diagnostics and therapeutics and/or wasted resources (13, 14). Hence, we aimed to evaluate diagnostic accuracy of telestroke consultations.

Ochsner Medical Center was the first hospital in Louisiana to implement telestroke and has become one of the fastest growing networks in the country with over 50 active spoke hospitals across Louisiana, Alabama and Mississippi. We performed a retrospective analysis to determine the diagnostic accuracy in patients presenting with symptoms of acute cerebrovascular disease via our large telestroke network. We furthermore aimed to explore the characteristics of misdiagnosed patients with a focus on stroke mimics.

Methods

Following approval from the Ochsner Institutional Review Board (IRB), we conducted a retrospective observational study of 874 consecutive patients who were evaluated in Ochsner Health's TeleStroke Program, between April 2015 and April 2016. During the study period, our Telestroke program provided a 24-h per day, 7 days per week, 365 days per year integrated service for recognition and treatment of patients with suspected acute stroke presenting within 12 h of symptom onset. Ochsner Medical Center in New Orleans is a tertiary academic medical center and serves as the "hub," with vascular neurologists providing collaborative care to "spoke" hospitals via telestroke technology. Telestroke alert is activated by ED physician, or any registered licensed nursing personal at the spoke hospital, if the patient's presentation suggests acute stroke. Ochsner's stroke team partners with onsite clinicians/nurses to evaluate, diagnose and directly care for patients. The workflow at the hub includes time-sensitive videoconferencing consultation to the patients at the spoke hospital, mimicking bedside consultation, following American Heart Association/American Stroke Association recommended guidelines for evaluation and management of acute stroke. Initial diagnosis, complete clinical picture, imaging evaluation & recommended treatment was recorded as determined by the telestroke consultant and integrated into patient's permanent electronic health records, including recommendations on post telestroke care regardless of whether the patient remains at the spoke or requires transfer to a higher level of care.

During the study period, Ochsner Health's TeleStroke Program had 36 spoke hospitals including Acadian Medical Center – Eunice, LA, Christus St. Frances Cabrini Hospital - Alexandria, LA, Christus St. Patrick Hospital – Lake Charles, LA, Franklin Foundation Hospital – Franklin, LA, Glenwood Regional Medical Center – West Monroe, LA, Ochsner Medical Center – Hancock, MS, Lady of the Sea General Hospital – Cut Off, LA, Mercy Regional Medical Center - Ville Platte, LA, Minden Medical Center – Minden, LA, Natchitoches Regional Medical Center – Natchitoches, LA, Ochsner Baptist Medical Center – New Orleans, LA, Ochsner Medical Center – Baton Rouge, LA, Ochsner Iberville Medical Complex - Plaquemine, LA, Ochsner Health Center – Kenner, LA, Ochsner North Shore Medical Center – Slidell, LA, Ochsner St Anne General Hospital - Raceland, LA, Ochsner Health Center – West Bank, LA, Pointe Coupee General Hospital - New Roads, LA, Ochsner River Parishes Medical Complex - Laplace, LA, Springhill Medical Center – Springhill, LA, St. Charles Parish Hospital – Luling, LA, St. James Parish Hospital – Lutcher, LA, St. Tammany Parish Hospital – Covington, LA, Teche Regional Medical Center - Morgan City, LA, Terrebonne General Medical Center – Houma, LA, and Union General Hospital - Farmerville, LA.

Demographic and clinical data were extracted for each patient, from the Ochsner Telestroke database and the electronic medical record. Specific data elements included: date of birth, gender, race/ethnicity, history of coronary artery disease (CAD), diabetes mellitus (DM), hyperlipidemia (HLD), hypertension (HTN), smoking, prior stroke, medical record number, payor status, date and time of presentation, time last known normal, consultation time, consultation duration (minutes), National Institutes of Health Stroke Scale (NIHSS) score, Glasgow Coma Scale (GCS) score, vascular neurologist name, tPA recommended (yes/no).

Final diagnosis was determined retrospectively via independent review by one of the investigators, which included all emergency department and/or hospital data inclusive of local neurologist (when applicable) final documentation for those admitted. Investigators involved in final diagnosis determination were blinded to the initial consultation diagnosis. Consultations were classified into one of three diagnostic categories: stroke/transient ischemic attack, mimic, and uncertain. The initial telestroke diagnosis was categorized after reviewing all teleconsultant documentation and the most likely diagnostic impression was then assigned. When it was unclear from the record (e.g., only a list of differential diagnoses) "uncertain" was assigned. Stroke was defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction or attributable to a focal collection of blood within the brain parenchyma or ventricular

system or attributable to bleeding into the subarachnoid space that is not caused by trauma, or attributable to thrombosis of a cerebral venous structure. Transient ischemic attach (TIA) was defined as brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction. Patients with missing data on initial and final diagnosis, related to any reasons, incomplete investigations or follow-up were excluded from the study.

Initial telestroke diagnosis was compared with the final diagnosis and classified as true positive, true negative, false positive, or false negative for the presence of cerebrovascular disease. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) for diagnosis of stroke/TIA versus mimic were calculated. Area under receiver-operating characteristic curve (AUC) analysis to predict true stroke was performed. Continuous data are described as mean (SD) or median (interquartile range), while categorical data are presented as absolute and relative frequencies (counts and percentages). Bivariate analysis based on the diagnostic categories examined association with sex, age, National Institutes of Health Stroke Scale (NIHSS), stroke risk factors (CAD, DM, HLD, HTN, history of stroke/TIA, smoking), tPA given, bleeding after tPA, symptom onset to last known normal, symptom onset to consult, timing in the day, and consult duration. Logistic regression was performed as indicated by bivariate analysis.

Results

Of the 904 telestroke consultations conducted between April 2015 and April 2016, 874 patients were included in the study. More than half (67%) had a final diagnosis of cerebrovascular disease, including ischemic stroke ($n = 460$), TIA ($n = 106$) or intracerebral hemorrhage ($n = 15$). Non-cerebrovascular final diagnoses accounted for 240 (27%) of cases with the most common mimics being encephalopathy ($n = 63$), conversion disorder ($n = 35$), migraine ($n = 34$) and seizure ($n = 33$). In fifty-three (6%), the underlying etiology remained uncertain at discharge.

Significant differences were observed between patients with final diagnosis of cerebrovascular disease versus mimic (Table 1). Patients with mimics and uncertain diagnosis were younger, more likely to be female and had lower prevalence of hypertension, diabetes, hyperlipidemia and coronary artery disease than patients with a stroke. A higher proportion of stroke mimics had NIHSS >10 compared to patients with final stroke diagnosis.

Overall, accurate diagnosis through teleneurological consultation was seen in 739/874 (85%) of which 532 were strokes (true positives) and 170 were mimics (true negatives). Thirty-seven of these patients remained uncertain of their diagnosis during final evaluation (Table 2). Clinical/demographic differences were observed between misdiagnosed patients and those with accurate diagnosis. Misdiagnosed patients were younger and more likely female. Fifteen (11%) with misdiagnosis received intravenous thrombolysis (IVT) during their teleneurological evaluation, with one experiencing non-fatal bleeding complication.

Non-cerebrovascular telestroke diagnosis was made in 49/581 (8.4%) of patients with final Stroke/TIA diagnosis (IS, $n = 36$; TIA, $n = 12$; ICH, $n = 1$). The majority of these 37 (75.5%) received an uncertain telestroke diagnosis. Amongst the remaining 12 false negatives cases, the following incorrect diagnoses were made: encephalopathy ($n = 5$), transient global amnesia ($n = 2$), seizure ($n = 1$), conversion disorder ($n = 1$), syncope ($n = 1$), intracranial mass ($n = 1$) and Bell's palsy ($n = 1$). Twenty-one of the 36 false negative patients presented within 4.5 h of symptom onset and had no known

TABLE 1 Demographics and clinical characteristics categorized according to the final diagnosis.

Variable	Stroke *N* =581	Mimic *N* =240	Uncertain *N* =53	value of *p*
Age, mean years (SD)	66.6 (14.3)	58.8 (16.5)	58.2 (17.2)	**<0.0001**
Female, *n* (%)	287 (49.4)	150 (62.5)	36 (67.9)	**0.0003**
NIHSS >10, *n* (%)	406 (72.1)	191 (84.5)	49 (94.2)	**<0.0001**
Comorbidities, *n* (%)				
Smoking	229 (39.5)	89 (37.4)	23 (44.2)	0.6403
Hypertension	488 (84.0)	170 (70.8)	39 (73.6)	**<0.0001**
Diabetes mellitus	253 (43.6)	80 (33.3)	20 (37.7)	**0.0222**
Hyperlipidemia	295 (50.8)	103 (42.9)	20 (37.7)	**0.038**
Coronary artery disease	160 (27.5)	46 (19.2)	6 (11.3)	**0.0019**
Cerebrovascular disease	165 (28.4)	77 (32.1)	23 (43.3)	0.0672
tPA administered, *n* (%)	190 (32.7)	13 (5.4)	1 (1.9)	**<0.0001**
Bleeding post tPA	23 (12.1)	0 (0.0)	0 (0.0)	0.1757*
LKN time, no. (%)				
12:01 AM – 6:00 AM	42 (8.3)	10 (5.5)	1 (2.3)	0.5548*
6:01 AM – 12:00 PM	165 (32.7)	10 (33.9)	17 (39.5)	
12:01 PM – 6:00 PM H	168 (33.3)	10 (33.9)	12 (27.9)	
6:01 PM – 12:00 AM	129 (25.6)	49 (26.8)	13 (30.2)	

Demographics and clinical characteristics categorized according to the final diagnosis. NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator; LKN, last known normal. Bold indicates a significant *p* value. *Fisher's exact value could not be calculated, therefore Chi-square values were reported.

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TABLE 2 Clinical characteristics of patients with accurate diagnosis versus misdiagnosis via teleneurology.

Variable	Accurate diagnosis *N* =739	Misdiagnosis *N* =135	value of *p*
Age, mean years (SD)	64.6 (15.19)	60.82 (17.3)	**<0.0103**
Female, *n* (%)	383 (51.8)	90 (66.7)	**0.0013**
NIHSS >10, *n* (%)	174 (24.4)	21 (16.4)	**<0.0414**
Comorbidities, *n* (%)			
Smoking	295 (40.1)	46 (34.1)	0.1816
Hypertension	596 (80.1)	105 (77.8)	0.5394
Diabetes mellitus	296 (40.1)	57 (42.2)	0.6375
Hyperlipidemia	356 (48.2)	62 (45.9)	0.6306
Coronary artery disease	182 (24.6)	30 (22.2)	0.5455
Cerebrovascular disease	217 (29.4)	48 (35.6)	0.155
tPA administered, *n* (%)	189 (25.6)	15 (11.1)	**<0.0001**
Bleeding post TPA	22 (11.6)	1 (6.7)	1
Consult duration, mins	17 (9–24)	19 (11–29)	**0.0304**

Clinical characteristics of patients with accurate diagnosis versus misdiagnosis. NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator. Bold indicates a significant *p* value.

TABLE 3 Accuracy of initial telestroke diagnosis.

		Final diagnosis		
		Stroke/TIA	Stroke mimic	
Initial diagnosis	Stroke/TIA	True positive 532	False positive 36	PPV = 93.7%
	Stroke mimic	False negative 12	True negative 170	NPV = 93.4%
		Sensitivity = 97.8%	Specificity = 82.5%	

Accuracy of telestroke diagnosis. Patients with uncertain diagnosis during initial consultation or after final evaluation were not included in the analysis.

contraindication for IVT, suggesting a percentage of 0.6% of potentially missed thrombolysis due to underdiagnosis.

Non-cerebrovascular final diagnosis was determined in 46/578 (8.0%) who received a diagnosis of cerebrovascular disease via telestroke consultation (i.e., false positive). Etiology remained uncertain in 10; in the remaining, migraine was the most common mimic ($n = 9$) followed by conversion disorder ($n = 7$) and seizure ($n = 6$).

When considering patients with non-uncertain diagnosis, of the 240 patients with final diagnosis of non-cerebrovascular disease, 36 (15%) received a cerebrovascular teleneurological diagnosis (i.e., false positive; IS, $n = 31$; TIA, $n = 5$; Table 3). Eleven (35.5%) false positive patients received IVT, with none experiencing bleeding complication. Of all false positives, 9 had migraine, 7 conversion disorder, 6 seizures and 3 metabolic encephalopathy at final diagnosis. In 34/240 (14.2%), etiology could not be determined during the initial teleneurological consultation.

The sensitivity for diagnosis of cerebrovascular disease was over 97% (sensitivity 97.8%; NPV 93.4%) with a lower tendency towards false-positive diagnosis (specificity 82.5%; PPV 93.7%). Patients with uncertain diagnosis during initial consultations or after final evaluation were not included in this analysis. The positive likelihood ratio and negative likelihood ratio were calculated to be 5.6 and 0.03,

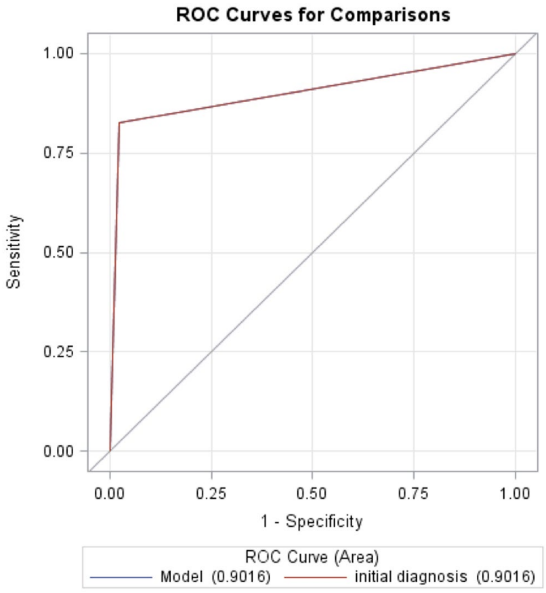

FIGURE 1
Receiver operating characteristic curves for comparisons. The probability of the test to predict a true stroke or accuracy of the test to discriminate between a true stroke and true mimic is 0.9016.

TABLE 4 Logistic regression predicting misdiagnosis.

Variable	OR	CI (95%)
Age	0.987	0.975–0.999
Female	1.915	1.279–2.869
NIHSS <10	1.633	0.970–2.748
Consult duration, mins	1.025	1.008–1.043

respectively. The overall diagnostic accuracy was good with area under the curve (AUC; 95% CI) 0.9016 (0.8749–0.9283; Figure 1).

The odds of misdiagnosis were 1.9 times higher for females than males (Table 4) and the odds of misdiagnosis decreased with increasing age. As regards NIHSS score, the odds of misdiagnosis increased by 1.6 for patients with NIHSS score ≤ 10 compared with NIHSS score > 10. Prolongation of consult time increased the odds of misdiagnosis.

Discussion

We demonstrated a high diagnostic accuracy of the Ochsner Telestroke Program, achieving 85% diagnostic correlation between the teleneurological diagnosis and final discharge diagnosis for patients with both stroke and stroke mimics. The sensitivity for diagnosis of cerebrovascular disease via teleneurology was over 97%, and the overall diagnostic accuracy was very high (AUC 0.9016). Data regarding diagnostic accuracy of teleneurological stroke consultations have been very limited, with reported sensitivity measures ranging wide from 60 to 95% (15–18). Our data comprised of a large cohort of 874 consultations provides greater evidence on the diagnostic accuracy of teleneurological stroke consultations, supporting the utility of telestroke systems in accurate assessment of patients with acute neurological presentations.

In 8.4% of our study population, diagnosis of cerebrovascular disease was missed during telestroke evaluation, with potentially a 0.6% missed thrombolysis or acute intervention due to underdiagnosis. Despite having certified stroke programs, missed opportunities have been reported to be greater than 20% in the ED in both the academic medical centers and community regional referral hospitals (19–21). Consistent with a previous study, we found NIHSS ≤4 and female gender as predictors of stroke chameleons (22). The most common stroke misdiagnosis in our sample was metabolic encephalopathy. Previously reported factors associated with missed stroke diagnosis such as younger age, less vascular risk factors or posterior circulation symptoms could not be established in our study (23, 24). Data regarding stroke chameleons in teleneurology are scarce. Although our volume of underdiagnosed patients was relatively small, our results raise further awareness for missed stroke diagnoses in females and those presenting with lower stroke scale.

As regards overdiagnosis, stroke mimic rates from emergency departments and telestroke networks have been reported from 20 to 45% (25–27), while the current study found a false positive rate of 27%. Stroke mimics were more common with younger age and female gender and in those with less vascular risk factors. Previous studies also have predominantly showed an inclination towards higher prevalence of mimics in females and younger age groups (28–30). Other reported factors associated with stroke mimics are lower median NIHSS at the time of consult, absence of facial droop, absence of atrial fibrillation and history of seizure disorder. Rapid identification of stroke mimics is critical, especially in those within the thrombolysis treatment window, as administration of thrombolysis to patients with stroke mimics remains prevalent and costly (14). Several stroke mimic prediction models have been formulated to aid in clinical decision-making in both the telestroke and prehospital settings, namely the FABS, simplified FABS, Telestroke Mimic Score (TMS) and Khan Score. These models warrant prospective validation in larger external cohorts (31, 32).

We also investigated the characteristics of patients with overall accurate diagnosis for cerebrovascular or non-cerebrovascular disorders. As for stroke specifically, we found female gender, lower age and lower NIHSS score to be predictors of misdiagnosis. In addition, consult duration was associated with misdiagnosis and may be reflective of the diagnostic challenges in such patients. An understanding of characteristics that place a patient at higher risk of misdiagnosis is valuable to the clinician and may lead to improved accuracy.

Our study has several strengths. The large sample size and inclusion of 36 spokes in the Stroke Belt permitted inclusion of a population with geographic, racial and socioeconomic diversity. Our findings provide insight into the real-world use of teleneurology and contribute to the globally growing experience from different telehealth services. As incomplete documentation was the only criterion for exclusion, discharge documentation was available for all included patients. The stroke neurologist's clinical diagnosis was the reference standard used in the analyzes and included imaging results, when available. Although diagnostic accuracy is recognized as an important indicator of quality, final diagnoses are not typically documented in teleneurology networks.

Nonetheless, there are inherent limitations in the interpretations of the retrospective study design. Data were not captured discretely in a prospective manner precluding a systematic recording of clinical presentation, risk factors and initial & final diagnostic impression. This can lead to incomplete data capture and inaccuracies in data abstraction. The stroke neurologist's clinical diagnosis was used as the reference standard to classify patients, with no alternative method to further validate this diagnosis. Additionally, teleconsultation is prone for observer bias, influencing the discharge diagnosis interpretation. Despite the effort to minimize the bias through independent reviewer analysis, diagnostic errors may still persist and the rates of misdiagnosed patients may be underestimated. Because we only analyzed clinical factors previously identified as predictive of stroke mimics and chameleons, we may have missed some important patient characteristics in this data set. Random measurement error and misclassification can lead to dilution bias and underestimation of the effects of the tested risk factors. Finally, the study period preceded guideline-supported thrombectomy which limits the generalizability to telestroke systems using a 24 h window.

Conclusion

We report high diagnostic accuracy of the Ochsner Telestroke Program in discriminating stroke/TIA and stroke mimics, with slight tendency towards over diagnosis of stroke. Female gender, younger age and lower NIHSS score were associated with misdiagnosis. Future studies should focus on refinement of diagnostic accuracy in these populations.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ochsner Health. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

RZ conceived the study and contributed to the study design. GV, DC, II, and HM contributed to acquisition of data. GS and SM contributed to study design and data aquisition. AM performed the statistical analysis. MP was involved in data analysis, data interpretation and drafting of the manuscript. RZ provided critical revision of the manuscript and important intellectual contribution in data analysis and interpretation. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Preclinical models of middle cerebral artery occlusion: new imaging approaches to a classic technique

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Stroke remains a major burden on patients, families, and healthcare professionals, despite major advances in prevention, acute treatment, and rehabilitation. Preclinical basic research can help to better define mechanisms contributing to stroke pathology, and identify therapeutic interventions that can decrease ischemic injury and improve outcomes. Animal models play an essential role in this process, and mouse models are particularly well-suited due to their genetic accessibility and relatively low cost. Here, we review the focal cerebral ischemia models with an emphasis on the middle cerebral artery occlusion technique, a "gold standard" in surgical ischemic stroke models. Also, we highlight several histologic, genetic, and *in vivo* imaging approaches, including mouse stroke MRI techniques, that have the potential to enhance the rigor of preclinical stroke evaluation. Together, these efforts will pave the way for clinical interventions that can mitigate the negative impact of this devastating disease.

KEYWORDS

ischemic stroke, middle cerebral artery occlusion, focal ischemia, rodent model, penumbra, core

Introduction

In the United States and worldwide, stroke is one of the leading causes of morbidity and mortality (1). Risk factors associated with stroke include age, hypertension, hyperlipidemia, cardiac disease, smoking, and diabetes (2–4). While many of these factors are modifiable, the risk and prevalence of stroke is expected to rise given the aging populations (2). In addition, there is a large cost burden associated with stroke, with direct medical costs estimated to be $17.9 billion, and up to $33.9 billion when factoring in indirect costs (1).

Strokes can be categorized as either ischemic or hemorrhagic, constituting 87 and 13% of strokes, respectively (1). Most ischemic strokes are a result of acute vessel occlusion from a thrombotic and/or embolic event, which causes transient or permanent hypoperfusion. Hypoperfusion can have varying effects; the magnitude of injury is determined by the degree to which the territory is reliant on perfusion from the occluded vessel, the duration of ischemia, and the metabolic demands of the tissue and its relative resistance to insult. First, there are regions with *benign oligemia*, in which perfusion is decreased but the functional and structural integrity of the brain are preserved. Second, there is a region of *penumbra* that is considered "at-risk" tissue, characterized by a loss of function without permanent structural damage. Therapeutic interventions aim to save these regions from devolving into infarct *core*. The ischemic *core* is the region where irreversible damage has occurred, and tissue is not salvageable.

Fundamental research is warranted to optimize management and explore new therapeutic interventions, and relevant animal models are mandatory to evaluate novel therapeutic strategies. Here, we review the middle cerebral artery occlusion (MCAo) techniques that are widely used in stroke research in rodents. We also highlight newly emerging approaches for *in vivo* imaging and staining that have the potential to provide more nuanced insights into the pathophysiology of stroke, as well as serve as indices for testing the effects of putative therapies for this devastating disease.

Rodent models of focal ischemia

Clinically, the most common site of ischemia occurs within the middle cerebral artery (MCA) territory, therefore MCA occlusion (MCAo) is a popular technique for experimentally-induced injury (5). There are a number of different rodent models for MCAo, each with its own advantages, disadvantages and limitations (summarized in Table 1).

Proximal middle cerebral artery occlusion

The classic proximal MCAo model was initially developed by Koizumi et al. in rats, and it features the use of an intraluminal filament to obstruct blood flow to induce focal brain ischemia (Figure 1) (6). This model mimics a *large vessel occlusion* stroke as it occurs in humans, and the duration of ischemia is easily controllable allowing for adequate control of stroke parameters. Of note, flow through the ICA is not re-established in this model as it must be tied off for hemostasis, and reperfusion of the MCA territory occurs via collateral flow through the circle of Willis after removal of the filament. The Longa method involves slight variations to Koizumi's method in order to reestablish flow through the ICA at the end of the procedure (7). In the Longa method, an ECA stump is used for filament insertion instead of the CCA, therefore on the removal of the filament, the ECA is tied off for hemostasis and flow through the CCA, and the ICA is re-established. Comparisons between these two models in mice show this leads to increased reperfusion after filament removal compared to the Koizumi technique. Interestingly, the Longa technique leads to a more robust inflammatory response than the Koizumi method as measured by leukocyte-endothelial interactions post-reperfusion (13). There is mixed data regarding whether there are significant differences in lesion volume or survival rates between the two techniques in mice (13, 14). A comparison done in rats showed the models led to similar infarct volume, mortality rate, and weight loss. However, the study did find the different models led to differences in interleukin-1B and corticosterone regulation (15) and a follow-up study showed only the Longa method led to a measurable increased memory deficit (16). There is a newer alternative approach that avoids ECA ligation or permanent occlusion through repair of the CCA arteriotomy at the end of the procedure through the use of fibrinogen and thrombin products, and this may decrease the infarct-size coefficient-of-variation (17). These models can easily be performed in either mice or rats (18, 19).

MCAo via these anterior cervical approaches to the CCA or ECA for filament insertion avoids some of the intracranial manipulations that may skew results, as opposed to other models that require craniotomies. Importantly, even if the ipsilateral cervical carotid circulation is permanently occluded, MCA reperfusion occurs after the removal of the filament. This is due to the redundant supply to the ipsilateral MCA through a robust circle of Willis. The proportion of the hemisphere that is infarcted is similar in mice and rats, and is dependent on the duration of ischemia, which is usually 30–90 min (18). Ultimately, these methods have the advantage that they allow for the study of transient ischemia and the effects of reperfusion.

Distal middle cerebral artery occlusion

The first model describing the ligation of the MCA using an open craniectomy technique occurred in 1975 (20). Either permanent or transient MCA occlusion can be obtained. Commonly, permanent MCA occlusion is obtained via electrocauterization of the artery. Transient occlusion can be accomplished by the application of ligatures or microclips that can be removed to allow for reperfusion (8). The occlusion of the proximal MCA produces ischemic damage that is seen in the cortex of the frontal lobe and the lateral part of the caudate nucleus with some involvement of the sensory and auditory cortex. The more proximal the occlusion site of the MCA is, the larger and more consistent the infarct will be (9, 21). Using more distal MCA occlusions, there is less damage to the hypothalamus, hippocampus, and midbrain (22).

A successful occlusion of the MCA can be readily visualized with this technique, and the ability to induce transient or permanent ischemia provides flexibility. This technique does involve direct manipulation of and exposure of brain tissue, which makes the model less like the human disease. This manipulation can induce intracranial inflammation that could cause pathophysiologic responses distinct from stroke and could impact intracranial pressure and blood–brain barrier function. Nevertheless, confining ischemic injury to the neocortical areas is often considered a significant experimental advantage. Norat et al. used distal MCAo to measure stroke improvement after intraarterial transplantation of the mitochondria (23).

Localized application of thrombin

As an alternative to mechanical ischemia, there are techniques that use pharmacologic means to induce ischemia and thrombogenesis that have been utilized in rodent models. The advantage of these

TABLE 1 Animal models of focal ischemia.

Models of focal ischemia	Technique	Advantages	Disadvantages	References
MCAo via filament	Filament inserted into vessel to cause occlusion. Approach is via an anterior cervical to expose the common carotid. Filament is advanced through an arteriotomy in the CCA to occlude the MCA origin.	High reproducibility. Can be permanent or transient. Does not require craniotomy.	The occlusion of the MCA is not visualized. Area of infarct can be variable depending on blood vessel anatomy.	(6, 7)
MCAo via cranial window	Coagulation or clipping of MCA branch. Approach is via a craniotomy over the MCA.	Successful MCAo can be visualized. Can be used for transient or permanent ischemia.	Technically challenging procedure. Invasive craniectomy	(8, 9)
Thrombin injection model	Intraluminal microinjection of thrombin. Approach is via a craniotomy over the MCA.	Responds well to tPA. Activates inflammatory cascades.	Requires craniectomy. Doppler laser measurement of blood flow might be needed to assess for successful stroke.	(10)
Photothrombosis model	Systemic injection of photosensitive dye such as Rose Bengal or erythrosine B combined with focal photoactivation to induce thrombosis.	High accuracy of ischemic area using stereotactic coordinates to target the radiating light.	Can cause early vasogenic edema that is uncharacteristic in human stroke. Invasive Craniectomy.	(11, 12)

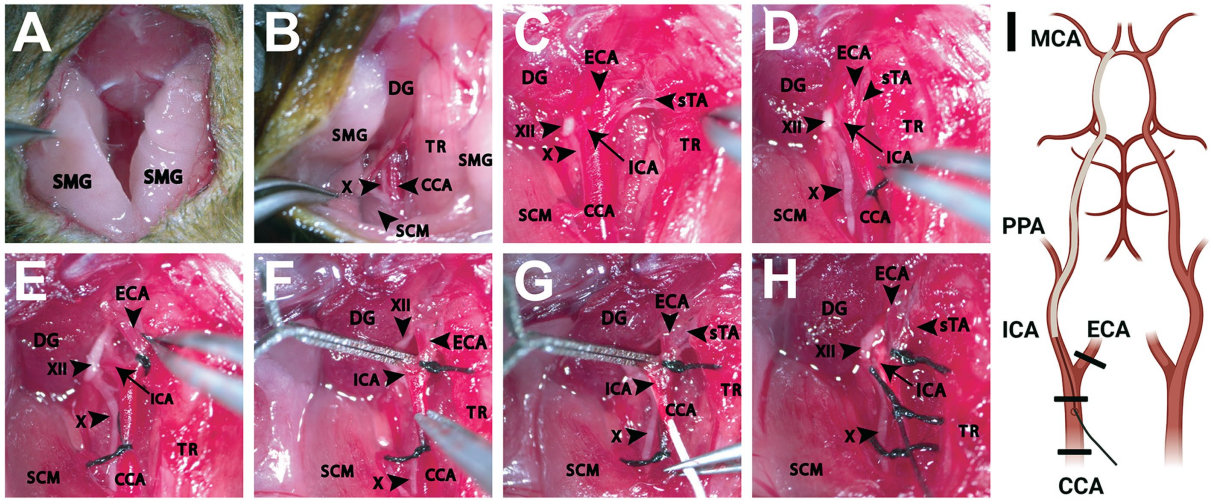

FIGURE 1
Dissection of the ventral neck region for intraluminal filament occlusion of the proximal middle cerebral artery. **(A)** Initial cervical incision made exposing the SMGs bilaterally. **(B)** Following retraction of the PGs and further blunt dissection, exposure of underlying anatomical structures is achieved. Adequate visualization of adjacent muscular landmarks including the SCM and DG aid in locating the CCA, which is often situated inferiorly to these structures. **(C)** Enhanced magnification and careful dissection reveal the CCA and its branches (ICA, ECA, sTA) as well as adjacent cranial nerves (X, XII). The TR can be retracted further medially as needed to better establish the surgical plane. **(D)** The CCA is then ligated (6–0, silk) with care being taken to avoid capturing the vagus nerve running inferolateral to the CCA. **(E)** A second ligation (6–0, silk) is performed around the ECA, inferior to the branch point of the sTA. **(F)** A temporary vessel clamp is then placed on the ICA, being careful to avoid the hypoglossal nerve running adjacent to the artery. Next, an arteriotomy is performed and any bleeding is addressed appropriately. **(G)** Once hemodynamic control is ensured, a silicone monofilament is then placed into the arteriotomy site and gently advanced toward the ICA branchpoint. **(H)** At this time, the temporary vessel clamp is removed, and the monofilament is advanced further into the ICA roughly 10mm until the ICA-MCA branchpoint is reached. Care should be taken to not force the monofilament once met with resistance. An additional suture (6–0, silk) is utilized to secure and prevent retropulsion of the monofilament. **(I)** A schematic shows the relevant anatomy from a ventral view with the filament inserted into the right ICA to occlude the origin of the MCA vessel. Thicker black lines represent the location of the suture ties (Created with BioRender.com). CCA, common carotid artery; DG, digastric muscle; ECA, external carotid artery; ICA, internal carotid artery; MCA, middle cerebral artery; PPA, pterygopalatine artery; SCM, sternocleidomastoid muscle; SMG, submandibular gland; sTA, superior thyroid artery; TR, trachea; X, vagus nerve; XII, hypoglossal nerve.

models is the ability to study thromboembolic mechanisms and clot dynamics, and evaluate potential means of intervention to address these stroke mechanisms.

The thrombin model entails local injections of thrombin directly into the MCA of a mouse (10, 24). Thrombin, normally activated via the coagulation cascade in response to endothelial blood vessel injury,

marks the initiation of secondary hemostasis. Thrombin catalyzes the polymerization of fibrinogen to fibrin, yielding a stable platelet-fibrin thrombus. Further structural stability is provided by factor XIIIa, which, activated by thrombin, promotes fibrin cross-linking and ultimately clot formation (25). By artificially inducing a thrombus, this model produces an occlusion that mimics a thromboembolic stroke. Applying the peptide endothelin-1 (ET-1) to blood vessels also causes strong and long-lasting vasoconstriction and hypoxia, which can block blood flow and lead to downstream ischemia. Furthermore, injecting ET-1 directly into brain tissue can induce prolonged focal ischemia (26). However, it should be noted that the particular type of injury caused by ET-1 is due to a distinct mechanism of constriction, rather than thrombosis or embolism, which are the main topics of this review.

The thrombin model procedure begins with a craniectomy and exposure of the right MCA for direct injection. If desired, IV-tPA can be administered through a tail vein catheter to induce thrombolysis and emulate vessel reperfusion (10, 24). A blood clot is considered successful if a 60% or more drop in CBF is observed via a laser Doppler flow probe. While a relatively simple procedure, there are some difficulties with this model. This includes spontaneous MCA recanalization, bleeding complications, and an inaccessible MCA bifurcation site. Additionally, upon further analysis of clot composition, it was found that clots contained primarily polymerized fibrin and a low number of cells and platelets. This is in contrast to humans in which clots consist of platelet/fibrin accumulation, linear neutrophil/monocyte deposition, and erythrocyte-rich accumulation (25).

There are drawbacks to these models, including the need to perform a craniotomy. In addition, there may be off-target effects. Otherwise, this is a useful model for assessing thrombolytic agents and their effectiveness in reducing infarction size in animals.

Photothrombotic stroke model

The photothrombosis model involves using photo-oxidation to induce an infarct based on the interaction of an organic dye with light to facilitate platelet aggregation. The technique was first described in by Rosenblum and El-Sabban (27) and was later modified in 1985 by Watson et al. (11) Watson and colleagues introduced a photosensitive dye called Rose Bengal, which can be injected intraperitoneally or intravascularly. Upon illumination, the dye is activated and generates free radicals causing endothelial damage that leads to platelet activation and a thrombus formation (28). By using specific coordinates to guide irradiation, a researcher can determine a specific area in which to induce ischemia.

The benefit of this model is its ability to target accurate regions of interest using stereotactic coordinates. This results in the reproducibility of lesions and low mortality rates. Another unique advantage is that photothrombosis has been adapted to be applied in live rodents while they are awake and freely moving. In this model, the bone in the region of interest is thinned until the cortical vessels are visible and a cranial window is made and a head-mounted miniature stage is placed. Injury is induced using illumination through an optical fiber combined with an aspheric lens to target the region of interest. A lesion can be induced in 15 min. Combining a high spatiotemporal resolution imager with the head stage allows for real-time CBF imaging and analysis during the process of infarction (29).

Unfortunately, photothrombotic injury differs from a stroke in humans in that it involves a relatively large number of vessels in the illuminated area. This is in contrast to human stroke where ischemia often is a result of interrupted blood flow of a single terminal artery. Photocoagulation insult also causes severe blood vessel damage and substantial early vasogenic edema that is not generally characteristic of human stroke (28). However, there is a newer adaptation of this method that uses artery-targeted photothrombosis, which confines illumination to desired arterial branches and minimizes off-target damage to neighboring tissue (30). Finally, classically, photothrombosis-mediated clots are highly refractory to tPA-mediated lytic treatment, presumably due to the predominance of platelets and fibrin-poor clot composition. Recent work has been done to circumvent this by creating a model that combines rose bengal with thrombin to produce fibrin-enriched and tPA-sensitive clots (31).

Optimizing stroke models for enhanced reproducibility

A widely held perspective on neuroprotective stroke research points out that treatments that are effective in animals often fail to show similar success in humans (32). In fact, hundreds of potential stroke treatments entered clinical trials based on promising preclinical data, but only recanalization therapies were successful (5). Notably, thrombolysis with tissue plasminogen activator (tPA), the only clinically effective pharmacological treatment of acute ischemic stroke, was first demonstrated and evaluated in an experimental model of stroke (33). The Stroke Preclinical Assessment Network (SPAN), a large research project funded by the National Institutes of Health, was developed to address the need for a better understanding of stroke research variability in rodent models (5).

In a significant advancement, a recent study from the 6 SPAN laboratories examined the heterogeneity caused by differences in biological and experimental model variables, as well as their impact on the MCAo performance (34). Factors such as age, time of day when MCAo was performed, choice of filament, maintaining anesthesia during occlusion, cerebral blood flow monitoring, and circadian stage of the animal at the time of MCAo were considered. Embracing this biological and methodological heterogeneity could better inform clinical trials, thereby enhancing the predictive value of preclinical testing. Furthermore, understanding the sources of heterogeneity and their effects on study performance may help refine study design and statistical modeling for future multicenter preclinical trials (17, 34, 35).

Candelario-Jalil and Paul have also discussed recent findings that emphasize the notable differences in stroke outcomes between young and aged animals, and how major comorbid conditions, such as hypertension, diabetes, obesity, and hyperlipidemia, significantly increase the brain's vulnerability to ischemic damage, leading to worse functional outcomes. The review indicates that incorporating animal models of aging and comorbidities during the initial stages of drug development would aid in identifying neuroprotective strategies with a higher chance of success in stroke clinical trials (36). Also, there are big differences between rodent and larger animal stroke models, and using larger animals may resemble human strokes more closely. However, these models come with practical issues and ethical concerns that limit their use in research. The debate continues about

whether using these models can help improve science and create treatments for human strokes (37).

Among the previously identified common factors, the failure to translate preclinical studies in rodents to clinical settings can be attributed to insufficient statistical power, poor experimental design, publication bias, lack of randomization and blinding in many preclinical studies, and an unrealistic therapeutic time window. Numerous recent articles and commentaries have addressed the primary causes of this translational roadblock in stroke research and proposed potential solutions to overcome it (38–42).

One crucial aspect of preclinical stroke research reproducibility involves monitoring ischemic injury and imaging the infarction. Advanced stroke imaging techniques, such as magnetic resonance imaging, serve as indispensable tools that allow researchers to visualize, map, and track the pathological changes in the brain post-stroke. These methods offer high-resolution images of brain structures and facilitate the identification and quantification of stroke lesions and related tissue damage, encompassing alterations in blood flow, edema, inflammation, and cellular injury. This data fosters a more precise comprehension of stroke processes, including the mechanisms behind stroke injury and repair. Consequently, the availability of advanced imaging methods significantly influences the reproducibility of targeted stroke treatments.

Stroke imaging and infarct analysis in animal models

Preclinical stroke research heavily depends on imaging and quantification methods to accurately determine infarct and penumbra volumes. The imaging approaches include radiological methods such as computed tomography (CT), positron emission tomography (PET), and Magnetic Resonance imaging (MRI) (43). The optical techniques involve Laser Speckle Contrast Imaging (LSCI) technology, Photoacoustic Imaging (PAI), and 2-photon laser scanning microscopy (2PLSM) (44). The traditional histological methods are also enhanced by new advancements in genetic and immunohistochemical strategies.

In vivo imaging of ischemic stroke and cerebrovascular disease

A variety of sensitive and specific radiology imaging techniques that are used for diagnostic purposes in patients are also available for imaging of the rodent brain. In addition to CT, MRI is particularly well suited for imaging stroke pathology and several optimized sequences have been established which can be used if the proper small animal scanners are available (43, 45).

CT is a quick, effective way to evaluate the presence of hemorrhage within the brain and can give an estimate of infarct territory in a subacute setting, but CT is inferior to MRI in its ability to identify infarct in the acute phase. MRI is the gold standard for assessing perfusion and ischemic injury in humans as it has the highest sensitivity and resolution. It is the modality that can most accurately predict regions at risk of ischemic injury and assess blood flow. Vessel imaging can be employed to confirm the location of large vessel occlusions, for example via magnetic resonance angiogram (MRA) (46), readily detecting MCA occlusion in the mouse brain (Figure 2A). On the other hand, diffusion-weighted imaging (DWI) and computed apparent diffusion coefficient (ADC) maps show regions of restricted diffusion, which estimates the core (Figures 2B–D) (47). MRI can be thus used to estimate the size of an infarct and can do so in the acute as well as subacute phase (48). Specifically, diffusion-weighted imaging (DWI) provides the ability to differentiate cytotoxic edema from vasogenic edema, something that CT and other MRI sequences including the T2-weighted MRI are unable to accomplish and limits their utility to distinguish ischemic tissue from edema (49). DWI also helps with establishing the age of an infarct as diffuse characteristics evolve with time from high signal to normal signal and finally to low signal (50). Diffusion imaging combined with perfusion imaging has the potential to identify ischemic changes to brain tissue that are reversible with the intervention (51).

Further, Perfusion-Weighted Imaging (PWI) MRI can identify areas with decreased perfusion in order to estimate tissue at risk of ischemia, the penumbra. The more sensitive perfusion technique to measure penumbra requires contrast and is known as the dynamic susceptibility contrast-enhanced (DSC) MR perfusion (52). This is a contrasted T1 sequence that measures relative cerebral blood volume, relative cerebral blood flow and mean transit time. It is more sensitive than Arterial Spin-Labelling (ASL) MR perfusion which is a technique that capitalizes on the ability of MRI to magnetically label arterial blood so that it essentially creates a tracer to measure cerebral blood flow (53). Work has been done to develop these protocols for use in rodents (54). Unlike CT imaging, for which acquisition can take seconds, MRI acquisition takes minutes per sequence, and therefore, animals must be completely immobilized to perform this imaging in order to obtain adequate resolution (55). This requires general anesthesia, and as mentioned above, this has the potential to alter biological processes and confound outcomes.

Optical imaging technologies are common in academic research but until recently only a few have been translated into the clinic. Among the wide-field imaging techniques, Laser Speckle Contrast Imaging (LSCI) is nevertheless gaining popularity as a versatile flow imaging technique based on the analysis of light speckle pattern fluctuations, which allows the analysis of tissue perfusion with blood (56). In mice, LSCI offers the ability to measure relative cerebral blood flow through the intact skull. LSCI can monitor the middle cerebral artery occlusion and reperfusion stroke model (57). LSCI technology compares favorably to Laser Doppler Flowmetry (LDF) which used to be a prevalent method to monitor real-time cortical perfusion in rodents. This technique measures the Doppler effect, analyzing wavelength shifts of the reflected light as it scatters off moving cells in blood vessels, thereby quantifying the rate of cerebral blood flow (58, 59). These measurements are evidently of paramount importance in ensuring the best possible reproducibility of research in ischemic stroke.

Wide-field fluorescence imaging also enables fundamental insights into functional recovery from ischemic injury. This technique, sometimes called Wide-field Functional Optical Imaging (WFOI), is employed in rodent models of stroke, primarily in the mouse. WFOI requires minimally invasive surgery to expose the skull prior to imaging, and a small Plexiglas window attached to the intact skull for chronic imaging (60). Following a stroke, functional MRI studies in humans have shown that local brain circuits lost to infarction remap to the peri-infarct cortex and are more spatially focused in patients exhibiting more complete recovery (61). In rodents, remodeling of

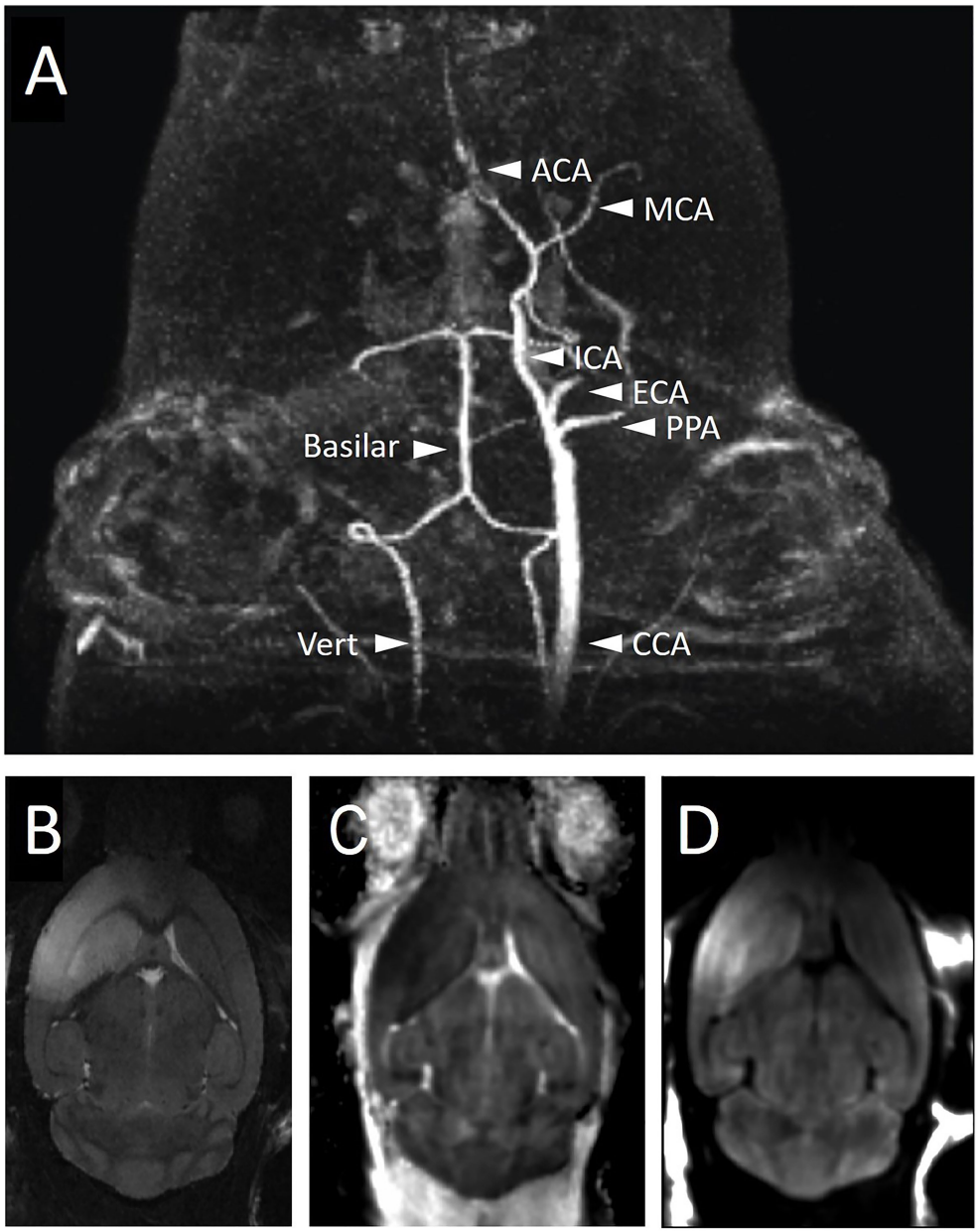

FIGURE 2
Imaging of mouse brain during and after right-sided MCAo with magnetic resonance imaging. **(A)** MRA during filament occlusion shows the absence of right-sided carotid circulation while the filament is in place. The intact posterior circulation and the left-sided carotid circulation are labeled. Mice were subjected to MCAo via filament for 1h followed by filament removal and then 24h of recovery time prior to the acquisition of T2 **(B)**, ADC **(C)**, and DWI **(D)** MRI sequences to visualize the infarct region. The infarct region in the right cortex and striatum is bright on T2 **(B)** and DWI **(D)** sequences and dark on ADC **(C)**. ACA, anterior cerebral artery; CCA, common carotid artery; ECA, external carotid artery; ICA, internal carotid artery; MCA, middle cerebral artery; PPA, pterygopalatine artery; Vert, vertebral artery.

local circuitry in the periinfarct cortex correlates temporally with the behavioral recovery (62). Thus, information learned from functional WFOI neuroimaging can be used to inform interventional strategies designed to affect plasticity mechanisms after injury (63).

Photoacoustic Imaging (PAI) is a new imaging technique that monitors the anatomical, molecular, and metabolic features of biological tissues by identifying their optical absorption properties, using sound as a readout. The device sends non-harmful laser pulses into tissues, where some of the energy is absorbed and changed into heat, causing temporary expansion and ultrasound emission. Ultrasound waves are picked up by sensors and used to create images. PAI is very flexible and can examine the same process at different scales from single cells to entire organs. With hemoglobin as a natural marker, PAI can image blood vessels in the brain without any added labels and track blood-related properties such as oxygen levels and flow. This makes PAI very helpful when investigating changes in blood flow and blood oxygen supply caused by the stroke (64). The potential of this technique was demonstrated by tracking the vascular and metabolic responses in an awake mouse brain during acute, subacute, and chronic stages of ischemic stroke. A side-by-side comparison of

the injured (ipsilateral) and control (contralateral) cortices revealed that, despite the early recovery of cerebral blood flow and increased microvessel density, a persistent deficit in cerebral oxygen metabolism was observed throughout the chronic stage in the injured cortex, leading to infarction. This advanced functional-metabolic imaging technique presents new possibilities for studying the long-term progression and treatment outcomes of neurovascular diseases (65).

Microscopic imaging using two-photon laser scanning microscopy (2PLSM) provides superior spatial and temporal resolution of specific pathological events associated with stroke-induced damage (44, 66). This technology utilizes pulsed, tunable infrared lasers, focused to about 1 cubic micron volume using high numerical aperture objectives and fast scanners (67). The resulting high photon density facilitates near-simultaneous absorption of two infrared photons in the focal volume, allowing the excitation and detection of visible dyes including green and red fluorescent proteins deep in the tissue (68). These approaches usually employ either a thinned skull or a glass-covered cranial window to perform *in vivo* imaging up to 500 microns deep. In combination with genetically encoded indicators of calcium or glutamate (69–71), 2PLSM has revealed a wealth of information about ionic shifts that are triggered during the cortical spreading depolarizations commonly seen in ischemic strokes (72, 73). Specifically, calcium transients in the neurovascular unit comprising neurons and astrocytes (74, 75), and more recently also microglia (76), have been characterized following stroke. Calcium overload plays a critical role in the pathophysiology of ischemic injury, leading to a cascade of detrimental effects including cell death. Further investigation of these processes is therefore highly warranted.

Histological detection and evaluation of ischemic damage in the infarcted area

The size of an infarct has been traditionally estimated using histological techniques. There are many different staining techniques used to assess the extent of ischemic injury, each with benefits and drawbacks. Common staining methods that are frequently used in stroke experiments include 2,3,5-triphenyltetrazolium chloride (TTC) and Fluoro-Jade B, in addition to the other classic stains such as Nissl, Hematoxylin and Eosin (H&E) and Cresyl Violet (CV) (77). TTC staining continues to be a mainstay for visualizing stroke injury in rodent models (Figure 3A). However, drawbacks of TTC include that it must be done immediately on fresh tissue and it may not truly label irreversible cell death as it is a marker of mitochondrial dysfunction and tissue dehydrogenase activity; thus, it may overestimate cell death (79,

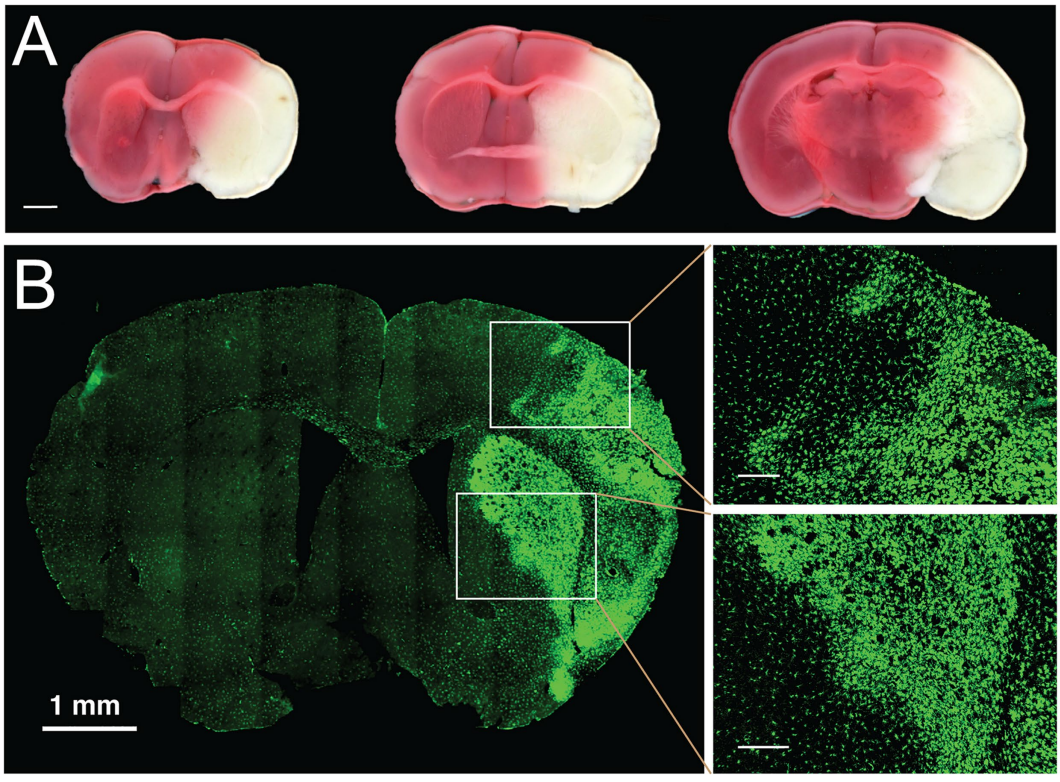

FIGURE 3
Histological and genetic cell lineage labeling of ischemic stroke injury. **(A)** Histological staining of live brain slices with TTC. Staining of freshly cut, 1-mm thick coronal brain slices with 2,3,5-Triphenyltetrazolium chloride (TTC) is commonly used to determine the size of the infarcted area in the brain. Three coronal planes are displayed from a brain with a permanently occluded middle cerebral artery and stained 24h after stroke induction. White areas delineate the infarcted tissue, red color indicates the tissue with normal mitochondrial activity. Scale bar, 1mm. **(B)** Genetic labeling of chronic infarction following focal ischemic stroke. Transient MCAo was performed in a transgenic mouse model expressing the Aif1-Dre allele and the RC::RLTG Dre/rox reporter (78). In this reporter system, Iba1-positive myeloid cells are robustly stained with antibodies against the lineage marker (tdTomato), shown in green. One week after transient occlusion, the labeling identifies the infarcted area by the morphological transformation of microglia and border macrophages. The panels on the right-side show in detail the morphological transition of myeloid cells at the border of chronic infarction in the cortex (right top) and in the striatum (right bottom). Scale bars in enlarged panels, 200μm.

80). An alternate method for staining is Fluoro-Jade B. This stain is an anionic dye that stains the soma and neurites of degenerating neurons, and it has been validated as a useful indicator in the acute cerebral ischemia (77). A drawback of Fluoro-Jade B is that the mechanism of labeling has not been elucidated, and it is unclear what underlying physiological process is indicated by staining. A disadvantage of both of these markers is that there is limited ability to define core versus penumbra and to perform colocalization experiments. There is a need for markers that more explicitly define the injury as apoptotic versus necrotic and allow co-labeling, for example, to characterize the immune response within and around the infarct.

Further insights into the pathology of ischemic brain injury and recovery are gained through cell fate mapping experiments with genetic labeling tools such as Cre, Dre, FLP, or other site-specific recombinases (78). Genetic labeling of immune cells can be particularly illuminating because these cell populations undergo a rapid and profound transformation in the infarcted area. For example, genetic labeling with the *Aif1-Dre* allele (similar to *Aif1-Cre* (81)) and the Dre/rox reporter line (78) robustly delineates the activation of the Iba1-positive myeloid cell population in the infarcted area after MCAo (Figure 3B). Further improvements in the resolution of cell fate mapping of ischemic injury will be achieved by dual recombinase-mediated approaches, whereby two gene promoters, and consequently two recombinases (e.g., Cre and Dre) identify specific cell types through intersectional or subtractive fate mapping with appropriately designed genetic reporters (82).

Immunohistochemistry is another versatile and informative method for characterizing infarct injury. Antibodies against activated caspases and caspase substrates provide some information about the nature of the injury as they indicate activation of the apoptotic cascade and can be used to indicate apoptotic cells. One such antibody is specific to a caspase-cleaved *fragment* of *actin*, known as *fractin* (83). This antibody marker is highly sensitive and specific to apoptotic cells and is able to label cell bodies as well as axons and dendrite of dying neurons. *Fractin* highlights apoptotic cells in the region of the penumbra 24 h after transient MCAo and can be used to estimate the size of the core and penumbra (Figure 4). Antibodies to caspase substrates, like *fractin*, can be used alongside other immunolabeling markers, for example, to examine the localization of immune cells around the infarct. A drawback of antibody labeling is that epitopes may be transient and once cell death has proceeded to necrosis, the epitopes will be degraded.

Conclusion

Rodent models of ischemic stroke appeal to researchers due to their ease of use and manipulability along with the ability to replicate experiments at economically reasonable costs. Middle cerebral artery occlusion remains the gold-standard approach for modeling cerebral vessel occlusion and recanalization. Selecting the right model for the experiment is a crucial step; when choosing a particular stroke model, factors to consider include desired infarct size and ability to reperfuse, as well as resultant penumbra: core ratios, behavioral deficits, inflammatory responses, and mortality rates.

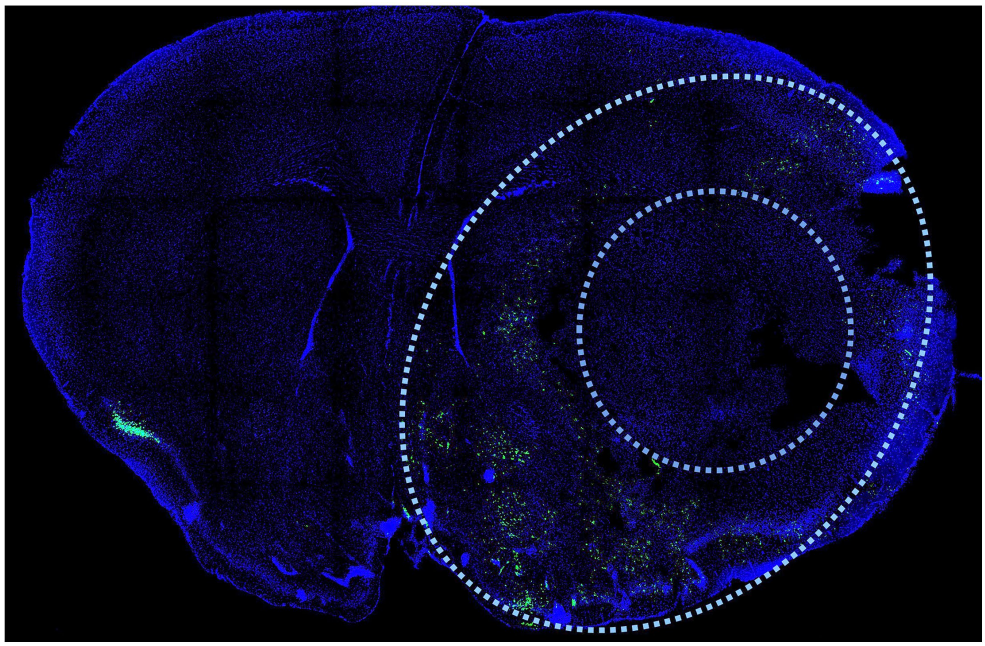

FIGURE 4
Immunodetection of cell death after MCAo. Antibodies against activated caspases and caspase substrates provide information about the nature of the injury as they indicate activation of the apoptotic cascade and can be used to indicate apoptotic cells in the penumbra region after stroke. One such antibody is specific to a caspase-cleaved fragment of actin, known as fractin. This antibody marker is highly sensitive and specific to apoptotic cells and is able to label cell bodies as well as axons and dendrite of dying neurons after stroke (83). Fractin (green) distinguishes the penumbra (outer limit defined by outer oval) from the necrotic core (inner circle) as it highlights apoptotic cells in the region of the penumbra 24h after transient MCAo. Coronal section prepared as described (83). DAPI (blue) is a stain that highlights nuclei.

There are significant limitations associated with the use of rodents for the study of stroke, including their distinct cerebral architecture, and variations in their thrombotic, inflammatory and cell death cascades compared to humans. However, advances in imaging in conjunction with immunohistochemical staining and the use of transgenic mouse models facilitates more pointed investigation, characterization, and interpretation of stroke processes. Regardless, interventions with promising results in rodents must be subject to further validation before assuming they will translate to success in human studies.

Author contributions

JS, SS, and PN: acquisition, analysis, or interpretation of data for the work, drafting the work or revising it critically for importance. KS, KK, LL, AW, and GM: acquisition and analysis. KY and PM: analysis and interpretation of data for the work. MK, MP, and RK: interpretation of data for the work. PT: analysis, interpretation of data, drafting the work or revising it critically for importance. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Imaging diagnosis of intracranial atherosclerosis stenosis-related large vessel occlusion before and during endovascular therapy

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It is becoming increasingly important to identify the type of stroke, especially the mechanism of occlusion, before and during its treatment. In the case of intracranial atherosclerotic stenosis-related large vessel occlusion, it is necessary to develop a treatment strategy that includes not only mechanical thrombectomy but also adjunctive therapies such as primary or rescue therapy (percutaneous angioplasty, intracranial/carotid stenting, local fibrinolysis) and perioperative antithrombotic therapy. However, in clinical practice we often encounter cases where it is difficult to identify the occlusive mechanism before endovascular treatment because of insufficient information in the minimal circumstances of the hyperacute phase of stroke. Here we focus on the imaging diagnosis before and during treatment of intracranial atherosclerotic stenosis-related large vessel occlusion with *in situ* thrombotic occlusion as the mechanism of thrombotic occlusion, based on previous reports. We describe the diagnosis of intracranial atherosclerotic stenosis-related large vessel occlusion from the perspectives of "thrombus imaging," "perfusion," and "occlusion margin."

KEYWORDS

imaging, diagnosis, intracranial atherosclerosis stenosis, large vessel occlusion, endovascular treatment

1. Introduction

Considering the extensively documented effectiveness and safety of mechanical thrombectomy (MT) in the management of acute ischemic stroke (AIS) due to intracranial large vessel occlusion (LVO) (1). It is increasingly crucial to prioritize the first-pass effect (2) and achieve successful endovascular treatment (EVT) without exacerbating intracranial hemorrhage, thus elevating the standard of care. The classification of stroke, particularly the occlusion mechanism, is becoming increasingly significant both preoperatively and during treatment. Embolic LVO is often the preferred indication for mechanical thrombectomy (MT) when an embolic source is discerned before the procedure. In cases of intracranial atherosclerotic stenosis (ICAS)-related LVO, it is imperative to design a treatment regimen that incorporates not only MT but also auxiliary therapies such as primary or rescue therapy (percutaneous angioplasty, intracranial/carotid stenting, and local fibrinolysis) and perioperative antithrombotic therapy. However, accurately determining the occlusion mechanism before EVT can prove challenging in clinical practice due to a dearth of information regarding the patient's medical history, pre-existing conditions, and comorbidities in the hyperacute stage of stroke. A full understanding of the situation is often not achieved until after EVT. Moreover, intracranial atherosclerotic stenosis (ICAS)-related large vessel occlusion (LVO) is more commonly observed in East Asia,

with a frequency of 15–25% (3, 4), as compared to Europe and the United States. Studies have demonstrated that ICAS-related LVO has a lower success rate of recanalization, a longer duration to successful recanalization, and worse outcomes as compared to embolic LVO (5, 6), underscoring the critical need to enhance the accuracy of etiologic diagnosis before initiating treatment.

This paper will focus on the imaging diagnosis of intracranial atherosclerotic stenosis (ICAS)-related large vessel occlusion (LVO) with *in situ* thrombotic occlusion as the occlusion mechanism, with reference to previous research. The diagnosis of ICAS-related LVO will be described from the perspectives of "thrombus imaging," "perfusion imaging," and "occlusion margin imaging."

2. Thrombus imaging

Recent research has shown that thrombi associated with cardioembolism have a greater proportion of fibrin compared to red blood cells, whereas those associated with intracranial atherosclerotic stenosis (ICAS)-related large vessel occlusion (LVO) have a higher concentration of red blood cells. The type of occlusive thrombus is closely linked to the mechanism of occlusion (7, 8). Non-contrast computed tomography (CT) and magnetic resonance imaging (MRI) are imaging modalities capable of visualizing the occlusive thrombi. In this context, we will discuss the "hyperdense middle cerebral artery (MCA) sign" detected on Non-contrast CT (NCCT) and the "susceptibility vessel sign (SVS)" detected on MRI scans.

2.1. Hyperdense MCA sign

The hyperdense middle cerebral artery (MCA) sign, as illustrated in Figure 1, has been observed to be associated with embolic large vessel occlusion (LVO) (9, 10). The appropriate threshold for detecting thrombus has been established as a Hounsfield Unit (HU) value of 51, which exceeds the standard value of 45 HU (11). Intracranial arterial wall calcification is a hallmark of atherosclerosis and has been correlated with lower rates of reperfusion following thrombectomy (12). A substudy within the MR CLEAN trial enrolled 344 patients, with 156 in the endovascular treatment (EVT) group and 188 in the control group, excluding individuals who were difficult to evaluate due to 3-mm ultraslice imaging or body motion. The results indicated significant differences in reperfusion rates and outcomes based on the type of intracranial carotid artery calcification. Patients with medial calcification, i.e., calcification within the occluded vessel, had better outcomes in the EVT group compared to the control group [adjusted common odds ratio (OR), 2.32; 95% confidence interval (CI), 1.23–4.39], while endovascular therapy did not have a significant impact on patients with intimal calcification (adjusted common OR, 0.82; 95% CI, 0.40–1.68) (12). In addition, a study on quantitative HU values measured the HU of intra-arterial radiation in 102 consecutive Chinese stroke patients who underwent multiphase CT angiography and EVT within 6 h of onset and examined the HU distal/proximal ratio to predict emboli The optimal cutoff was an HU ratio < 0.6 measured at 2 mm from the embolization site (area under the maximum curve = 0.87, sensitivity 96%, specificity 81%) (13).

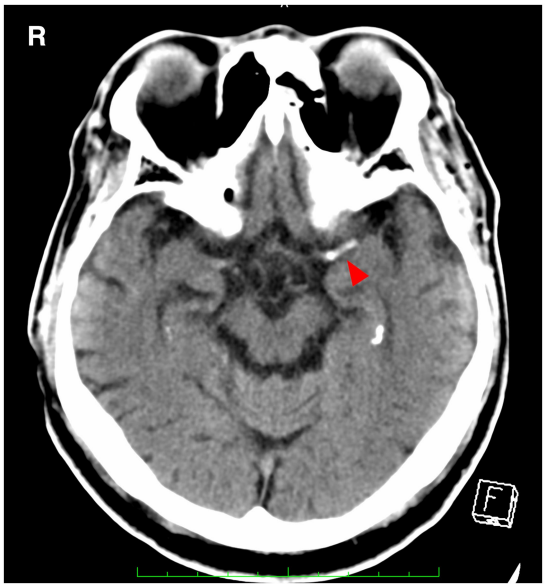

FIGURE 1
A hyperdense MCA sign (arrowhead) is seen in the left middle cerebral artery. MCA, middle cerebral artery.

2.2. Susceptibility vessel sign/2-layered susceptibility vessel sign

The concept of SVS has been classically defined as "a manifestation of low signal intensity in occluded thrombi on T2*-weighted Gradient Echo (GRE) images, caused by the magnetic susceptibility effect of deoxyhemoglobin in red blood cells" (14). The diagnostic value of SVS in ischemic stroke is widely acknowledged, with a prevalence of 77.5% in cases of cardioembolism (15). This is particularly evident in thrombi with high concentrations of red blood cells (known as "red thrombi") (16). Moreover, the presence of GRE-SVS has been associated with cardioembolism and spontaneous recanalization of occluded vessels (17, 18). The diameter of SVS has been independently linked to the likelihood of cardioembolism (adjusted odds ratio [OR], 1.97; 95% confidence interval [CI], 1.34–2.90; $p < 0.01$). However, it is important to note that a diagnosis of SVS does not necessarily indicate cardioembolism, as 25.5% of patients without cardioembolism also exhibit SVS (14). In cases of the middle cerebral artery (MCA) diagnosed *via* cerebral angiography, the sensitivity of SVS was higher than that of the hyperdense MCA sign NCCT (82% vs. 54%) (14). The concept of "2-layer SVS" (as shown in Figure 2) on 3-T MR T2*-weighted GRE has been reported in Japan, where 47.7% of 132 patients (72 men, mean age 74.5 years) were diagnosed with cardioembolism. The sensitivity of SVS for cardioembolism and large-artery atherosclerosis was not statistically significant (74.6% vs. 58.0%), but the sensitivity of 2-layer SVS alone was found to be significantly higher for cardioembolism (42.9%) than for large-artery atherosclerosis (2.9%; $p < 0.001$) (19). The specificity of 2-layer SVS for cardioembolism and the diagnostic ratios were 97.1 and 25.1%, respectively (42.0 and 2.1% for SVS). These findings may be attributed to the magnetic heterogeneity within the thrombus, suggesting a significant correlation between 2-layer SVS and higher thrombus weight and red blood cell components (19–21).

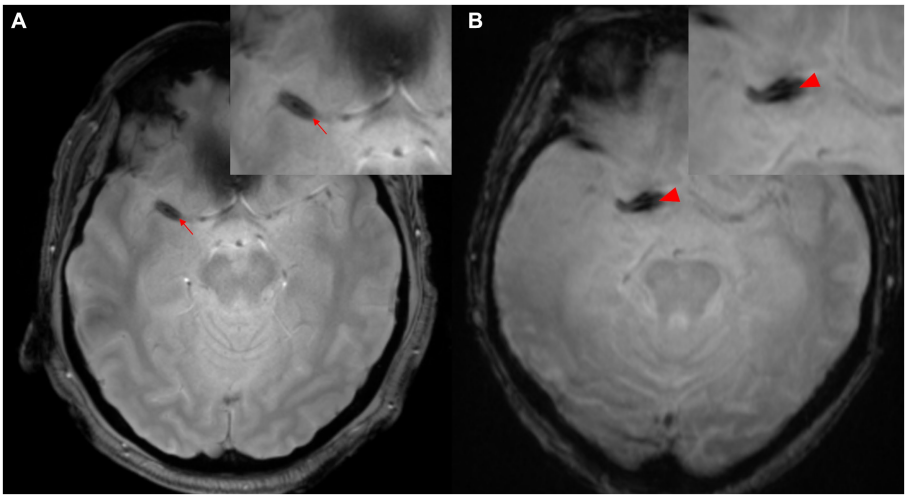

FIGURE 2
Two-layer SVS. **(A)** SVS (arrowhead) is seen distal to M1 of the right MCA. **(B)** SVS (arrowhead) is seen in the right internal carotid artery proximal to M1 segment of MCA. MCA, middle cerebral artery; SVS, susceptibility vessel sign.

3. Perfusion imaging

A substantial distinction exists in the cerebral perfusion status preceding the manifestation of LVO AIS between ICAS-LVO and embolic LVO. The former is characterized by a chronic reduction in cerebral perfusion due to severe ICAS and *in situ* thrombus occlusion, while the latter is distinguished by the absence of abnormal intracranial perfusion and the acute reduction in perfusion caused by emboli. The diagnostic differentiation between the two forms of LVO AIS may be facilitated by evaluating the cerebral perfusion status through MR perfusion or CT perfusion.

3.1. Perfusion profile (T_{max}, hypoperfusion intensity rate)

The EPITHET-DEFUSE study disclosed a correlation between cerebral perfusion imaging attributes and atrial fibrillation. Of the 124 patients who underwent perfusion imaging and were enrolled in DEFUSE (22) or EPITHET (23), 28 patients were designated as the "definite AF group," having been identified as having atrial fibrillation (AF) upon admission, while the remaining 96 were classified as the "NO AF group." The comparison of perfusion imaging profiles revealed that the definite AF group displayed elevated profiles relative to the NO AF group, as indicated by higher time to maximum concentration (T_{max}) values ($T_{max}>4$ s: 136 mL vs. 81 mL, $p<0.01$; $T_{max}>6$ s: 83 mL vs. 50 mL, $p<0.01$; $T_{max}>8$ s: 48 mL vs. 29 mL, $p=0.02$) (24). The DEFUSE 2 (25) trial quantified hypoperfusion intensity rate (HIR) as $T_{max}>10$ s divided by $T_{max}>6$ s, with a median HIR value of 0.4 being linked to the extent of collateral bleeding (26). In a recent single-center observational study, HIR $\leq$0.22 (OR, 22.5; 95% CI, 2.9–177.0; $p=0.003$) and cerebral blood volume index $\geq$0.9 (OR, 75.7; 95% CI, 5.8–994.0; $p<0.001$) were found to be associated with ICAS-related LVO and to potentially predict underlying ICAS prior to EVT (27); (Figure 3). Moreover, cortical collateral vessels are also helpful in the preoperative differentiation of stroke etiology. Cortical vessels are prominent on prominent cortical vessels on susceptibility-weighted imaging (PCV-SWI) in 30.3% of ICAS-related LVO patients, whereas PCV-SWI is positive in only 13.4% of ICAS-related LVO patients, and PCV-SWI helps diagnose stroke etiology (28). Previous studies have also reported that prominent cortical and/or medullary veins on SWI can indicate to neuro-interventionists that the cause of LVO is more likely cardioembolism rather than ICAS-related LVO (29). A summary of previous reports of useful PWI diagnostic markers in the diagnosis of ICAS is shown in Table 1.

4. Occlusion margin

In recent years various studies have documented the correlation between the characteristics of the proximal occluded vessel margin and LVO related to intracranial arteriosclerosis by utilizing initial cerebral angiography, which may prove valuable in the diagnosis of LVO related to intracranial arteriosclerosis prior to therapeutic intervention. In this context, here we focus on the features of the occluded vessel margin and recent relevant literature.

4.1. Significant fixed focal stenosis after reperfusion

"Fixed focal stenosis of substantial magnitude" has been proffered as a diagnostic hallmark of ICAS-related LVO (Figure 4) (34). This criterion is articulated as "a concentration of significant stenosis circumscribed to the site of occlusion," as observed on postoperative or definitive imaging of the MCA and was initially a term employed to characterize ICAS-related LVO. Although few systematic investigations have focused on fixed focal stenosis, a Korean registry utilizing stent retrievers noted an incidence of approximately 15–20% (35).

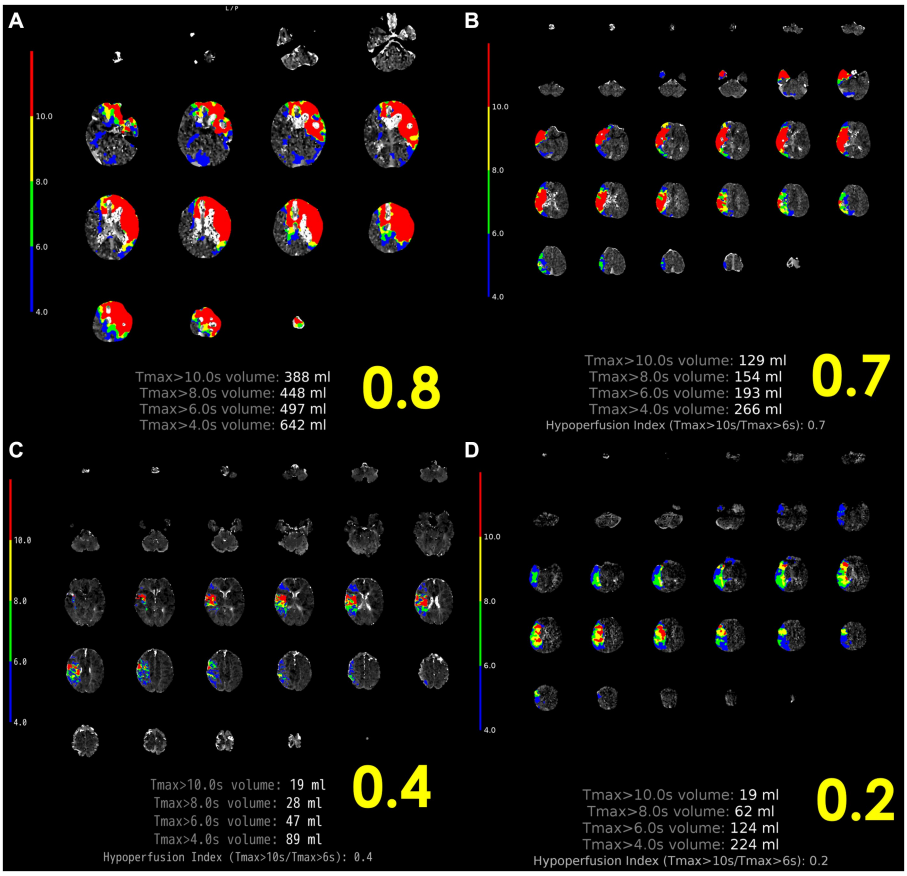

FIGURE 3
Representative case of HIR. **(A)** Left internal carotid artery occlusion, 2h after onset, HIR 0.8, rapid progression, cardiogenic cerebral embolism. **(B)** Proximal occlusion of the right MCA M1, 10h after last healthy control, HIR 0.7, rapid progression, other cerebral infarction (cerebral embolism with unknown embolic source). **(C)** Distal occlusion of right MCA M2, onset 4h, HIR 0.4, immediate progression, cardioembolism. **(D)** Proximal occlusion of the right MCA M1, HIR 0.2, slow progression, ICAS-related LVO. ICAS-related LVO, intracranial atherosclerotic stenosis-related large vessel occlusion; HIR, hypoperfusion intensity ratio; MCA, middle cerebral artery; SVS, susceptibility vessel sign.

TABLE 1 Summary of previous reports of useful perfusion imaging diagnostic markers in the diagnosis of ICAS.

Year	Study design	Number	Patients	Diagnostic pathophysiology	Diagnostic markers
2015	Meta-analysis (EPITHET-DEFUSE) (24)	175	AIS, NIHSS >4 in EPITHET and > 5 in DEFUSE	No AF	Tmax profile (>8, >6 s, >4 s) volume
2018	Observational study (30)	250	Anterior Circulation LVO AIS	ICAS-LVO	Tmax >4 s/Tmax >6 s ratio ≥ 2
2021	Observational study (31)	42	symptomatic ICAS cases	Infarct pattern; internal borderzone	Δ Tmax >4 s – Tmax >6 s
2022	Observational study (32)	143	Anterior Circulation LVO AIS	LAA	HIR <0.4
2022	Observational study (27)	47	LVO AIS	LVO underlying ICAS	HIR ≤ 0.22 CBV index ≥0.9

AF indicates atrial fibrillation; AIS, acute ischemic stroke; CBV, cerebral blood volume; EVT, endovascular therapy; HIR, hypoperfusion intensity ratio; ICAS, intracranial atherosclerotic stenosis; LVO, large vessel occlusion; NIHSS, National Institutes of Health Stroke Scale; Tmax, time to maximum concentration.

4.2. Branching-site and truncal-type occlusion

A multicenter observational study from Korea determined that occlusions of a truncal type were correlated with a lack of responsiveness to stent retrievers and were the fundamental cause of strokes (36). The subjects were patients undergoing MT for intracranial occlusions of the internal carotid artery, MCA, proximal MCA, intracranial vertebral artery, or basilar cerebral artery. The occlusions were classified as either branching-site

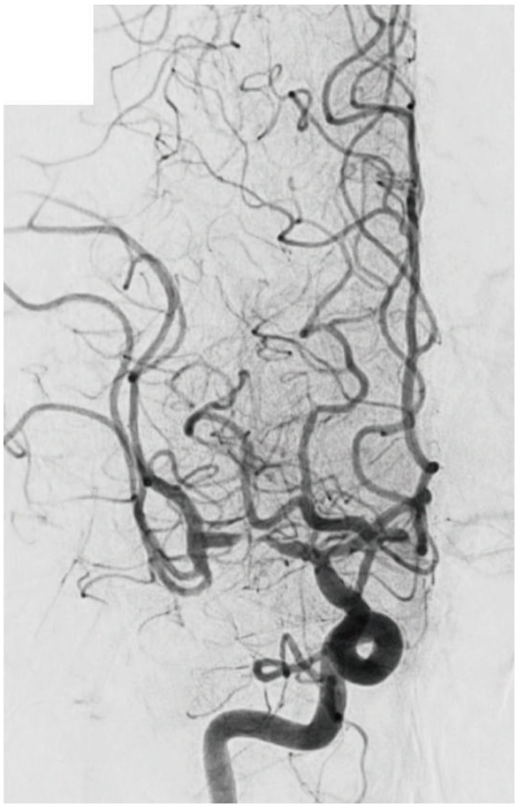

FIGURE 4
Significant fixed focal stenosis. A 59-year-old man was diagnosed with significant fixed focal stenosis. The right MCA M1 occlusion was recanalized in a single pass with a stent retriever, but the site of occlusion was found to have a fixed focal stenosis. MCA, middle cerebral artery.

occlusion or truncal-type occlusion. Branching-site occlusion was defined as at least one of the following three conditions (Figure 5); (1) anterior communicating artery collateral flow that could not proceed to the contralateral ICA or MCA because it involved the internal cerebral artery bifurcation site (T occlusion); (2) direct visualization of a Y-or T-shaped filling defect involving a bifurcation site (Y-or T-shaped clot); and (3) another branch could not be visualized or was only partially visualized when the retriever was deployed to a branch across the occlusion site. Truncal-type occlusion, on the other hand, was defined as all branches and bifurcations visible beyond the occluded vessel, including those observed at recanalization. After a comprehensive evaluation involving chest electrocardiogram, echocardiography, cardiac CT, and cervical vascular echocardiography, the patients were classified as having embolic or non-embolic LVO. Of the 259 patients (mean age 70.3 years; male/female ratio 132:127), 83.4% had embolic LVO. Multivariate analysis revealed that younger age, prior coronary artery disease, and truncal-type occlusion were independently linked to the absence of embolic LVO (OR, 9.07; 95% CI, 3.74–22.0). Furthermore, truncal-type occlusion was associated with a higher frequency of reocclusion and a longer time to recanalization during stent retriever treatment. In a subanalysis of this study, truncal-type occlusion was associated with 93% of ICAS-related LVO and 10% of embolic LVO ($p < 0.01$) (35), whereas branching-site occlusion was associated with 7% of ICAS-related LVO and 90% of embolic LVO. In a separate study among 115 LVO patients in China, truncal-type occlusion was present in 93% of ICAS-related LVO and 10% of embolic LVO, while branching-site occlusion was observed in 7% of ICAS-related LVO and 90% of embolic LVO, yielding a significant difference between the two LVO types ($p < 0.01$ for each). The area under the curve of

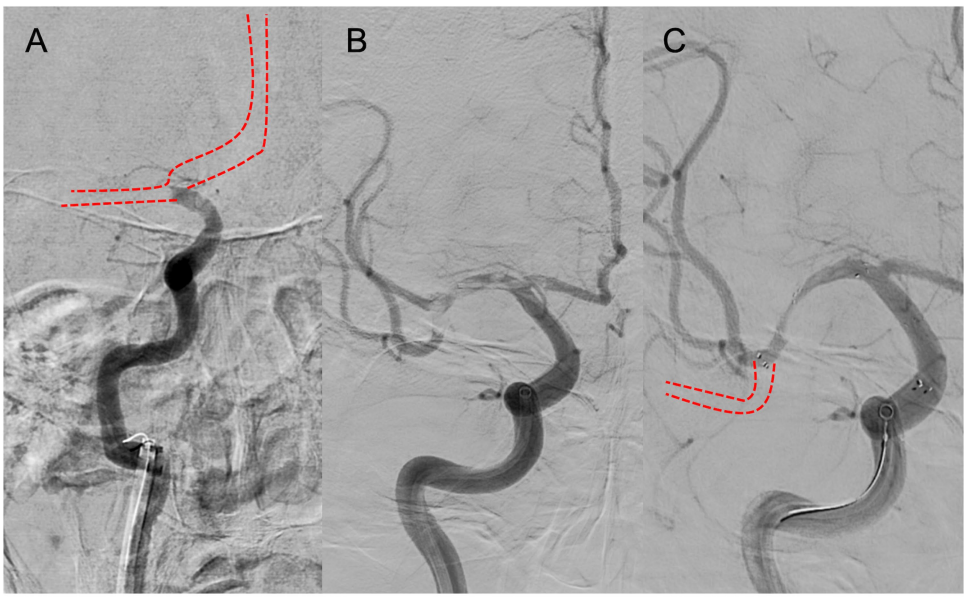

FIGURE 5
Branching-site occlusion. **(A)** Intracranial carotid artery occlusion without visualization of the anterior communicating artery (IC-T occlusion). **(B)** Y- or T-shaped visualization defect including vessel branches. **(C)** Partial or complete lack of visualization of vessel branches on angiography after stent retriever deployment.

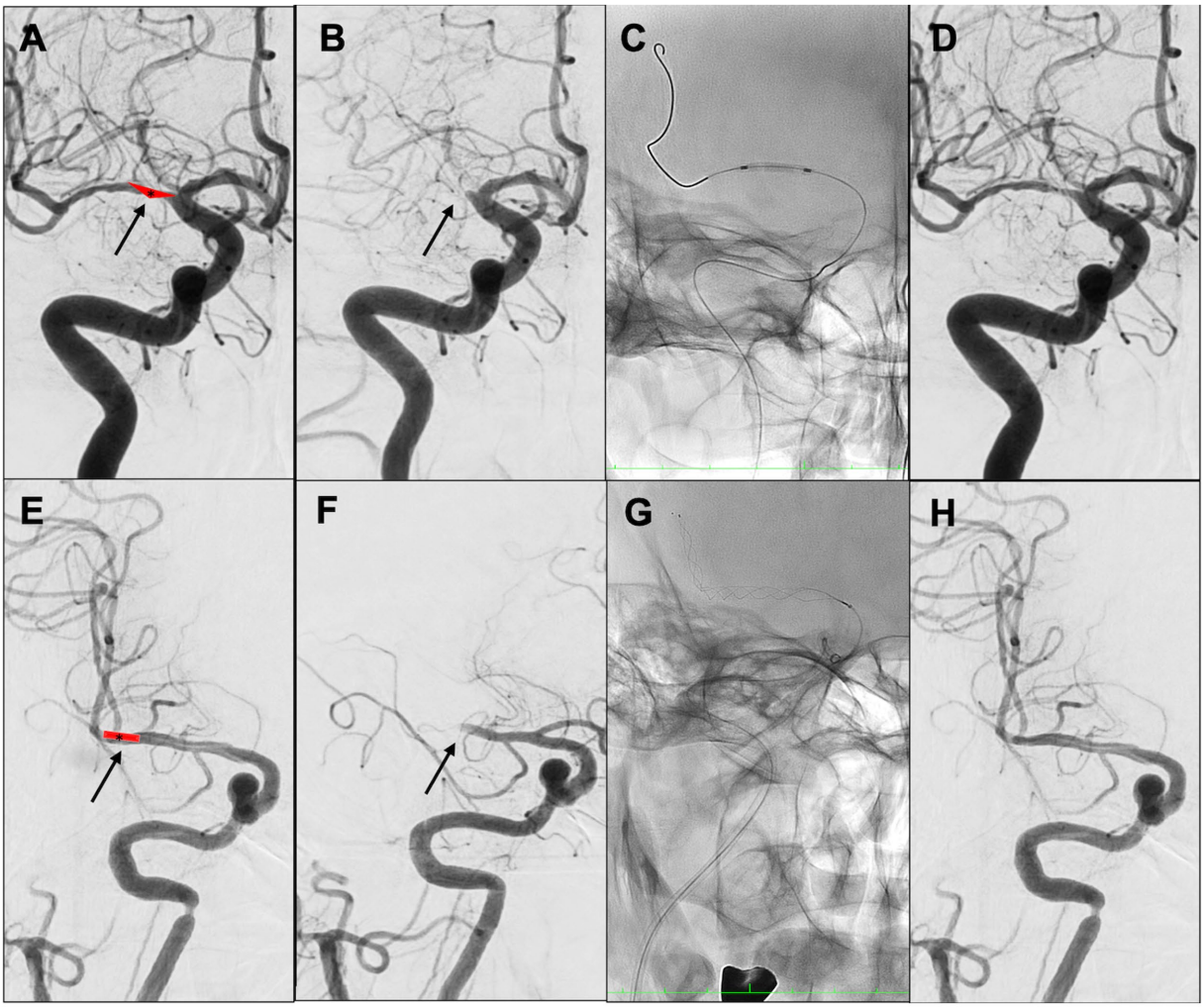

FIGURE 6
Representative cases of truncal-type occlusion/branching-site occlusion. **(A–D)** Truncal-type occlusion. **(E–H)** Branching-site occlusion. **(A)** Schema of *in situ* thrombus of right middle cerebral artery (MCA) M1 truncal type (asterisk). **(B)** Initial angiography shows occlusion of right MCA M1 (arrow). **(C)** Angioplasty. **(D)** Identification of residual stenosis in the right MCA M1 (ICAS-related LVO). **(E)** Embolic schema of the right MCA M1/M2 bifurcation (asterisk). **(F)** Initial angiography showed occlusion of right MCA M1 (arrow). **(G)** Stent retriever was deployed. **(H)** After retrieval of red thrombus, the bifurcation was found to be occluded. Angioplasty and stent retrieval were then performed.

ICAS-related LVO in truncal-type occlusion was 0.916, with the sensitivity of 92.86% and specificity of 90.41% (36). CT angiography can also assess truncal-type occlusion, and although it is not a direct predictor of pathogenesis, branching-site occlusion as determined by CT angiography has been reported to independently predict the success of recanalization with stent retrievers (OR, 8.20; 95% CI, 3.45–19.5) (37). Representative cases of truncal-type occlusion/branching-site occlusion are shown in Figure 6.

4.3. Jet-like appearance

Jet-like appearance on cerebral angiography is characterized by a tapered end of the occluded vessel (Figure 7). In a Chinese observational study of 164 cases of LVO, 20.7% presented with this distinctive trait. Patients with the jet-like appearance were determined to be younger (mean age 68 years compared with 62.7 years) and had fewer severe symptoms (as indicated by a lower National Institutes of Health Stroke Scale [NIHSS] score of 16.6 compared with 12.4) than those without this feature. Multivariate logistic regression analysis revealed that a jet-like appearance was independently correlated with ICAS-related LVO (OR, 180.813; 95% CI, 17.966–1819.733; $p < 0.001$). The diagnostic performance of the jet-like appearance for identifying ICAS-related LVO was determined to have the sensitivity of 96%, specificity of 78%, and accuracy of 83% (38).

4.4. "Tapered" or "non-tapered"

A Canadian study delineated two patient groups based on the occlusion location at the initial angiography and compared

their demographic characteristics. Of 131 participants, 31 (23.6%) were classified as having a tapered presentation, while 100 (76.3%) were in the non-tapered group (Figure 8). The tapered group delivered a lower NIHSS score (10 vs. 16, with a significance level of $p < 0.001$), higher Alberta Stroke Program Early CT Score (9 vs. 7, with a significance level of $p = 0.003$), higher immediate reocclusion rate (26.7% vs. 8.2%, with a significance level of $p = 0.025$), and a lower rate of complete recanalization (45.2% vs. 71.0%, with a significance level of $p = 0.028$). The tapered group was also more likely to have LVO associated with ICAS (54.8% vs. 18.0%, with a significance level of $p < 0.001$) and to present with truncal-type occlusions (76.9% vs. 31.1%, with a significance level of $p < 0.001$) (39).

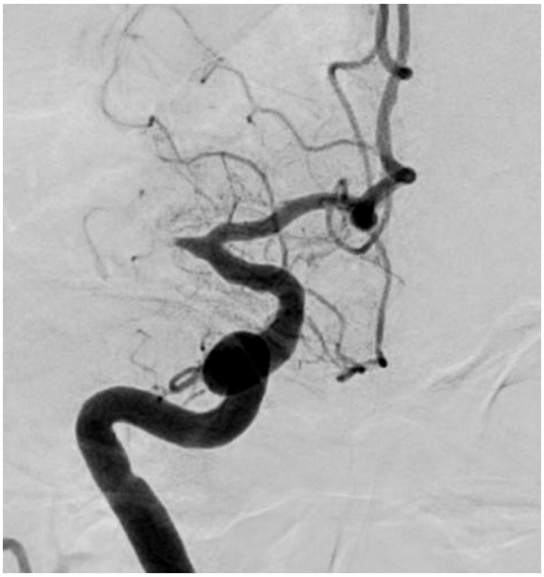

FIGURE 7
Jet-like appearance.

The benefits of identifying such occlusion margins through digital subtraction angiography are considerable, as they remain unaltered by therapeutic intervention and are thus useful in determining the causative mechanism of occlusion, even if complete recanalization of the affected vessel is not realized. Representative cases of "tapered" or "non-tapered" types are shown in Figure 8.

5. Conclusion

The diagnosis of ICAS-related LVO is informed by three key elements: "thrombus imaging," "perfusion," and "occlusion margin." Preoperative assessment of the occlusion mechanism considers not only imaging results but also a comprehensive examination of these three elements along with factors indicative of ICAS-related LVO, such as progressive symptoms, low NIHSS scores, male sex, history of hypercholesterolemia and smoking, absence of AF, and posterior circulation strokes (33, 40, 41). It is imperative that a diagnosis is based on a holistic evaluation of these three elements as well as factors associated with ICAS-related LVO, including the absence of evidence of embolic LVO and posterior circulation stroke. In

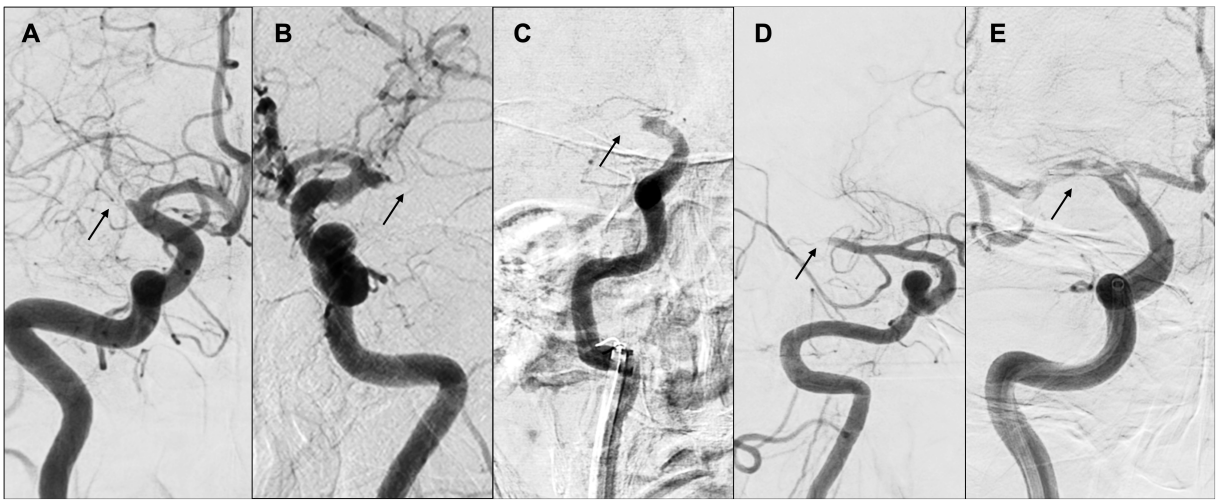

FIGURE 8
"Tapered" or "non-tapered" type. **(A,B)** Tapered; **(C)** meniscus; **(D)** cutoff; **(E)** tramtrack. Arrows indicate occlusion sites. **(A)** Right internal carotid arteriography showed the right middle cerebral artery (MCA) proximal to M1. The lumen of the occlusion gradually narrowed, and the occlusion site was severed at an acute angle at the superior wall of the artery. **(B)** Left internal carotid arteriography showed an acute occlusion angle in the distal left MCA M1, with the same pattern as in **(A)**. **(C)** Right internal carotid arteriography showed occlusion of the right internal carotid artery, concavity into the lumen representing meniscus occlusion. **(D)** Right internal carotid angiography showed distal M1 cerebral artery and cutoff occlusion. **(E)** Right internal carotid angiography showed partial occlusion of the right MCA from M1 proximal to M2, and multiple thrombus transillumination images indicating tramtrack occlusion were observed.

the case of LVO related to coronary artery disease, a non-embolic type of LVO, key patient histories characteristics such as young age and headache onset often play a significant role in clinical practice. There are limited systematic reports on the characteristic imaging findings before therapeutic intervention. Furthermore, there exist conditions, beyond ICAS-related LVOs, that warrant further investigation, such as unmet needs.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Identifying risk factors for in-stent restenosis in symptomatic intracranial atherosclerotic stenosis: a systematic review and meta-analysis

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Background: In-stent restenosis (ISR) is an adverse and notable event in the treatment of intracranial atherosclerotic stenosis (ICAS) with percutaneous transluminal angioplasty and stenting (PTAS). The incidence and contributing factors have not been fully defined. This study was performed to evaluate factors associated with ISR after PTAS.

Data source: We identified studies on ISR after PTAS from an electronic search of articles in PubMed, Ovid MEDLINE, and the Cochrane Central Database (dated up to July 2022).

Results: A total of 19 studies, including 452 cases of ISR after 2,047 PTAS, were included in the meta-analysis. The pooled incidence rate of in-stent restenosis was 22.08%. ISR was more likely to occur in patients with coronary artery disease (OR = 1.686; 95% CI: 1.242–2.288; $p = 0.0008$), dissection (OR = 6.293; 95% CI: 3.883–10.197; $p < 0.0001$), and higher residual stenosis (WMD = 3.227; 95% CI: 0.142–6.311; $p = 0.0404$). Patients treated with Wingspan stents had a significantly higher ISR rate than those treated with Enterprise stents (29.78% vs. 14.83%; $p < 0.0001$).

Conclusions: The present study provides the current estimates of the robust effects of some risk factors for in-stent restenosis in intracranial atherosclerotic stenosis. The Enterprise stent had advantages compared with the Wingspan stent for ISR. The significant risk factors for ISR were coronary artery disease, dissection, and high residual stenosis. Local anesthesia was a suspected factor associated with ISR.

KEYWORDS

intracranial atherosclerotic stenosis, percutaneous transluminal angioplasty and stenting, in-stent restenosis, risk factors, meta-analysis

Introduction

Intracranial atherosclerotic stenosis (ICAS) leads to a dramatic decline in cerebral perfusion and is the main cause of approximately 8%-10% of all ischemic strokes (1, 2). Current treatments for ICAS include medical and endovascular therapies, but rarely surgical therapy. Percutaneous transluminal angioplasty and stenting (PTAS) is considered a minimally invasive approach to reduce stroke recurrence in patients with symptomatic ICAS and has shown potential efficacy and acceptable periprocedural morbidity in initial studies

(3–6). Stents commonly used in PTAS include self-expanding stents (SES) and balloon-expandable stents, each with its own advantages and disadvantages. Balloon-expandable stents have relatively rapid one-step exchange systems that do not need more complex exchange length guidewires than self-expanding stents (7, 8). In addition, with balloon-mounted stents (BMS), the lesion does not need to be navigated more than once, which may reduce the risk of embolic stroke and hemorrhagic complications (9–11). In-stent restenosis (ISR) is an adverse and notable event in PTAS, especially with balloon-mounted bare-metal stents, and has been shown to be reduced with drug-eluting stents (12, 13). It is significantly associated with long-term stroke recurrence in stent-treated patients. The incidence of ISR varies from 5% to 30% in present studies, and systematic research on risk factors for ISR is still lacking (14–17). To investigate the risk factors related to in-stent restenosis, we performed this meta-analysis.

Materials and methods

Search strategy

This study searched the following electronic databases for potentially relevant studies published up to July 2022: PubMed, Ovid MEDLINE, and the Cochrane Central Database. The keywords and medical subject headings (MeSH) used in the searches were "Arterial Disease, Intracranial" OR "Intracranial Arterial Disease" OR "Intracranial Arterial Disorders" OR "Arterial Disorder, Intracranial" OR "Arterial Disorders, Intracranial" OR "Intracranial Arterial Disorder" OR "Arterial Diseases, Intracranial" OR "Brain Diseases, Arterial" OR "Arterial Brain Disease" OR "Arterial Diseases, Brain" OR "Arterial Disease, Brain" OR "Brain Arterial Disease" OR "Brain Arterial Diseases" OR "Brain Disorders, Arterial" OR "Arterial Brain Disorder" OR "Arterial Brain Disorders" OR "Brain Disorder, Arterial" OR "Arterial Brain Diseases" AND "risk factor" OR "risk factors" AND "restenosis". These words were combined using the Boolean operators OR and. The articles were limited to English as the only language of publication. In addition, the references listed in the identified articles were manually read to identify any additional eligible articles; a research assistant obtained and reviewed all potentially relevant articles.

Two authors independently analyzed the titles and abstracts of the identified articles. Inclusion criteria were as follows: (1) Full-length, peer-reviewed publications on stents for symptomatic ICAS in which the onset of restenosis was related to specific variables such as patient characteristics, stent technique, and other factors; (2) Cohort studies and single-arm studies were defined based on the study protocol; (3) Adequate data were presented to enable the computation of odds ratios (ORs) or weighted mean differences (WMDs) with 95% confidence intervals (CIs); (4) The median follow-up was at least 6 months; and (5) There were at least 10 patients per treatment group. Studies with any of the following characteristics were excluded: (1) Commentaries, reviews, protocols, letters, editorials, animal studies, or case reports; (2) Studies investigating the treatment strategy for complex cerebral artery stenosis; (3) Studies with imaging evaluation or treatment of ISR; and (4) Patients were treated without stent deployment. Disagreements in the evaluation of study inclusion were resolved by consensus between the two authors.

Data extraction and quality assessment

Data were extracted from all eligible studies by the two authors with a structured data extraction form. The following characteristics were extracted from each study: name of the first author, year of publication, country, risk factors for ISR, number of patients in the ISR and control groups, and the number of patients with each potential risk factor for ISR. Any disagreement was resolved by discussion, and consensus was reached on all data. The definition of ISR was an angiographically verified >50% stenosis after stent deployment. The quality of the included cohort studies was assessed in conformity with the Newcastle–Ottawa Scale (NOS) (18), which is recommended by the Cochrane Collaboration as a bias assessment tool in observational studies. Single-arm studies were assessed using the Methodological Index for Nonrandomized Studies (MINORS) (19). Studies with a MINORS score of >10 or a NOS score of >5 were considered high-quality studies.

Meta-analyses

This study complied with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Q-test statistics were used to qualitatively test for heterogeneity between studies, with significance set at $p < 0.10$ (20), and then tested by I^2 statistics, with I^2 >50% regarded as quantitative inconsistency. In the case of significant heterogeneity (p <0.10 or I^2 >50%), a random effects model was used to calculate pooled ORs or WMDs; otherwise, a fixed model was utilized (21). A forest plot was used to graphically summarize the meta-analysis of significant risk factors. All analyses were performed with the "meta" and "metafor" packages of the R statistical and computing software, version 4.1.2 (http://www.r-project.org/).

The possibility of publication bias was assessed by the Egger test and by framing a funnel plot of the effect size of each study relative to the standard error (Supplementary Figures 2, 3). A sensitivity analysis was performed to investigate the potential sources of heterogeneity (Supplementary Figure 4). Data on comparable factors, such as BMS and SES or local and general anesthesia, were extracted from studies with comparable results for pooled analysis; otherwise, subgroup analyses were performed. The following factors were analyzed with subgroup analyses: study type of the included studies, anesthesia type, dual antiplatelet time, and stent.

Results

Literature search and basic features of the included studies

A total of 136 references were initially evaluated; 19 studies were confirmed as eligible. These consisted of 9 cohort studies and 10 single arm studies, which included 452 cases of ISR after

2,047 PTAS, giving a cumulative incidence of ISR after PTAS of 22.08% (Supplementary Figure 1). In 17 studies, in-stent restenosis was defined as >50% stenosis at the time of angiographic follow-up, in one study as >70% stenosis, and as >20% increase in stenosis comparing to the residual post-procedural stenosis in the last study. The median follow-up for these studies was 12.6 months. All subjects were treated with aspirin and clopidogrel before the procedure and stayed on dual antiplatelet therapy for at least 3 months, or 6 months if necessary. The basic features of the included studies and participants are summarized in Table 1. The analysis of 17 potential risk factors for ISR was extracted from the included studies and is presented in Table 2. The PRISMA flow diagram of this analysis is presented in Figure 1.

Methodological quality assessment

The outcome of the quality assessment of the included studies was as follows: within the single arm studies, four studies received a score of 14, four studies received a score of 12, and two studies received a score of 10; within the cohort studies, five studies received a score of 8, three studies received a score of 7, one study received a score of 6, and one study received a score of 5. Detailed information on the quality assessment is shown in Supplementary Tables 1, 2.

Pooled analyses of risk factors

A meta-analysis of individual relative results indicated that various risk factors were associated with the development of ISR after PTAS (Table 2). The comprehensive OR ranged from 0.567 to 14.147. Significant heterogeneity between studies was observed for diabetes, lesion length, Mori type, residual stenosis > 30%, and CRP.

Regarding procedure-related variables, ISR was more likely to occur in patients with coronary artery disease (OR = 1.686; 95% CI: 1.242–2.288; $p = 0.0008$), dissection (OR = 6.293; 95% CI: 3.883–10.197; $p < 0.0001$), residual stenosis > 30% (OR = 14.147; 95% CI: 1.419–140.99; $p = 0.0239$) and higher residual stenosis (WMD = 3.227; 95% CI: 0.142–6.311; $p = 0.0404$) (Supplementary Figures 5–8).

Overall, ISR was not associated with gender, age, smoking, hypertension, diabetes, posterior location, degree of stenosis, lesion length, or stent type, which was divided into the self-expanding stent and the balloon-mounted stent (all p >0.05). All analysis outcomes are shown in Table 2.

Subgroup analyses and heterogeneity

Subgroup analyses were performed to further investigate the risk factors for ISR. Different choices of anesthesia resulted in significantly different in-stent restenosis rates, with local anesthesia having the highest rate of ISR (18.4% vs. 25.8% vs. 33.0%; $p = 0.0088$) (Table 3). Patients treated with Wingspan stents were more prone to ISR than those treated with Enterprise stents (29.78% vs. 14.83%; $p < 0.0001$) (Supplementary Figures 9, 10). Study type and DAPT duration were not found to be associated with ISR (Table 3).

Significant heterogeneity between effect estimates was found for the following variables: diabetes, CRP, lesion length, Mori type A, residual stenosis, residual stenosis >30%, general anesthesia, and dissection. Mild heterogeneity between effect estimates was observed for age, gender, hypertension, smoking, coronary artery disease, posterior location, degree of stenosis, and stent type.

Discussion

ISR is an important post-procedural complication of PTAS. The present meta-analysis revealed that 22.18% of symptomatic ICAS patients may suffer from ISR after stent deployment. Risk factors for the development of ISR were identified as the Wingspan stent, coronary artery disease, dissection, and high residual stenosis. In addition, patients who received local anesthesia were more likely to develop ISR. ISR was not associated with gender, age, smoking, other morbidities, or other lesion characteristics.

Patients who were implanted with a Wingspan stent were more likely to develop in-stent restenosis than those treated with Enterprise. The ISR rate for the Enterprise procedure was found to be 14.83% compared to 29.78% for Wingspan. The Enterprise stent is a self-expanding, closed-cell stent that was originally designed for coiling assistance of wide neck intracranial aneurysms (40). This stent has been shown to perform better than the Wingspan stent in complex intracranial atherosclerotic stenoses due to its high flexibility, special carrier system structure, decreased radial force, and capability to reduce the risk of damage to the arteries and prevent elastic recoil and in-stent restenosis (31, 41). In addition, Zsolt et al. reported satisfactory ISR rates with the Enterprise stent (24.7% restenosis at 6 months follow-up) compared to the Wingspan stent (42). On the other hand, Xu et al. found that the ISR rate was significantly higher in the balloon-mounted stent group than in the Wingspan stent group (35), which was not supported by this meta-analysis. The present study revealed that patients treated with BMS had a similar ISR rate than those implanted with Wingspan. New neuro-interventional devices have been developed in recent years. For example, the drug-eluting stent was shown to have an ISR rate of 9.5% in a recent clinical trial (43), which is significantly lower than that of the present stent. Therefore, endovascular treatment of intracranial atherosclerotic stenosis will become increasingly accurate and effective with technological development.

This study found that ISR was significantly more common in patients with coronary artery disease (CAD). In fact, CAD shares the same pathology as ICAS, which is atherosclerosis of the vascular walls. The instability or rupture of atherosclerotic plaques can lead to both cardiovascular and cerebrovascular events (44, 45). Essentially, atherosclerosis appears to be an inflammatory disease, and inflammation plays an important role in the progression of atherosclerosis (46). The severity of atherosclerosis may partly reflect the level of inflammatory activity in the systemic vessel walls. ICAS patients with CAD may have more severe atherosclerosis in the systemic vessels, and the plaques may be prone to instability and rupture, which means a more vibrant systemic inflammatory response in the vessel walls and a greater opportunity for ISR.

TABLE 1 The detailed information on the basic characteristics of the 23 included studies and participants.

Study	Year	Country	Design	Stent type	Restenosis	ISR symptoms	Total	Follow-up (mo)	Dual antiplatelet (mo)	Significant factors
Levy et al. (15)	2007	America	single arm	Wingspan	25	4	80	5.9	3–6	Balloon diameter, posterior circulation
Turk et al. (22)	2008	America	cohort	Wingspan	29	9	93	7.3	3–6	Posterior circulation
Miao et al. (23)	2009	China	single arm	BMS	16	4	89	29	3	NR
Zhu et al. (24)	2010	China	single arm	BMS	18	3	61	7	6	Stent diameter, lesion length, diabetes
Al-Ali et al. (25)	2011	America	cohort	BMS and SES	30	NR	165	26	3–6	Lesion morphology
Li et al. (26)	2011	China	cohort	Wingspan	11	1	43	12.92	3	Balloon diameter equal to normal vessel
Yue et al. (27)	2011	China	cohort	BMS and SES	14	3	57	16.6	6	Stent type, residual stenosis
Jin et al. (28)	2013	China	cohort	BMS and SES	57	12	233	25.3	3–6	Gender, diabetes, smoking
Park et al. (29)	2013	Korea	cohort	BMS and SES	5	NR	19	6	6	NR
Shin et al. (30)	2013	Korea	single arm	Wingspan	17	3	69	18.9	3	Inflation speed
Feng et al. (31)	2015	China	single arm	Enterprise	3	0	44	25.6	1.5	NR
Wang et al. (32)	2016	China	single arm	Enterprise	6	5	45	6	3–6	Residual stenosis
Zhang et al. (33)	2016	China	cohort	BMS and SES	6	4	92	6–72	3	Residual stenosis
Ma et al. (34)	2018	China	single arm	BMS and SES	21	NR	76	12.5	3	Irregular medication intake
Guo et al. (35)	2021	China	cohort	BMS and SES	24	4	97	12.7	3	Stent length, hs-CRP, general anesthesia, stent type
Jia et al. (36)	2021	China	single arm	BMS and SES	8	NR	98	24	3–6	Diabetes, hypertension, coronary heart disease, age
Zhang et al. (37)	2021	China	cohort	Enterprise	62	NR	359	5.7	6	Residual stenosis, calcification, inflation pressure, nTICI
Haidegger et al. (38)	2021	Austria	single arm	Wingspan	38	7	115	11	3	Recurrent ischemic stroke
Yu et al. (39)	2021	China	single arm	BMS and SES	80	42	279	11	3	Residual stenosis, coronary heart disease

BMS, balloon-mounted stent; SES, self-expanding stent; NR, not reported.

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TABLE 2 Detailed data on 15 potential risk factors and pooled results of meta-analyses.

Potential risk	No. of studies	No. of patients	Pooled OR or WMD[d]	LL 95% CI	UL 95% CI	*p*-value	Q-test (*p*)	*I*
Demographic variables								
Age (y)	6	924	0.6245	−0.8723	2.1213	0.4135[a]	0.7604	0.00%
Gender (male)	8	1,044	0.8607	0.6143	1.2059	0.3833[a]	0.8066	0.00%
Smoking	6	894	1.1069	0.7883	1.5542	0.5577[a]	0.118	43.10%
Hypertension	9	1,386	1.2645	0.9065	1.7638	0.167[a]	0.6485	0.00%
Diabetes	9	1,386	1.412	0.9053	2.2023	0.1282[b]	0.0142	58.20%
Coronary artery disease	8	1,294	1.6858	1.2421	2.288	0.0008[a]	0.0951	42.50%
CRP	3	491	−0.3915	−7.8477	7.0684	0.918[b]	0.0035	82.30%
Lesion variables								
Posterior location	11	1,200	0.863	0.6445	1.1555	0.3225[a]	0.2498	20.30%
Stenosis grade (degree)	5	456	−0.4078	−2.5014	1.6858	0.7026[a]	0.6976	0.00%
Lesion length (mm)	5	456	0.4094	−1.517	2.3358	0.677[b]	0.0009	78.60%
Mori type A	3	442	0.5673	0.1005	3.2016	0.5208[b]	0.0073	79.70%
Procedure-related variables								
Residual stenosis (degree)	6	644	3.2268	0.1418	6.3117	0.0404[b]	<0.0001	84.90%
Residual stenosis>30%	2	423	14.1472	1.4195	140.99	0.0239[b]	0.0042	87.80%
General anesthesia	3	441	0.6148	0.1952	1.9367	0.406[b]	0.0319	71.00%
Dissection	2	524	6.2926	3.8833	10.1968	<0.0001[a]	0.0505	73.80%
Stent type	8	953	1.0309	0.8462	1.2559	0.7625[a]	0.1253	38.20%

CI, confidence interval; LL, lower limit; UL, upper limit; WMD, weighted mean difference; OR, odds ratio.
[a]Fixed-effects model was framed.
[b]Random-effects model was framed.
[c]I^2 statistic was defined as the proportion of heterogeneity not due to chance or random error.
[d]Weighted mean difference (WMD) for continuous variables and odds ratio (OR) for bilateral variables.

CRP is a representative inflammatory biomarker mainly produced by hepatocytes and has been suggested to be a strong predictor of intracranial ISR in two Chinese studies (35, 39). High CRP levels are a predictor of asymmetric progression of stenotic tissue because of the differential distribution of shear stress and the effect on neointimal tissue shape mediated by the inflammatory process (47). However, the association between CRP levels and ISR was not detected in Melanie et al. (38), which may be explained by the relatively old study population, as CRP increases with age and comorbidities (48). Therefore, the value of CRP as a predictive marker for ISR after stenting may be limited.

Dissection was another significant risk factor for ISR. Previous studies evaluated the association between dissection and ISR (25, 37), and concluded that dissection was associated with ISR. The presence of dissection during intervention indicates damage to the endarterium of the lesioned vessel, which may induce intimal hyperplasia and the inflammatory cascade. The exact pathophysiological mechanism requires further investigation. Therefore, a small balloon should be utilized for predilation, and the one utilized for dilatation should be selected with 80% of the diameter of the adjacent normal artery to avoid dissection of the atherosclerotic plaque (37).

High residual stenosis is also one of the risk factors for ISR. Yue et al. (49) and Zhang et al. (37) revealed that patients with residual stenosis > 30% were more likely to develop ISR than those with residual stenosis <30%. In addition, eight other studies defined residual stenosis as a continuous variable, which summarized that patients in the restenosis group had a significantly higher stenosis rate immediately after the procedure. However, there were few detailed illustrations to explain the relationship between residual stenosis and ISR. Yue et al. suggested that higher residual stenosis might induce atherosclerotic plaques to protrude into the remodeled vessel. Some studies found the situation to be theoretically true. In our group, we thought it might be related to hemodynamics. For example, different residual stenosis rates resulted in different blood flow velocities and turbulence on either side of the stenosis.

The subgroup analysis other than the pooled analysis showed that ISR occurred more frequently in patients who underwent surgery with local anesthesia. Xu Guo et al. recently determined that local anesthesia was significantly associated with ISR (35), but Zhu et al. and Ying et al. did not reach this conclusion (24, 39). The management of anesthesia in the endovascular treatment of non-acute stroke patients with ICAS has been little discussed in the recent literature. Local anesthesia is easy to achieve during the surgical procedure, with the advantages of lower cost, less time consumption, and earlier detection of patient deterioration

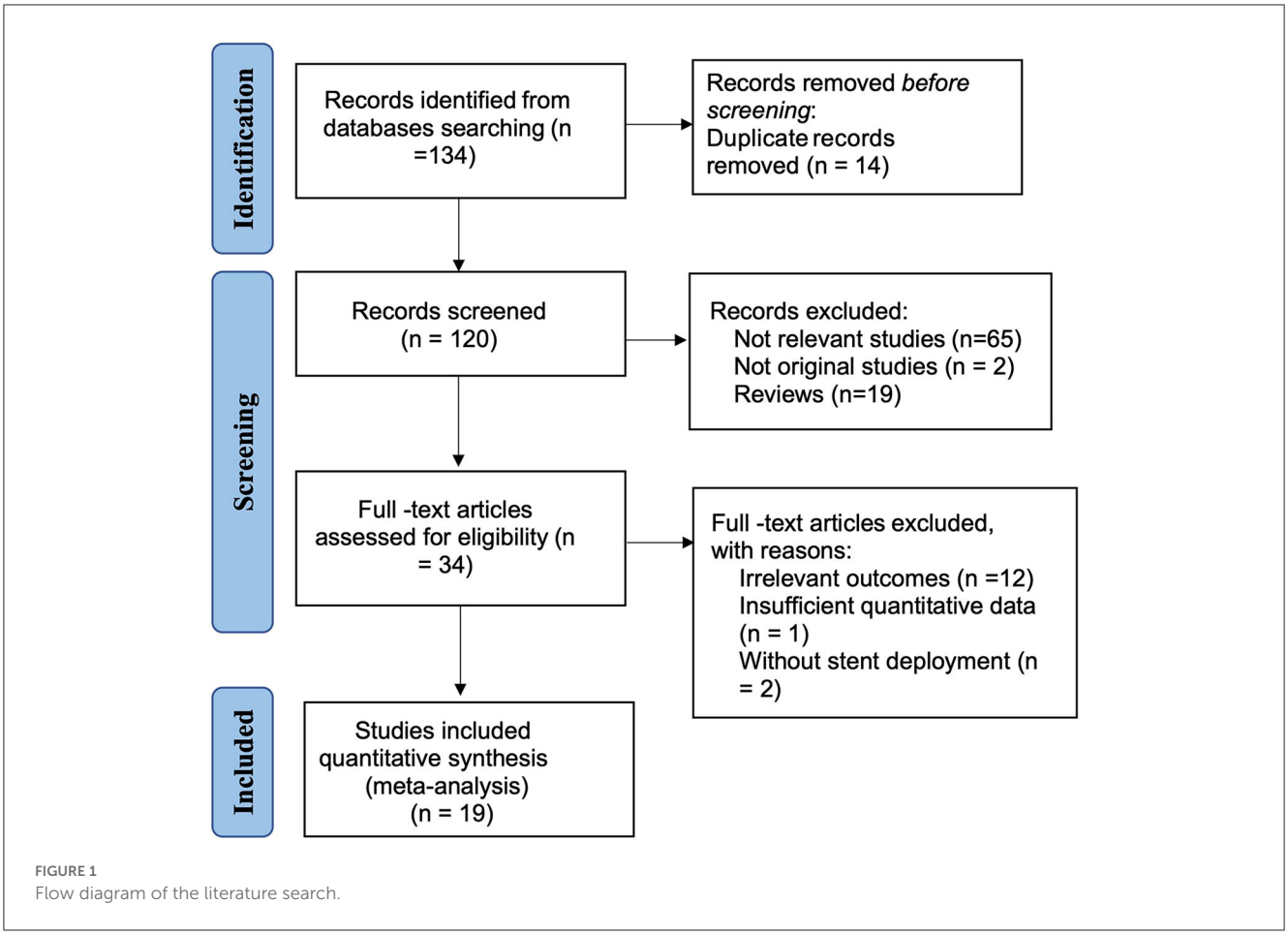

FIGURE 1
Flow diagram of the literature search.

TABLE 3 Subgroup analysis of ISR patients.

	Subgroup	Proportion	LL 95% CI	UL 95% CI	*p*-value
Design	Cohort	0.2018	0.144	0.2596	0.6954
	Single arm	0.2189	0.1557	0.2821	
Antiplatelet	Dual antiplatelet <6M	0.2055	0.1557	0.2553	0.5877
	Dual antiplatelet ≥6M	0.2299	0.157	0.3029	
Anesthesia	Local anesthesia	0.3304	0.2445	0.4164	0.0088
	Local and general anesthesia	0.2584	0.2119	0.305	
	General anesthesia	0.1838	0.1325	0.235	
Stent type	Wingspan	0.2978	0.2531	0.3425	<0.0001
	Enterprise	0.1483	0.1156	0.181	

CI, confidence interval; LL, lower limit; UL, upper limit.

(24); however, it is hard for patients to keep still during the entire procedure. On the other hand, general anesthesia could minimize patient activity during surgery and allow for substantial submaximal inflation to be performed to reduce complications of technical surgery, such as iatrogenic perforation or dissection.

This study showed no association between ISR and age. Turk et al. (22) reported that ISR was more common in younger patients, with a cutoff age of 55 years. The authors hypothesized that the lesions in younger patients displayed more inflammatory arteriopathy than those with primary atherosclerosis. This study identified age as a continuous variable to be analyzed, and a negative correlation was found between the ISR and age. Different types of stents were also found not to be associated with ISR. Further studies are needed to identify whether younger patients or lesions with self-expanding stents have higher restenosis rates and physiopathological mechanisms.

The present study had several limitations that need to be discussed. First, only study-level data rather than raw data were

extracted from the published literature, and the sample size in 80% of the series was <100 patients. The target population of the studies varied with the inclusion criteria, resulting in limited generalization of population features such as distribution of lesion location, preprocedural stenosis grade, and proportion of stent type. Second, all included studies were nonrandomized observational studies, and specific biases were unavoidable. Third, the variables extracted from the studies were limited for the meta-analysis design. The complicated lesion morphology, balloon diameter of 80% of the normal vessel, stent length, inflation speed, irregular medication intake, calcifications, inflation pressure, and ulcerations, which may lead to ISR, were rarely mentioned in previous studies. This study also has its strengths, such as the comprehensive literature search, the careful evaluation of methodological quality, and the assessment of heterogeneity. In this respect, the level of evidence in this study was higher than that of some of the individual studies (50). The present results will give neurointerventionists suggestions on how to prevent ISR after PTAS and highlight the need for further studies on ISR after PTAS.

Conclusions

The present study provides the current estimates of the robust effects of some risk factors for in-stent restenosis in intracranial atherosclerotic stenosis. The Enterprise stent had advantages compared to the Wingspan stent for ISR. The significant risk factors for ISR were coronary artery disease, dissection, and high residual stenosis. Local anesthesia was a suspected factor associated with ISR. Further studies should be conducted on patients undergoing PTAS for different inciting conditions to elucidate the underlying mechanism of ISR.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

NW wrote the manuscript. NW and YG performed the statistical analyses. NW, YL, and LF gathered the data and responsible for the integrity of the extracted data. SW, JW, and MW designed and coordinated the study. DL contributed to the analysis and interpretation of the data. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1170110/full#supplementary-material

SUPPLEMENTARY FIGURES 1–4
The cumulative incidence of ISR after PTAS along with a funnel plot, Egger test, and sensitivity analysis of the extracted data.

SUPPLEMENTARY FIGURES 5–8
Possible risk factors for ISR.

SUPPLEMENTARY FIGURES 9–10
The result of the subgroup analysis.

SUPPLEMENTARY TABLES 1, 2
Detailed quality assessment information was provided.

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Machine learning in the prediction of post-stroke cognitive impairment: a systematic review and meta-analysis

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Objective: Cognitive impairment is a detrimental complication of stroke that compromises the quality of life of the patients and poses a huge burden on society. Due to the lack of effective early prediction tools in clinical practice, many researchers have introduced machine learning (ML) into the prediction of post-stroke cognitive impairment (PSCI). However, the mathematical models for ML are diverse, and their accuracy remains highly contentious. Therefore, this study aimed to examine the efficiency of ML in the prediction of PSCI.

Methods: Relevant articles were retrieved from Cochrane, Embase, PubMed, and Web of Science from the inception of each database to 5 December 2022. Study quality was evaluated by PROBAST, and c-index, sensitivity, specificity, and overall accuracy of the prediction models were meta-analyzed.

Results: A total of 21 articles involving 7,822 stroke patients (2,876 with PSCI) were included. The main modeling variables comprised age, gender, education level, stroke history, stroke severity, lesion volume, lesion site, stroke subtype, white matter hyperintensity (WMH), and vascular risk factors. The prediction models used were prediction nomograms constructed based on logistic regression. The pooled c-index, sensitivity, and specificity were 0.82 (95% CI 0.77–0.87), 0.77 (95% CI 0.72–0.80), and 0.80 (95% CI 0.71–0.86) in the training set, and 0.82 (95% CI 0.77–0.87), 0.82 (95% CI 0.70–0.90), and 0.80 (95% CI 0.68–0.82) in the validation set, respectively.

Conclusion: ML is a potential tool for predicting PSCI and may be used to develop simple clinical scoring scales for subsequent clinical use.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php? RecordID=383476.

KEYWORDS

cognitive impairment, prediction, machine learning, stroke, meta-analysis

1. Introduction

Stroke is a serious condition and a leading cause of death and long-term disability, which places a huge burden worldwide (1). Post-stroke cognitive impairment (PSCI) is a prevalent prognosis and cause of death following a stroke. Stroke patients have a higher incidence of 1-year cognitive impairment than non-stroke populations (2, 3). As society and economy progress,

more emphasis is placed on disease and health, especially cognitive impairment. Early identification and diagnosis of PSCI, as well as early prophylaxis and treatment, can help improve stroke patient's prognosis and reduce social and economic burdens.

Clinical tools for early PSCI diagnosis in stroke patients are currently lacking. Researchers have tried to apply existing cognitive impairment risk prediction models constructed based on the general population to the prediction of PSCI, but their predictive performance was not ideal in stroke patients (4). As a result, researchers have shifted their focus to machine learning (ML) in the hopes of developing more accurate PSCI prediction models. ML is an emerging field in medicine that utilizes computer science and statistics to solve healthcare problems (5). In recent years, ML has been increasingly applied to stroke research, and it was shown that ML-based stroke image prediction can outperform existing prediction tools (6). However, the diversity in mathematical modeling and sensitivity of ML algorithms to factors such as patient sampling, missing data and sample size continue to fuel debates over the accuracy of these models in disease prediction.

The performance of existing stroke prediction models has been inconsistent due to the use of different types of ML (e.g., logistic regression or other alternative) and modeling variables. In these predictive models, there are differences in the types of machine learning utilized, with most researchers using logistic regression while some may consider it lacking and opt for alternative models. Furthermore, we note discrepancies in the selection of modeling variables, which ultimately contributes to the uncertainty of their results. Unfortunately, evidence-based studies investigating the efficiency of ML in the prediction of PSCI are still lacking. As a result, the aim of this study is to examine the predictive accuracy of ML in PSCI and comprehensively summarize the modeling variables included in this prediction model in order to provide a useful reference for the subsequent development of simple clinical prediction tools.

2. Materials and methods

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplementary material) (7).

This study has been registered in PROSPERO (CRD42022383476).

2.1. Eligibility criteria

2.1.1. Inclusion criteria

(1) Patients diagnosed with ischemic stroke or hemorrhagic stroke.
(2) Randomized-controlled trials (RCTs), case–control studies, cohort studies, and case-cohort studies.
(3) Complete construction of a ML prediction model for PSCI.
(4) Studies without external validation are also included.
(5) Different studies published using the same data set.
(6) Studies reported in English.

2.1.2. Exclusion criteria

(1) Meta-analysis, review, guidelines, and expert opinions.
(2) Only risk factor analysis was performed and lacks a complete ML model.
(3) Missing outcome measures (ROC, c-statistic, c-index, sensitivity, specificity, accuracy, recovery rate, accuracy rate, confusion matrix, diagnosis table, F1 score, and calibration curve).
(4) Validation of the maturity scale only.
(5) Study on the accuracy of single-factor prediction models.

2.2. Search strategy

Relevant articles were systematically searched in Cochrane, Embase, PubMed, and Web of Science from the inception of each database to 5 December 2022 using MeSH and entry terms without restriction on language or region. The detailed retrieval process is outlined in Supplementary material.

2.3. Literature screening and data extraction

Retrieved articles were imported into Endnote for management, and duplications were deleted. The titles and abstracts were screened to exclude irrelevant studies, and the full texts of the remaining records were downloaded and checked for eligibility. Data were collected from the included studies using a customized data extraction form. The collected data comprised title, first author, year of publication, author country, type of study, source of patient, type of stroke, diagnostic criteria for cognitive impairment, length of follow-up, number of PSCI cases, total subject number, training set, validation set, type of model used, imputation method for missing value, variable screening, and modeling variables. Two independent researchers (YY and HY) performed the literature screening and data extraction, and subsequently cross-checked their results. Any disagreement was resolved by a third researcher (XSL).

2.4. Risk of bias assessment

The Prediction model Risk Of Bias Assessment Tool (PROBAST) was employed to evaluate the quality of the included studies. The PROBAST consists of four domains, namely participants, predictors, outcome, and analysis (8). The four domains contain 2, 3, 6, and 9 specific questions, respectively. Each question has three options: yes/probably yes (Y/PY), no/probably no (N/PN), and no information (NI). If a domain has at least one N/PN, it is rated as high risk. To be graded as low risk, a given domain must have Y/PY for all questions. When all domains are at low risk, the overall risk of bias is low; alternatively, when at least one domain is assessed as high risk, the overall risk of bias is high (9). Two researchers (XSL and DDY) independently evaluated the risk of bias in the included studies and subsequently cross-checked their results. Any disagreement was resolved by a third researcher (BYW).

2.5. Outcome measures

The primary outcome was the C-index, which can be used to reflect the overall accuracy of ML models. However, this indicator

alone may not fully reflect the predictive accuracy of ML models in PSCI because the percentage of PSCI patients and non-PSCI patients in the included literature is severely unbalanced. Therefore, sensitivity and specificity were included as complementary outcome measures to evaluate the predictive accuracy of ML in PSCI.

2.6. Data synthesis and statistical analysis

The c-index and accuracy of ML models were meta-analyzed. If a 95% confidence interval (CI) and standard error were missing for the c-index, they were estimated using the methods by Debray (10). Given the differences in modeling variables and parameters, the c-index was pooled using a random effects model while sensitivity and specificity were pooled by a bivariate mixed effects model. In systematic reviews based on machine learning, heterogeneity is difficult to avoid. According to the Cochrane tool, percentages of around 25% ($I^2 = 25$), 50% ($I^2 = 50$), and 75% ($I^2 = 75$) are deemed to represent low, medium, and high levels of heterogeneity, respectively (11). The sensitivity and robustness of the results were evaluated using the leave-one-out method. Publication bias was qualitatively assessed using a funnel plot and quantitatively assessed by Egger's regression test (value of p). All meta-analyses were conducted in R4.2.0 (R development Core Team, Vienna, http://www.R-project.org). A $p < 0.05$ was considered statistically significant.

3. Results

3.1. Study selection

The literature screening process is illustrated in Figure 1. We identified a total of 5, 053 unique records. After reviewing the full texts of 41 reports, 21 studies were ultimately included (12–32).

3.2. Characteristics of included studies

Of the 21 eligible studies, 10 were conducted in China (12, 13, 17, 19, 21, 25, 26, 28, 29, 32), 2 in Norway (14, 27), 1 in Australia (20), 2 in German (15, 16), 2 in the Republic of Korea (18, 30), 1 in the Netherlands (14), 1 in France (23), 1 in the UK (24), and 1 in Singapore (31). These studies were published between 2015 and 2023, predominantly in 2021–2023 ($n = 17$) (12–27, 32).

Of the 7,822 subjects in the included studies, 2,876 developed PSCI. The subject cohort size ranged from 72 to 22,950. The diagnostic criteria used in the included studies were Mini-Mental State Examination (MMSE) (33), Montreal Cognitive Assessment (MoCA) (34) ($n = 5$) (20, 21, 28, 29, 31), MMSE ($n = 6$) (12–14, 18, 24, 32), MoCA ($n = 6$) (17, 19, 22, 25–27), Center of Cancelation (CoC) (35) ($n = 1$) (15), Global Deterioration Scale (GDS) (36) ($n = 1$) (16), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (37) ($n = 1$) (23), and vascular dementia criteria of the AHA/ASA scientific statement (38) ($n = 1$) (30). The duration of follow-up was predominantly 3 to 12 months, and was 36 years in only one study (23). The incidence of PSCI during follow-up was 12.5%–66.1%.

3.3. Characteristics of included prediction models

There were 31 models in the included studies, which were constructed based on logistic regression (LR) nomogram ($n = 18$) (12, 14–16, 18, 19, 22, 25, 26, 29–32), random forest ($n = 1$) (20), ridge regression ($n = 1$) (23), LASSO regression ($n = 1$) (21), mixed effects model ($n = 3$) (24), support vector machine (SVM) classifier ($n = 3$) (27), and decision trees ($n = 3$) (28) (Table 1). Modeling variables were selected using a multivariate approach. In the training set, 15 models reported c-index and 13 models reported sensitivity and specificity. In the validation set, 10 models reported c-index and 7 models reported sensitivity and specificity. The main modeling variables used in the included studies were age, gender, education level, stroke history, stroke severity, lesion volume, lesion site, stroke subtype, and vascular risk factors (Table 2).

3.4. Risk of bias assessment

The high risk of bias in the included studies was attributed to the limited sample size, retrospective cohort study, and lack of validation set. Therefore, these attributes should be improved in subsequent model construction. The results of the risk of bias assessment are summarized in Figure 2.

3.5. Meta-analysis

Meta-analysis showed that the training set had a c-index of 0.82 (95% CI 0.77–0.87, $n = 15$), sensitivity of 0.77 (95% CI 0.72–0.80, $n = 13$), and specificity of 0.80 (95% CI 0.71–0.86, $n = 13$). Subgroup analysis of the training set showed that the c-index was 0.81 for LR (95%CI 0.74–0.88, $n = 12$), 0.80 for mixed effects model (95%CI 0.76–0.81 $n = 1$), 0.88 for SVM classifier (95%CI 0.84–0.92 n = 1), and 0.84 for decision trees (95%CI 0.77–0.92 $n = 1$; Figures 3, 4).

The c-index, sensitivity, and specificity of the validation set were 0.82 (95% CI 0.77–0.87, $n = 10$), 0.82 (95% CI 0.70–0.90, $n = 7$), and 0.76 (95% CI 0.68–0.82, $n = 7$), respectively. Subgroup analysis of the validation set showed that the c-index was 0.80 for LR (95%CI 0.75–0.85, $n = 8$) and 0.89 for LASSO regression (95%CI 0.84–0.93 $n = 2$; Figures 5, 6).

The follow-up period or the meta-regression based on study design showed that there were no significant differences in the c-index between the training and validation sets, even considering the variations due to different study designs or changes in follow-up time (Figures 7–10; Tables 3, 4).

3.6. Sensitivity analysis and publication bias

Sensitivity analysis indicated that the results of both the training and validation sets were robust (Supplementary Figures S1, S2). However, the asymmetry in the funnel plot and the results of Egger's regression test suggest that publication bias may be present in the training set ($p = 0.056$ for Egger's regression test), and publication bias is clearly present in the validation set ($p = 0.005$ for Egger's regression test; Supplementary Figures S3–S6). There were fewer independent

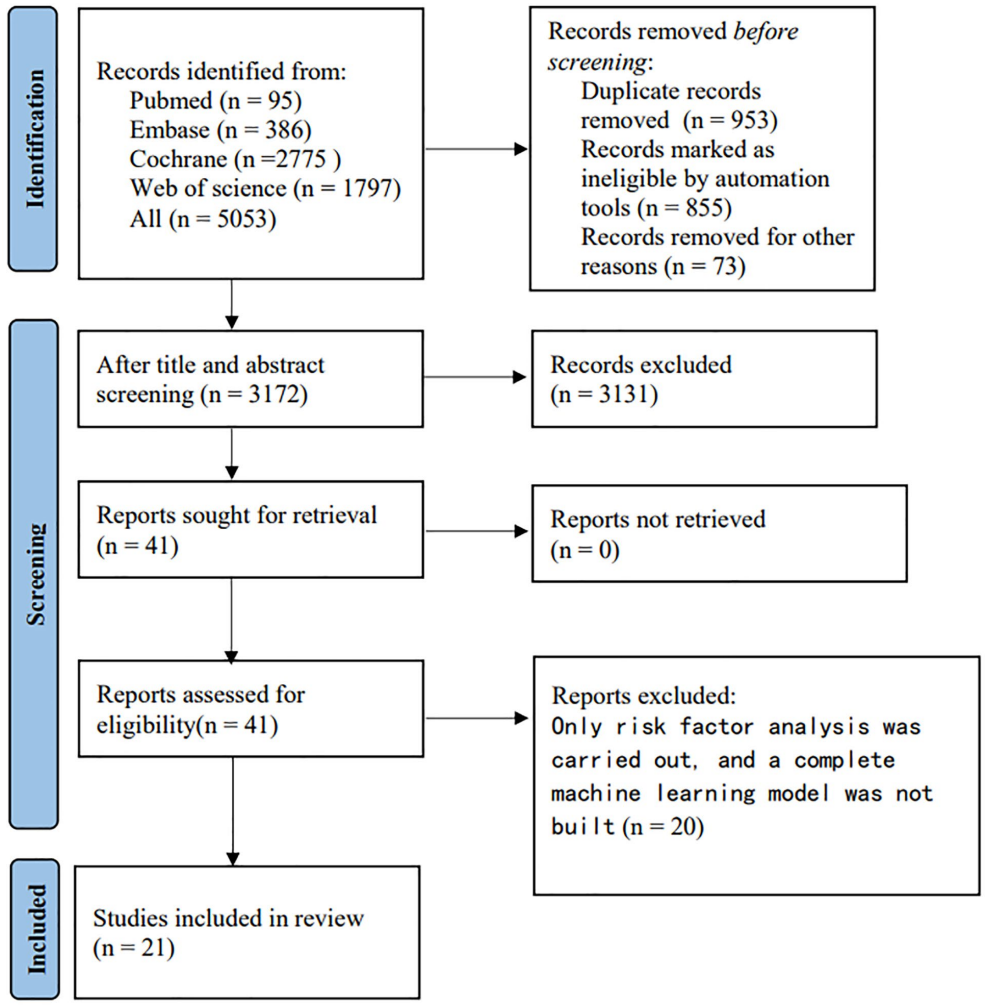

FIGURE 1
Flowchart of study selection.

validation cohorts in the included literature, and the presence of multiple independent validation cohorts in the same study may have contributed to publication bias.

4. Discussion

Our meta-analysis of 21 original studies demonstrated that ML may be an ideal tool for predicting PSCI. The training set had a c-index of 0.82 (95% CI 0.77–0.87) and sensitivity and specificity of >70%, indicating considerable predictive accuracy in PSCI. Furthermore, the accuracy of the validation set was not significantly lower than that of the training set, indicating that the ML model has good applicability. Currently, LR is the preferred model in clinical practice because it is simple for generating highly accessible nomograms, such as the nomogram on lymph node metastasis developed by the Sloan-Kettering Cancer Center (39–41). In our study, LR was also the preferred model among researchers as it exhibited comparable c-index performance to other ml algorithms while achieving higher sensitivity and specificity. As a result, we conclude that LR demonstrates satisfactory predictive ability for PSCI in this study.

We found that LR is the primary type of model utilized for predicting stroke. LR is a classification algorithm that aims to establish the relationship between features and probability of specific outcomes (42). ML is commonly used to address issues encountered in clinical practice, with supervised learning and unsupervised learning being the most common approaches. Supervised learning primarily focuses on diagnosing and predicting disease prognosis or progression, which involves the process of training, validation, and testing. The training process involves inserting predictive factors into the model and using the model's inherent parameter calculation rules (e.g., maximum likelihood estimation, iteration) to estimate the optimal model parameters. Selection of modeling variables (feature selection methods) is crucial for the training process and has been a subject of ongoing debate due to their diversification. Furthermore, validation and testing are crucial for a completed model as they reflect the model's robustness. Unfortunately, in actual research, most studies lacked effective external validation. The original studies included in our analysis predominantly utilized a supervised ML process with

TABLE 1 General characteristics of included studies.

No.	First author	Year of publication	Author country	Study type	Souce of patients	Stroke type	Diagnostic criteria for cognitive impairment
1	Yinwei Zhu (12)	2022	China	RCT	Multicenter	Acute ischemic stroke	MMSE < 25
2	Fei Zha (13)	2022	China	Retrospective cohort study	Single center	Cerebral stroke	MMSE score ≤ 19 (illiteracy), ≤ 22 (primary education), ≤ 26 (Secondary school and above)
3	Georgios Vlachos (14)	2023	Norway	Retrospective cohort study	Multicenter	Mild acute stroke	The Barthel ADL index and the modified Rankin Scale (mRS).
4	Lisa R¨ohrig (15)	2022	Germany	Prospective cohort study	Multicenter	Right hemisphere stroke	Letter cancelation test; bells cancelation test the Center of Cancelation [CoC; (35)]; The CoC.
5	Ragnhild (16)	2022	Norway	Prospective cohort study	Multicenter	Cerebral stroke	Premorbid cognitive status based on GDS
6	Zhao-Yin Ma (17)	2022	China	RCT	Single center	Acute ischemic stroke	MoCA score ≥ 26 indicates normal cognitive function; < 26 indicates MCI; < 20 indicates CI
7	Reeree Lee (18)	2021	Republic of Korea	Prospective cohort study	Multicenter	Cerebral stroke	Objective neuropsychology tests, including MMSE and CDR
8	Yongzhe Gu (19)	2022	China	Retrospective cohort study	Multicenter	Ischemic stroke	MoCA score < 26
9	Nacim Betroun (20)	2022	Australia	Prospective cohort study	Multicenter	Cerebral stroke	MMSE score < 27 or MoCA score < 25
10	Xueling Yuan (21)	2021	China	Retrospective cohort study	Single center	Cerebral stroke	MMSE score ≤ 17 (illiteracy), ≤ 20 (Primary education), ≤ 24 (Secondary school and above), MOCA score ≤ 26
11	Nick A Weaver (22)	2021	Netherlands	Retrospective cohort study	Multicenter	Cerebral stroke	Performance below the fifth percentile of local normative data in at least one cognitive domain on the Multidomain Neuropsychological Assessment or the Montreal Cognitive Assessment
12	Renaud Lopes (23)	2021	franc	Retrospective cohort study	Multicenter	Cerebral stroke	IQCODE 49 ± 2
13	Youssef Hbid (24)	2021	UK	Prospective cohort study	Single center	First occurrence of cerebral stroke	MMSE score < 24 or AMT < 8
14	Li Gong (25)	2021	China	Prospective cohort study	Multicenter	Mild acute stroke	MoCA score < 22
15	Yi Dong (26)	2021	China	Retrospective cohort study	Multicenter	Acute ischemic stroke	MoCA score < 22
16	Eva Birgitte Aamodt (27)	2021	Norway	Prospective cohort study	Multicenter	Cerebral stroke	TMT A and B, CERAD, COWAT, MoCA, AD-8, GDS (36), NPI Q, HADS, and the Cornell scale.
17	Yueli Zhu (28)	2020	China	Prospective cohort study	Multicenter	First occurrence of cerebral stroke	MMSE score < 27 and MoCA score < 21
18	Zhengbao Zhu (29)	2019	China	Prospective cohort study	Multicenter	Ischemic stroke with elevated blood pressure	MMSE score < 27 or MoCA score < 25
19	Jae-Sung Lim (30)	2017	Republic of Korea	Prospective cohort study	Multicenter	Cerebral stroke	AHA-ASA Criteria, at least two cognitive defects
20	Nagaendran Kandiah (31)	2015	Singapore	Retrospective cohort study	Multicenter	Mild acute ischemic stroke	MMSE score ≤ 2 5 or MoCA score ≤ 22
21	Sheng Ye (32)	2022	China	Retrospective cohort study	Single center	Lacunar infarction	MMSE score < 24

(Continued)

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TABLE 1 (Continued)

Follow-up duration	Number of patients with cognitive impairment after stroke	Total sample size	Number of patients with cognitive impairment in training set	Total sample size of training set (deriving set and modeling cohort)	Validation set generation method [internal validation (k-fold cross-validation, leave-one-out method, random sampling), external validation (prospective, institutional)]	Number of patients with cognitive impairment in validation set	Total sample size of validation set	Variable screening/ feature selection method	Model type
3 m	228	599	228	599	No validation set			Multivariate	Logistic regression
3 m	87	367	58	245	Random sampling at a ratio of 2:1	29	122	Multivariate	Logistic regression
12 m	21	117	21	117	No validation set			Multivariate	Logistic regression
	27	103	27	103	No validation set			Multivariate	Logistic regression
3 m	91	589	91	589	No validation set	No	No	Multivariate	Logistic regression
	94	161	94	161	No validation set	No	No	Multivariate	Logistic regression
6 m	19	110	19	110	Random internal validation	12	70	Multivariate	Logistic regression
6 m	69	123	69	123	External validation	38	60	Multivariate	Logistic regression
1y	77	327	62	262	5-fold cross validation	15	65	Multivariate	random forest
1y	118	376	118	376	External validation	75	125	Multivariate	LASSO regression
			106	338	10-fold cross validation	12	38		
15 m	1,286	2,950	1,286	2,950	External validation	107	246	Multivariate	Logistic regression
			1,179	1,704	12-fold cross validation				
36y	9	72	9	72	External validation		40	Multivariate	Ridge regression
5y	1,000	2,468	1,000	2,468	External validation	204	940	Multivariate	Mixed effects model
					Internal validation				
1y	112	228	112	228	External validation	No	1,000	Multivariate	Multivariate logistic regression
6 m	131	383	131	383	External validation		281	Multivariate	Multivariate logistic regression
					Internal validation		102		
3 m	125	227	125	227	Leave-one-out cross validation		227	Multivariate	Classifier model
6 m	66	104	66	104	Internal cross validation	66	104	Multivariate	Decision tree
3 m	340 MMSE scoring	638			No			Multivariate	Logistic regression
	422 MoCA scoring								

(Continued)

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TABLE 1 (Continued)

Follow-up duration	Number of patients with cognitive impairment after stroke	Total sample size	Number of patients with cognitive impairment in training set	Total sample size of training set (deriving set and modeling cohort)	Validation set generation method [internal validation (k-fold cross-validation, leave-one-out method, random sampling), external validation (prospective, institutional)]	Number of patients with cognitive impairment in validation set	Total sample size of validation set	Variable screening/ feature selection method	Model type
3 m	50	308			No			Multivariate	Logistic regression
6 m	78	209	70	88	10-fold cross validation	8	21	Multivariate	Logistic regression
			78	209	External validation	35	185		
12 m	52	313	38	219	Random sampling at a ratio of 7:3	14	94	Multivariate	Logistic regression

MMSE, mini-mental state examination; CDR, clinical dementia rating; GDS, global deterioration scale; MoCA, Montreal cognitive assessment; IQCODE, informant questionnaire on cognitive decline in the elderly; AMT, abbreviated mental test; TMT A and B, neuropsychological test battery included Trail making A and B; CERAD, 10 word memory and recall test; COWAT, the controlled oral word association test; AD-8, ascertain dementia 8-item informant questionnaire; NPI Q, neuropsychiatric inventory; HADS, hospital anxiety and depression scale.

TABLE 2 Modeling variables in the included studies.

Variables	Frequency
Age	29
Gender	26
Educational level	24
Diabetes	15
Smoking	15
Hypertension	14
History of stroke	11
Stroke severity	11
Lesion size	10
Hyperlipemia	9
Drinking	9
Stroke subtype	8
Body mass index	8
NIHSS	7
Site of lesion	7
Race	7
Coronary heart disease	6
NIHSS score	6
Atrial fibrillation	6
MoCA (baseline)	5
MMSE (baseline)	5
Antiplatelet before stroke	5
Glycosylated hemoglobin (HbA1c)	5
Information about cognitive decline in the elderly	4
homocysteine	4
Number of days after stroke	4
APOE ε4 positive	3
Fazekas	3
mRS (baseline)	3
sTREM2	3
WMH size	3
Fluvastatin	3
Hypercholesteremia	3
Family history of stroke	3
Transient ischemic attack, a prestroke vascular risk factor	3
Uroclepsia	3
Cortical thickness	3
Cognitive examination	3
Socioeconomic group	3
Use of antihypertensive drugs	3
Cardiovascular risk factors	3
aCL	2
aPS	2
DS-WMH	2
HS	2
PV-WMH	2
RF	2
β2-GPi	2
Imaging time (days after the event)	2
The time from disease onset to randomization	2
Red blood cell distribution width	2
Mean corpuscular volume	2
Diastolic blood pressure	2
Random treatment	2

(Continued)

TABLE 2 (Continued)

Variables	Frequency
Hemoglobin	2
Scan sequence or pattern for infarct segmentation	2
Hypoglycemic drugs	1
Comorbidity2	1
Fazekas score	1
FBG	1
FDG PET DL-based cognitive assessment	1
hsCRP	1
IQCODE score	1
LDL-C	1
MTA pathology	1
NINDS-CSN 5-minute protocol score	1
NLR	1
OCSP classification	1
SAA	1
Imaging features of T1-weighted (T1w) image texture analysis	1
OCSP classification and functional level in advanced TOAST	1
TOAST classification	1
White blood cell count	1
White matter hyperintensity	1
Premorbid cognitive decline	1
At discharge (NIHSS, mRS, Barthel scores)	1
Low density lipoprotein	1
Triglyceride	1
Cysteine proteinase inhibitor	1
Country	1
Marital status	1
Progression of acute stroke	1
Memory	1
Employment situation	1
Anticoagulant drugs	1
Infections treated with antibiotics	1
1 point for six or more correct answers	1
Hexagonal orientation	1
Number of intracranial atherosclerotic stenosis	1
Incranial volume	1
Chronic lacunes	1
Uric acid	1
Global cortical atrophy and stenosis of large intracranial vessels	1
Presence of any APOE-e4 allele	1
Visual space function	1
Affected vascular area	1
Pentaterial memory	1
Pre-existing depression	1
Fibrinogen	1
Myocardial infarction	1
Serum albumin	1
Language	1
Speech fluency raw score	1
Executive function	1
Stroke classification	1
Stroke feature	1
Neutrophil-lymphocyte ratio (NLR)	1
NCD	1

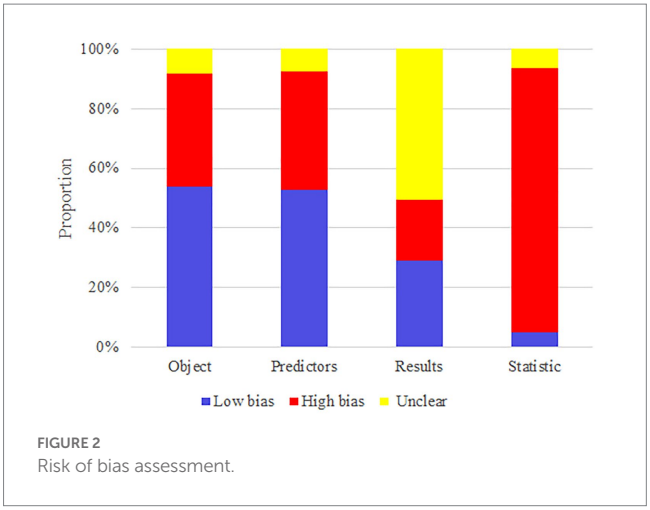

FIGURE 2
Risk of bias assessment.

single-factor + multi-factor LR model selection method and performed internal validation through random sampling (43–45).

In our study, the c-index of LR did not significantly lag behind other types of ML models, which demonstrates relatively high sensitivity and specificity. Hence, we believe that LR exhibits promising predictive potential for PSCI.

In addition, we found that the major modeling variables for the ML-based PSCI prediction models were age, gender, education level, white matter hyperintensity (WMH), stroke history, stroke severity, lesion volume, lesion site, stroke subtype, and vascular risk factors. These modeling variables were still mainly based on past identified risk factors (race, age, gender, education level, vascular risk factor, stroke severity, and stroke lesion site and volume) (46), and very few or no newly identified risk factors were used for modeling, such as blood proteins [homocysteine (Hcy), C-reactive protein (CRP), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC)] that have been recognized as effective biomarkers for PSCI (47), cognitive reserve (CR) (48), activity and participation of stroke survivors (49), and intestinal dysbiosis (50). Therefore, the newly identified risk factors should be prioritized for further validation as their efficacy as modeling variables remains uncertain.

It was reported that common cognitive screening tools have similar predictive accuracy in PSCI. Although the MoCA has significantly better sensitivity in PSCI prediction than other cognitive screening tools, its specificity is less than desirable (51, 52). This demonstrates that there is a lack of effective prediction models for the early screening of PSCI. However, our findings showed that ML has considerably high predictive accuracy (c-index, sensitivity, and specificity) in PSCI and is a promising tool for predicting PSCI.

A recent systematic review indicated that although PSCI has unique risk factors (e.g., Vascular risk factors, lifestyle, overweight, and obesity), it is currently unclear whether the intervention of these risk factors can effectively reduce the incidence of PSCI. Most approaches for lowering PSCI incidence are still dependent on effective prophylaxis for stroke (46). Therefore, effective prediction tools for the early identification and diagnosis of PSCI are urgently needed. Despite the uncertainty in the intervention measures for post-stroke cognitive functions, some researchers found that physical

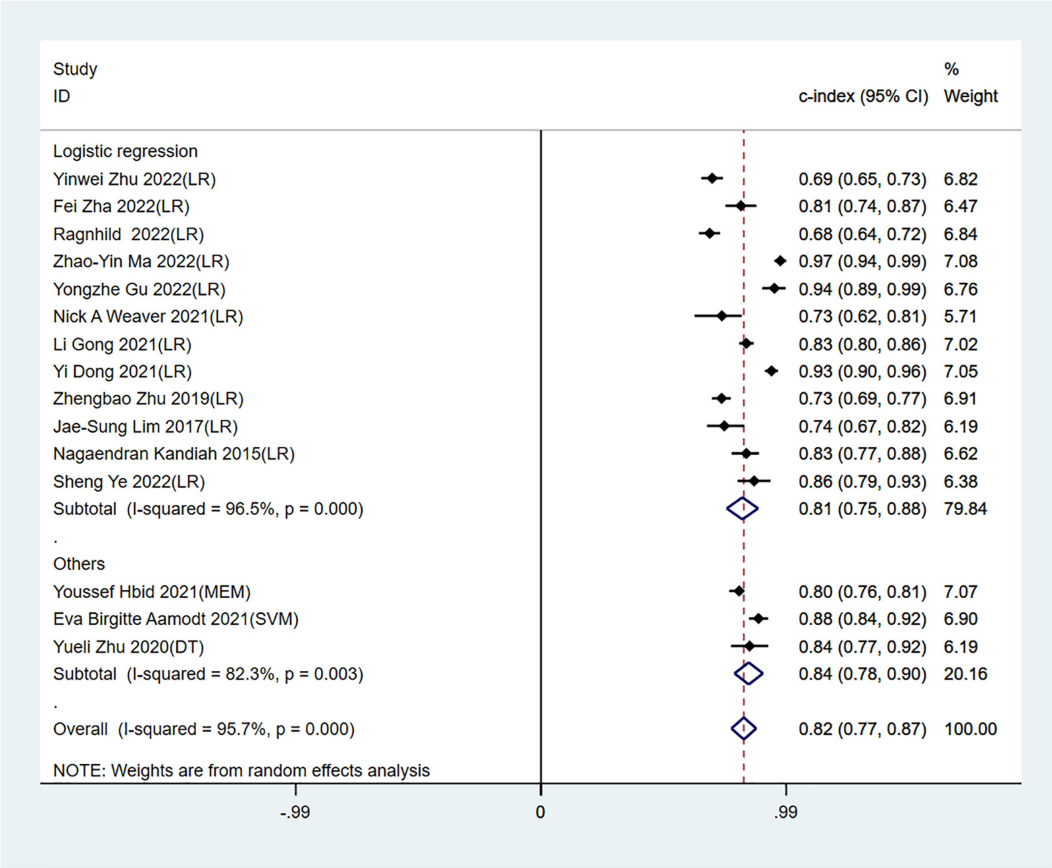

FIGURE 3
Forest plot of c-index in the training set. LR, logistic regression; SVM, Support Vector Machines; DT, decision trees; MEM, mixed effects model.

activity intervention and noninvasive brain stimulation can improve post-stroke cognitive functions compared with conventional care (53). Though, the ≥2-year improvement in PSCI after intervention was small (54). Moreover, patients with cognitive impairment have significantly increased risks of subsequent ischemic and fatal stroke (55, 56). Hence, early identification of appropriate treatment and rehabilitation measures are critical for improving the health and life expectancy of PSCI patients. Our study demonstrated the feasibility of ML in the development of PSCI prediction tools and that ML is also an important means for PSCI prediction.

Given the low number of PSCI prediction models for hemorrhagic stroke included in this study ($n = 3$) (19), the predictive accuracy of ML vs. common cognitive screening tools in PSCI in hemorrhagic stroke patients remains unclear and warrants further investigation.

ML plays an important role in the clinical management of stroke and improvement of the accuracy and efficiency of stroke prediction, diagnosis, personalized treatment, and prognosis assessment (57). For prediction of stroke risk, ML algorithms can be trained using patient data to establish predictive models and estimate the risk of stroke based on individual patient information, clinical indicators, and biomarkers. As for stroke diagnosis, ML can learn and identify radiological features of stroke and assist physicians with early and accurate diagnosis. In addition, ML can predict the efficacy and safety of different treatment options based on the patient's personal information, medical history, and clinical manifestations, enabling physicians to develop personalized treatment strategies. Furthermore, ML algorithms can predict post-stroke recovery and long-term prognosis based on patients' clinical and biomarker data. ML has been extensively used in stroke diagnosis, particularly in brain imaging, with SVM being the optimal model for stroke imaging (6, 44, 57). However, in our study, SVM exhibited inferior sensitivity to LR despite higher c-index, and the model size was limited ($n = 1$). Therefore, further exploration and development of SVM in predicting PSCI are warranted. We can attempt to optimize the accuracy of PSCI prediction by using different SVM models and parameter settings. SVM has various variants, such as non-linear SVM, multi-kernel SVM, and support vector regression, which are selected based on specific circumstances. Additionally, the combination of SVM with other ML methods can be explored for PSCI prediction. For instance, integrating SVM with deep learning techniques can improve the accuracy and robustness of predictions when analyzing images or text data. Moreover, extensive clinical validation studies are required to assess the actual effectiveness of SVM in PSCI prediction. The application value of SVM in PSCI prediction can be comprehensively assessed by collecting more data from PSCI patients and evaluating the models on independent

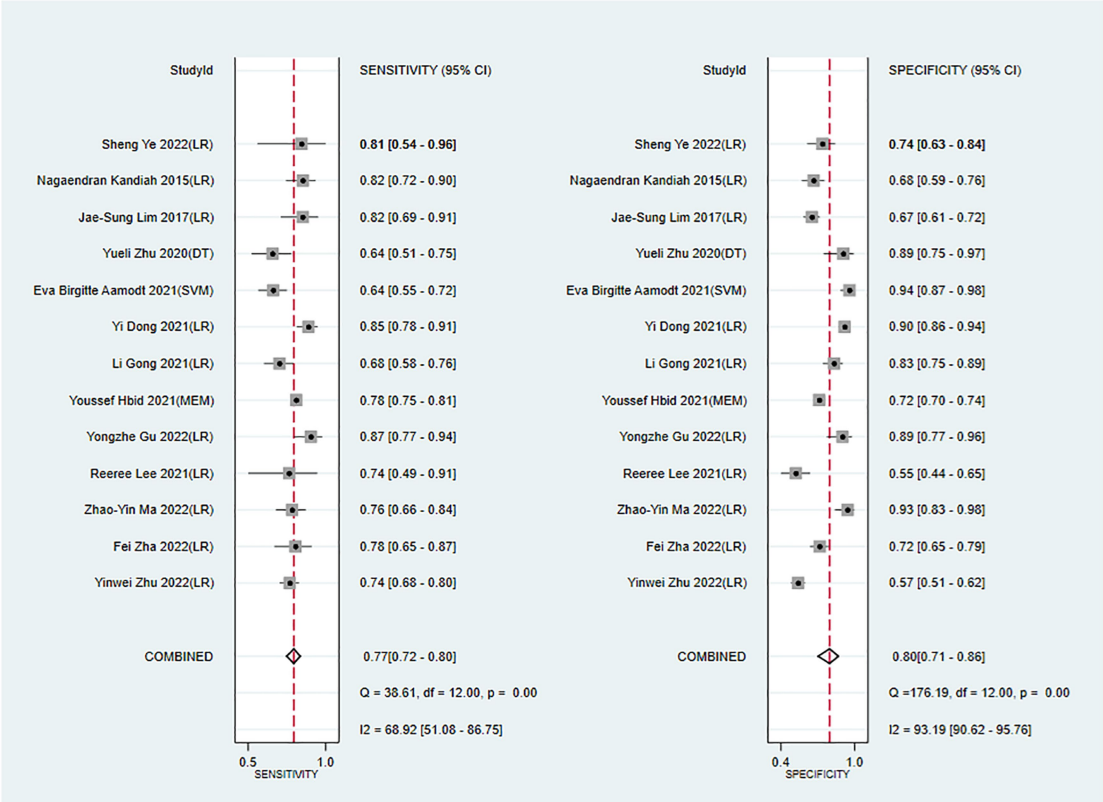

FIGURE 4
Forest plot of sensitivity and specificity in the training set. LR, logistic regression; SVM, Support Vector Machines; DT, decision trees; MEM, mixed effects model.

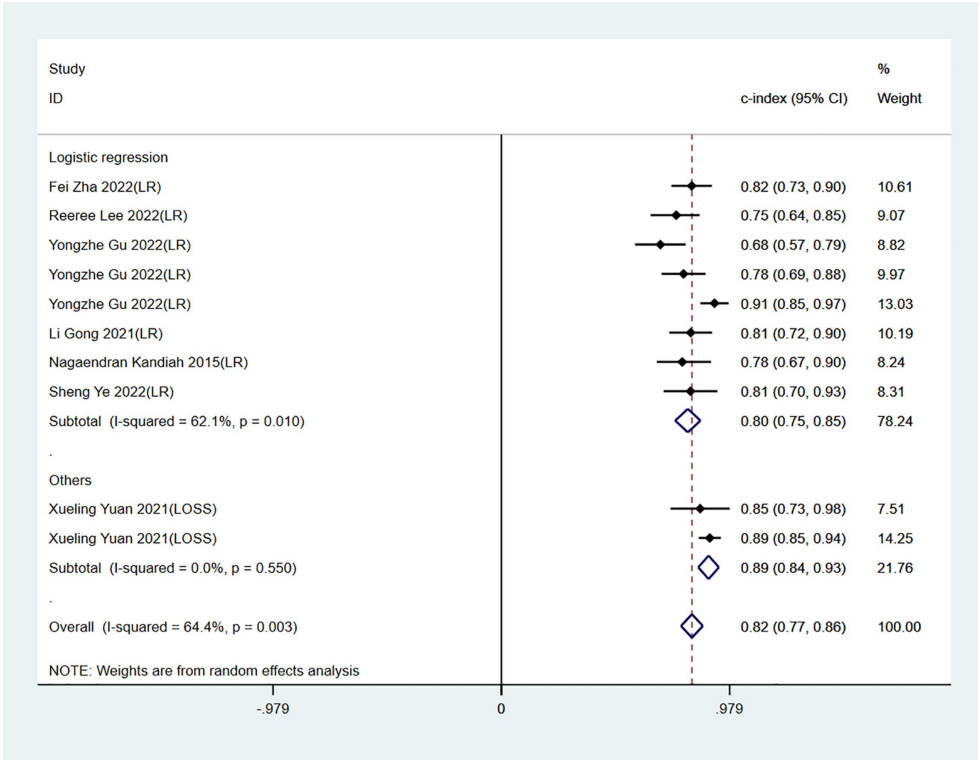

FIGURE 5
Forest plot of c-index in the validation set. LR, logistic regression; LASSO, least absolute shrinkage and selection operator.

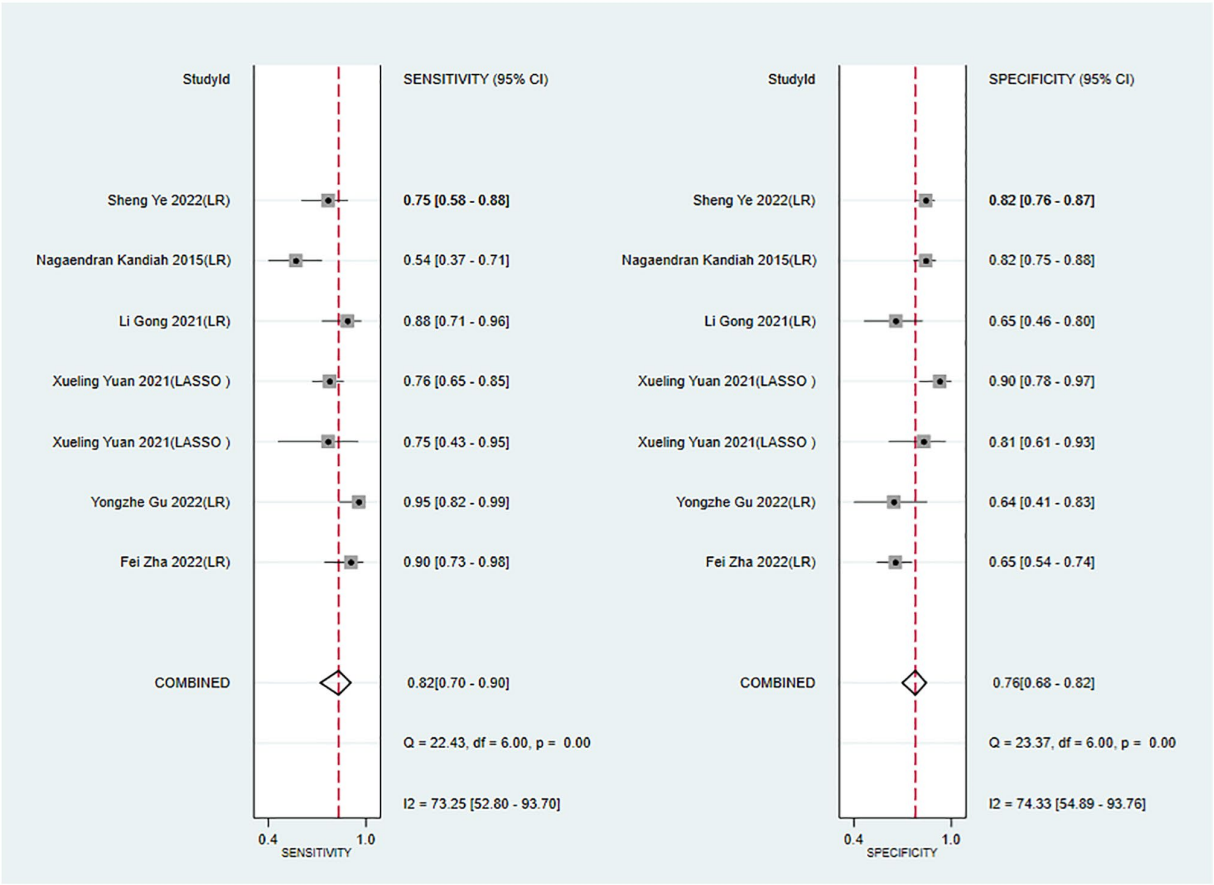

FIGURE 6
Forest plot of sensitivity and specificity in the validation set. LR, logistic regression; LASSO, least absolute shrinkage and selection operator.

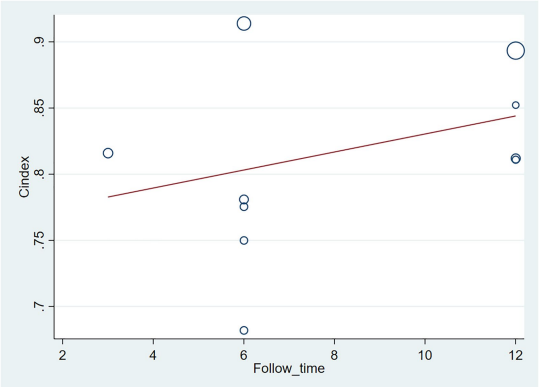

FIGURE 7
Meta-regression bubble plot of follow-up time in the training set (circles represent weights, with larger circle indicating greater weight and smaller confidence interval).

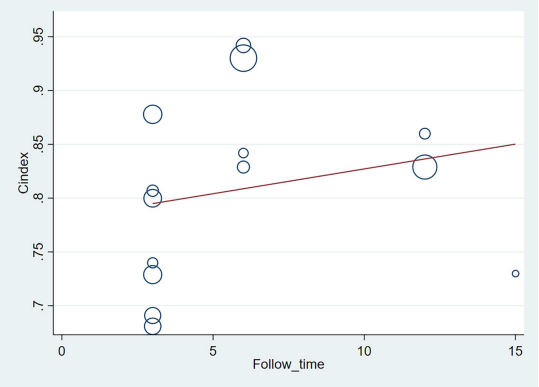

FIGURE 8
Meta-regression bubble plot of follow-up time in the validation set (circles represent weights, with larger circle indicating greater weight and smaller confidence interval). (1) Randomized controlled trial; (2) Prospective cohort study. (3) Retrospective cohort study.

validation sets. In conclusion, SVM, as a widely used ML method, has untapped potential in PSCI prediction. Continuous learning and research efforts can further refine and optimize the application of SVM in PSCI prediction, providing more accurate diagnostic and treatment decision support for clinical practitioners.

For this systematic review, the literature search was performed up until December 2022 and additional studies on this topic may become available subsequently. Hence, a regular review of the literature is recommended to obtain the most updated progress on this research topic.

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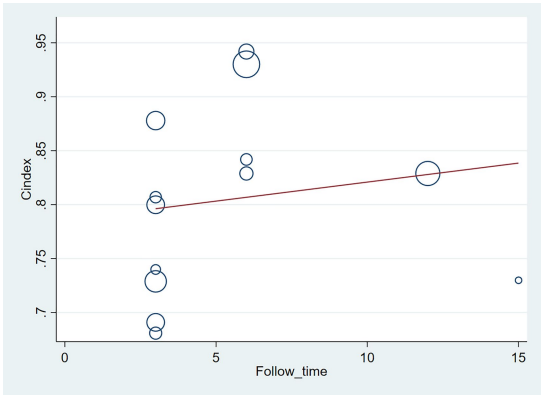

FIGURE 9
Meta-regression bubble plot of design in the training set (circles represent weights, with larger circle indicating greater weight and smaller confidence interval. (1) Randomized controlled trial; (2) Prospective cohort study; (3) Retrospective cohort study).

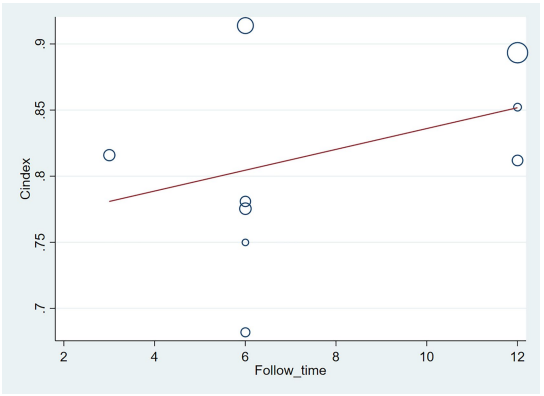

FIGURE 10
Meta-regression bubble plot of design in the validation set (circles represent weights, with larger circle indicating greater weight and smaller confidence interval).

4.1. Strengths and limitations

This systematic review is the first to demonstrate the feasibility of ML in PSCI prediction. The included models were highly consistent and were predominantly logistic regression nomograms, which minimized heterogeneity.

Despite a comprehensive literature search, the number of included studies and models was still relatively low, and bias may be present in model construction.

5. Conclusion

ML has considerable predictive accuracy and is a promising prediction tool for PSCI. Therefore, future studies should concentrate on constructing ML models based on multi-racial, multi-center, and large-cohort samples and transforming them into simple clinical scoring tools with wide application. This will

TABLE 3 Meta-regression results (follow-up time) in the training and validation sets.

Meta-regression													
Number of obs				REML estimate of between-study variance tau2		% residual variation due to heterogeneity I-squared_res		Proportion of between-study variance explained Adj R-squared					
Training sets		Validation sets		Training sets	Validation sets	Training sets	Validation sets	Training sets	Validation sets				
14		10		0.00649	0.003267	93.53%	63.72%	−1.07%	−2.04%				
With Knapp-Hartung modification													
Cindex	Coefficient		Std. err		t		P>t		[95% conf. interval]				
	Training sets	Validation sets	Training sets	Validation sets	Training sets	Validation sets	Training sets	Validation sets	Training sets		Validation sets		Training sets	Validation sets
Follow_time	0.0046061	0.0068074	0.0060551	0.0070785	0.76	0.96	0.462	0.364	−0.0085867		−0.0095157		0.0177989	0.0231306
_cons	0.7810826	0.7623026	0.0420074	0.0619474	18.59	12.31	0.000	0.000	0.6895563		0.6194516		0.8726088	0.9051536

TABLE 4 Meta-regression results (study design) in the training and validation sets.

Meta-regression					REML estimate of between-study variance		% residual variation due to heterogeneity		Proportion of between-study variance explained	
Number of obs					tau2		I-squared_res		Adj R-squared	
Training sets		Validation sets			Training sets	Validation sets	Training sets	Validation sets	Training sets	Validation sets
15		10			0.007951	0.003363	95.86%	63.50%	−3.08%	−5.03%
With Knapp-Hartung modification										
Cindex	Coefficient		Std. err		t		P>t		[95% conf. interval]	
	Training sets	Validation sets	Training sets	Validation sets	Training sets	Validation sets	Training sets	Validation sets	Training sets	Validation sets
Design	0.0265053	0.0195741	0.0353083	0.0297913	0.75	0.66	0.466	0.530	−0.0497738	−0.0491247	0.1027843	0.088273
_cons	0.7595276	0.7680337	0.0828655	0.0785483	9.17	9.78	0.000	0.000	0.5805077	0.586901	0.9385476	0.9491663

undoubtedly help with the development of follow-up strategies or rehabilitation measures for stroke patients to reduce their risk of developing cognitive impairment.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1211733/full#supplementary-material

SUPPLEMENTARY FIGURE S1

Sensitivity analysis of the training set.

SUPPLEMENTARY FIGURE S2

Sensitivity analysis of the validation set.

SUPPLEMENTARY FIGURE S3

The funnel plot of the training set.

SUPPLEMENTARY FIGURE S4

The funnel plot of the validation set.

SUPPLEMENTARY FIGURE S5

Egger's regression test of the training set.

SUPPLEMENTARY FIGURE S6

Egger's regression test of the validation set.

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Intravenous thrombolysis and endovascular therapy for acute ischemic stroke in COVID-19: a systematic review and meta-analysis

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Background: The impact of COVID-19 on clinical outcomes in acute ischemic stroke patients receiving reperfusion therapy remains unclear. We therefore aimed to synthesize the available evidence to investigate the safety and short-term efficacy of reperfusion therapy in this patient population.

Methods: We searched the electronic databases MEDLINE, Embase and Cochrane Library Reviews for randomized controlled trials and observational studies that investigated the use of intravenous thrombolysis, endovascular therapy, or a combination of both in acute ischemic stroke patients with laboratory-confirmed COVID-19, compared to controls. Our primary safety outcomes included any intracerebral hemorrhage (ICH), symptomatic ICH and all-cause in-hospital mortality. Short-term favorable functional outcomes were assessed at discharge and at 3 months. We calculated pooled risk ratios (RR) and 95% confidence intervals (CI) using DerSimonian and Laird random-effects model. Heterogeneity was evaluated using Cochran's Q test and I^2 statistics.

Results: We included 11 studies with a total of 477 COVID-19 positive and 8,092 COVID-19 negative ischemic stroke patients who underwent reperfusion therapy. COVID-19 positive patients exhibited a significantly higher risk of experiencing any ICH (RR 1.54, 95% CI 1.16–2.05, $p < 0.001$), while the nominally increased risk of symptomatic ICH in these patients did not reach statistical significance (RR 2.04, 95% CI 0.97–4.31; $p = 0.06$). COVID-19 positive stroke patients also had a significantly higher in-hospital mortality compared to COVID-19 negative stroke patients (RR 2.78, 95% CI 2.15–3.59, $p < 0.001$). Moreover, COVID-19 positive stroke patients were less likely to achieve a favorable functional outcome at discharge (RR 0.66, 95% CI 0.51–0.86, $p < 0.001$) compared to COVID-19 negative patients, but this difference was not observed at 3-month follow-up (RR 0.64, 95% CI 0.14–2.91, $p = 0.56$).

Conclusion: COVID-19 appears to have an adverse impact on acute ischemic stroke patients who undergo reperfusion therapy, leading to an elevated risk of any ICH, higher mortality and lower likelihood of favorable functional outcome.

Systematic review registration: PROSPERO, identifier CRD42022309785.

KEYWORDS

acute ischemic stroke, COVID-19, reperfusion therapy, intravenous thrombolysis, endovascular therapy

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) caused a global pandemic of Coronavirus Disease 2019 (COVID-19) since its emergence in December 2019. By the time the World Health Organization declared the end to the COVID-19 global health emergency in May 2023, over 765 million confirmed cases of COVID-19 and more than 6.9 million reported deaths had been recorded worldwide (1). COVID-19 has been linked to a higher incidence of acute ischemic stroke, possibly due to disease-associated complications such as endothelial inflammation, hypercoagulopathy and cardiac thromboembolism (2–6).

Acute ischemic stroke is a leading cause of permanent disability in adults and death in the Western countries (7). COVID-19 patients with coincident acute ischemic stroke have been found to have worse outcomes, including higher mortality, compared to those without COVID-19 (6). Reperfusion therapies including intravenous thrombolysis (IVT) with tissue plasminogen activator (tPA) and endovascular therapy (EVT) are effective and approved treatments for mitigating the risk of long-term disability and death in acute ischemic stroke patients (8). However, COVID-19 patients are generally at a higher risk of systemic bleeding complications due to coagulation disorders, which might be exacerbated by these reperfusion therapies (9). Moreover, COVID-19 patients are frequently treated in designated COVID-19 units, which may not provide the same level of stroke care as stroke units, leading to suboptimal neurological and hemodynamic monitoring and potentially increasing the risk of early bleeding complications from reperfusion therapies (4).

As literature on the utilization of reperfusion therapies in COVID-19 positive ischemic stroke patients is limited, we conducted a systematic review and meta-analysis of available literature to explore the safety and short-term efficacy of reperfusion therapies in this patient population.

Methods

Protocol registration

The pre-specified protocol for this systematic review and meta-analysis was registered with the international prospective register of systematic reviews (PROSPERO; Registration No. CRD42022309785) and the methodology adhered to updated preferred reporting items for systematic reviews and meta-analyzes (PRISMA) guidelines (10). The PRISMA checklist is provided in the Supplementary material.

Literature search and study eligibility

A systematic literature search using the electronic databases MEDLINE accessed by PubMed, Embase and Cochrane Library was performed from February 14 to March 8, 2022. The study eligibility criteria were defined in terms of: (1) *Participants*, which included acute ischemic stroke patients with concurrent laboratory-confirmed SARS-CoV-2 infection or COVID-19; (2) *Intervention*, involving reperfusion therapy by means of IVT, EVT or a combination of both; (3) *Controls*, consisting of a comparator group of acute ischemic stroke patients without SARS-CoV-2 infection or COVID-19 who were concurrently recruited; (4) *Outcomes*, which encompassed safety outcomes such as any intracerebral hemorrhage (ICH), symptomatic ICH, and all-cause in-hospital mortality, as well as short-term functional outcomes as indicated by the modified Rankin Scale (mRS) score at discharge or at 3 months; and (5) *Study design*, which included randomized controlled trials, observational cohort or case–control studies, or case series including at least 10 patients.

The search strategy was pre-defined without language restrictions and encompassed all publications from December 01, 2019 until our last search date March 8, 2022. Two reviewers (IS and AK) conducted the literature search independently and assessed all identified articles by screening of titles, abstracts and full texts using citation manager software to remove duplicates. In case of any discrepancies, a third investigator (JB) was consulted and disagreement was resolved by consensus. The search strings included various relevant terms and their combinations related to stroke and COVID-19 including "stroke," "cerebrovascular disease," "ischemic stroke," "ischaemic stroke," "brain ischemia," "cerebral ischemia," "embolic stroke," "cerebrovascular disorders," "coronavirus," "COVID," "COVID-19," "2019-nCoV," "severe acute respiratory syndrome coronavirus 2," and "SARS-CoV-2." No additional limits or filters were applied. The complete search algorithm is provided in the Supplementary materials. A snowball search in bibliographies of identified full-text articles and relevant review articles was also performed. If aforementioned outcomes of interest were not reported in eligible studies, the corresponding authors were asked to provide these data. Failure to provide at least one outcome of interest resulted in study exclusion. Furthermore, studies that did not confirm SARS-CoV-2 or COVID-19 cases by laboratory criteria (i.e., positive rapid antigen/PCR test) were considered unsuitable and excluded.

Data collection and data items

The extracted information from full text articles included first authors names, publication year, study design, sample size, total number of acute ischemic stroke patients with SARS-CoV-2 or COVID-19, absolute numbers of acute ischemic stroke patients without SARS-CoV-2 or COVID-19, patients' demographics including age and sex, baseline stroke severity using the National Institutes of Health Stroke Scale (NIHSS) score, reperfusion therapy time metrics, and the absolute numbers of aforementioned outcome events. All data were independently collected by two reviewers (IS and

AK) and inserted into a standardized data extraction form (Excel; Microsoft, Redmond, WA, United States).

Risk of bias assessment

We employed the Risk Of Bias In Non-randomized Studies - of Exposures (ROBINS-E) tool for quality control and bias assessment of included studies (11). Details of bias assessment for each study are listed in the Supplementary materials.

Statistical analysis

Categorical variables were reported as percentages, while continuous variables were presented as either mean ± standard deviation (SD) or median and interquartile range (IQR). The modified Wald method was used for computation of corresponding 95% confidence intervals (95%CI). To determine the pooled relative risks (RR) and their 95%CI for each categorial outcome of interest, we used a DerSimonian and Laird random-effects model (12). In addition, weighted mean differences (WMD) were calculated for continuous data such as time metrics. In studies where only the IQR was provided, we estimated the SD by dividing the range by 1.35 (13). Continuity correction of 0.5 was applied to studies with a zero cell. Sensitivity analyzes were performed on studies with consistent definitions for corresponding outcomes. We assessed the heterogeneity across the included studies using Cochran Q and the Higgins I^2 test. Specifically, I^2 values of 0 to 40% indicated absent or low heterogeneity, 30 to 60% indicated moderate heterogeneity, 50 to 90% indicated substantial heterogeneity, and 75 to 100% indicated considerable heterogeneity (14). Significance level of heterogeneity was set at $p < 0.1$. To examine the possibility of publication bias, we utilized Egger's test. We also visually inspected the corresponding funnel plots for the presence of small study effects. All statistical analyzes were conducted using STATA (version 16, StataCorp, College Station, TX). Statistical significance was set at $p < 0.05$.

Results

Systematic literature review

Out of 1,279 titles retrieved from the electronic databases and the bibliographies from published articles, 160 were excluded due to duplication. After screening 1,119 abstracts, 186 full articles were evaluated for eligibility. Ultimately, 11 studies with a total of 8,569 acute ischemic stroke patients with ($n = 477$) and without ($n = 8,092$) concurrent SARS-CoV-2 infection or COVID-19 were included for quantitative synthesis (15–25). Two corresponding authors provided necessary outcome data upon request (24, 25). The systematic screening and selection process is shown in Figure 1. Of the included studies, eight were retrospective observational studies and three were prospective. The majority of the included studies ($n = 7$) provided data on a combination of IVT and EVT (15, 19–22, 24, 25), while three studies provided data on EVT (16–18). One study focused on IVT only (23). Table 1 summarizes the characteristics of the included studies.

Among the COVID-19 positive stroke patients included in the studies, 226 patients (47.4%; 95%CI, 42.9–51.9) received IVT, 275 patients (57.7%; 95%CI, 53.2–62) underwent EVT, and a total of 44 patients (9.2%; 95%CI, 6.9–12.2) received both treatments.

Quantitative analysis of safety

Among the included studies, six provided data on any ICH (15, 19–23), while five studies reported on symptomatic ICH (15, 20–23). The definition of any ICH relied on radiological evidence of intracerebral blood, while symptomatic ICH mostly required a neurological deterioration of at least 4 points in the NIHSS score based on the Heidelberg bleeding classification (15, 20, 21, 23, 26). One study did not provide details on symptomatic ICH definition (22). The overall rate of any ICH was 17% (95%CI, 13–21.9) in the COVID-19 positive group and 10.6% (95%CI, 9.5–11.8) in the control group. The overall rate of symptomatic ICH was 3.9% (95%CI, 1.8–7.9) in the COVID-19 positive group and 3.9% (95%CI, 2.9–5.1) in the control group.

COVID-19 positive stroke patients were found to have a significantly higher risk of developing any ICH following reperfusion therapy compared to COVID-19 negative patients (RR 1.54, 95%CI, 1.16–2.05; $p < 0.001$), with no evidence of heterogeneity between the studies ($I^2 = 0\%$, $p = 0.65$). Although the risk of symptomatic ICH appeared to be nominally increased in COVID-19 positive acute ischemic stroke patients compared to COVID-19 negative patients (RR 2.04, 95%CI, 0.97–4.31), this association did not reach statistical significance ($p = 0.06$). There was no evidence of heterogeneity between the studies ($I^2 = 0\%$, $p = 0.76$).

According to 10 included studies, in-hospital mortality for COVID-19 positive stroke patients who received any reperfusion therapy was 28.8% (95%CI, 24.9–33.1) in the treatment group and 12.7% (95%CI, 11.9–13.4) in the control group (15, 17–25). COVID-19 positive stroke patients who received any reperfusion therapy had significantly higher in-hospital mortality compared to COVID-19 negative stroke patients (RR 2.78, 95%CI 2.15–3.59, $p < 0.001$). There was moderate heterogeneity across the included studies ($I^2 = 47.5\%$, $p = 0.05$). The corresponding forest plots are depicted in Figure 2.

Quantitative analysis of short-term efficacy

Six studies assessed favorable functional outcomes at discharge defined as an mRS of 0 to 2 ($n = 5$) or mRS of 0 to 1 ($n = 1$) (15, 16, 21, 23–25). COVID-19 positive stroke patients had a significantly lower likelihood of achieving a favorable functional outcome at discharge compared to COVID-19 negative patients (RR 0.66, 95%CI 0.51–0.86; $p < 0.001$). No heterogeneity was observed between the studies ($I^2 = 0\%$, $p = 0.47$; Figure 3). A sensitivity analysis including the five studies with an mRS of 0 to 2 as the favorable outcome definition confirmed the robustness of the results (RR 0.57, 95%CI 0.41–0.79; $p < 0.001$), with no heterogeneity ($I^2 = 0\%$, $p = 0.73$).

Two studies reported on favorable functional outcomes (mRS 0 to 1) at 3 months (16, 25). The data synthesis suggested that COVID-19

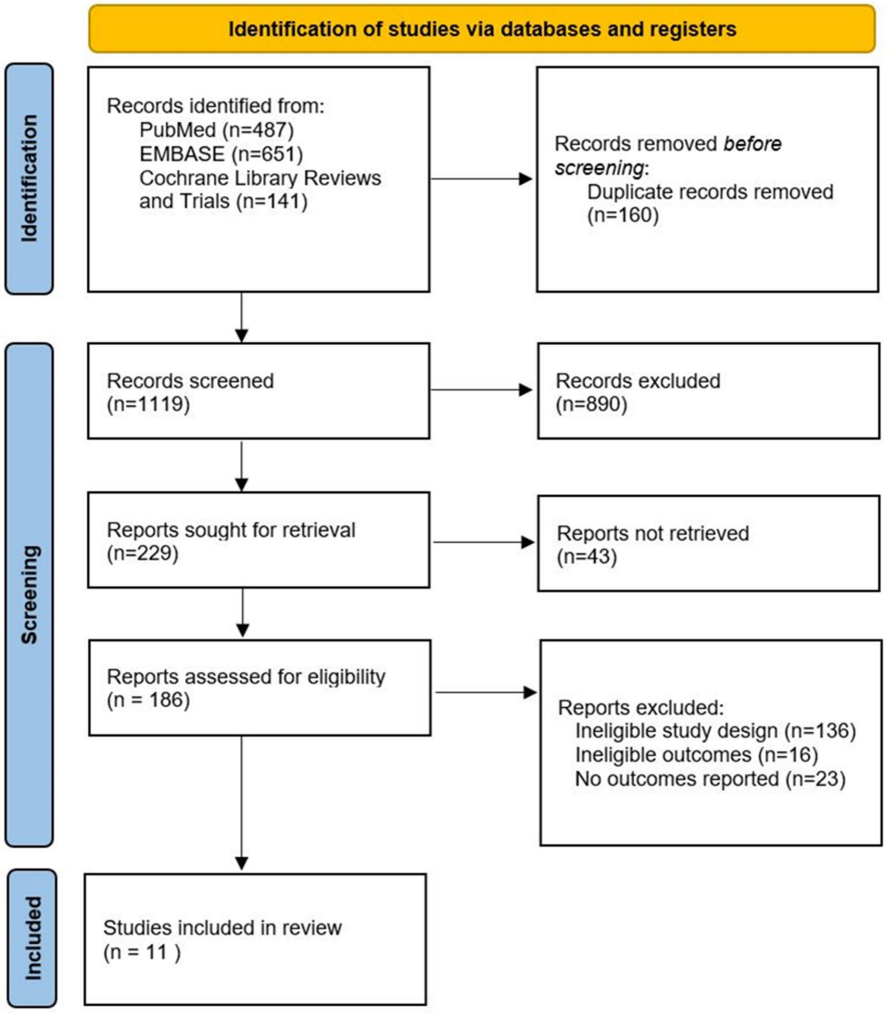

FIGURE 1
Flow chart of study selection.

positive stroke patients had a lower likelihood of achieving a favorable functional outcome at 3 months compared to COVID-19 negative patients (RR 0.64, 95%CI 0.14–2.91; $p = 0.56$). However, these results did not reach statistical significance and showed substantial heterogeneity ($I^2 = 64.5\%$, $p = 0.09$).

Quantitative analysis of time metrics

Door-to-needle times were reported in three studies (20, 21, 23) and door-to-groin or onset-to-groin times in four studies (15, 21, 22, 25). The synthesis of the available data did not show a significant difference in terms of door-to-needle time (WMD 9.88, 95%CI −13.02-32.78, $p = 0.4$) or onset-to-groin or door-to-groin time (WMD 26.5, 95%CI −13.85-66.85, $p = 0.2$) between COVID-19 positive and controls. There was substantial heterogeneity observed across the included studies (Figure 4).

Additional analysis

Synthesis of data provided by three studies on the necessity of mechanical ventilation revealed that stroke patients who tested positive for COVID-19 had a significantly higher risk of ventilation dependency compared to ischemic stroke patients without COVID-19 (RR 1.58, 95%CI 1.03–2.44, $p = 0.037$) (15, 17, 19). However, this association exhibited substantial heterogeneity ($I^2 = 73.7\%$, $p = 0.02$).

Bias and quality control assessment

Publication bias assessment was only conducted for in-hospital mortality due to a limited number of studies meeting the eligibility criteria for other outcome variables. This decision aligns with the Cochrane Handbook for Systematic Reviews of Interventions, which recommends a minimum of 10 studies for appropriate bias assessment (27). The findings indicated no presence of publication bias, supported

TABLE 1 Characteristics of the studies included in the quantitative data synthesis.

Study	Study design	Study size, *n**		Age, years, mean ± SD/median (IQR)		Female, *n* (%)		NIHSS, median (IQR)		Intravenous thrombolysis, *n* (%)		Endovascular therapy, *n* (%)		Door-to-needle time, min, median (IQR)		Door-to-groin-time, min, median (IQR)	
		COVID-19	Non-COVID-19	COVID-19	Non-COVID-19	COVID-19	Non-COVID-19	COVID-19	Non-COVID-19	COVID-19	Non-COVID-19	COVID-19	Non-COVID-19	COVID-19	Non-COVID-19	COVID-19	Non-COVID-19
Al Kasab et al. (2020) (15)	Prosepective	13	445	58 (50–71)	72 (60–80)	5 (38.5)	205 (46.1)	19 (16–24)	15 (10–20)	4 (30.8)	180 (40.4)	13 (100)	445 (100)	NA	NA	56 (37–150)	82 (50–127)
Asteggiano et al. (2021) (16)	Retrospective	5	28	66.1 ± 10.8	75.4 ± 8.8	0	18 (64.3)	NA	NA	NA	NA	5 (100)	28 (100)	NA	NA	NA	NA
De Havenon et al. (2020) (17)	Retrospective	104	3,061	NA	NA	33 (31.7)	1,490 (48.7)	NA	NA	NA	NA	104 (100)	3,061 (100)	NA	NA	NA	NA
Gabet et al. (2021) (18)	Retrospective	55	2036	66.9	70.9	19 (34)	1,059 (52)	NA	NA	NA	NA	55 (100)	2036 (100)	NA	NA	NA	NA
Qureshi et al. (2021) (19)	Retrospective	96	1,588	NA	NA	33 (34.4)	783 (49.3)	NA	NA	55 (57.3)	751 (47.3)	35 (36.5)	729 (45.9)	NA	NA	NA	NA
Sasanejad et al. (2021) (20)	Prosepective	101	444	68.19 ± 13.3	68.34 ± 14.5	41 (40.6)	200 (45.2)	13 (9–19)	11 (7–17)	101 (100)	444 (100)	11 (10.9)	55 (12.4)	41 (24.5–60)	40 (25–58)	NA	NA
Pezzini et al. (2021) (21)	Retrospective	34	262	76 (63–82.25)	74 (61–80)	10 (29.4)	132 (50.4)	12 (7–20.25)	10 (6–16)	16 (47.1)	99 (37.8)	18 (52.9)	163 (62.2)	215 (184–258.75)[#]	185 (145–225)[#]	245 (207.5–294)[‡]	194.5 (150–255)[‡]
Requena et al. (2020) (22)	Retrospective	10	19	70.8 ± 14.8	71.0 ± 15.9	4 (40)	8 (42.1)	18 (11–25)	17 (9–21)	1 (10)	5 (26.3)	10 (100)	19 (100)	NA	NA	118 (45.5–134.5)	75 (46–93.5)
Sobolewski et al. (2021) (23)	Retrospective	22	48	74.5 ± 7.9	72.9 ± 12.8	7 (34.5)	27 (58)	11 (3–20)	6.5 (2–25)	22 (100)	48 (100)	0	0	52 (15–123)	61 (10–170)	NA	NA
Fuentes et al. (2021) (24)	Retrospective	30	138	NA	NA	NA	NA	NA	NA	25 (83.3)	81 (58.6)	17 (56.6)	90 (65.2)	61[$]	48.2[$]	232.2[$]	242[$]
Genchi et al. (2022) (25)	Prosepective	7	23	70.9 ± 12.4	74.7 ± 9.6	3 (42.9)	13 (56.5)	24 (20–26)	16 (9–22)	2 (28.6)	7 (30.4)	7 (100)	23 (100)	NA	NA	330 (255–495)[‡]	280 (193–675)[‡]

NA indicates not available; SD, standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale Score.

*Numbers of patients correspond to available outcome data in the included studies (and do not account for missing data); [#]onset-to-needle time; [$]number corresponds to mean, standard deviation not available; [‡]onset-to-groin time.

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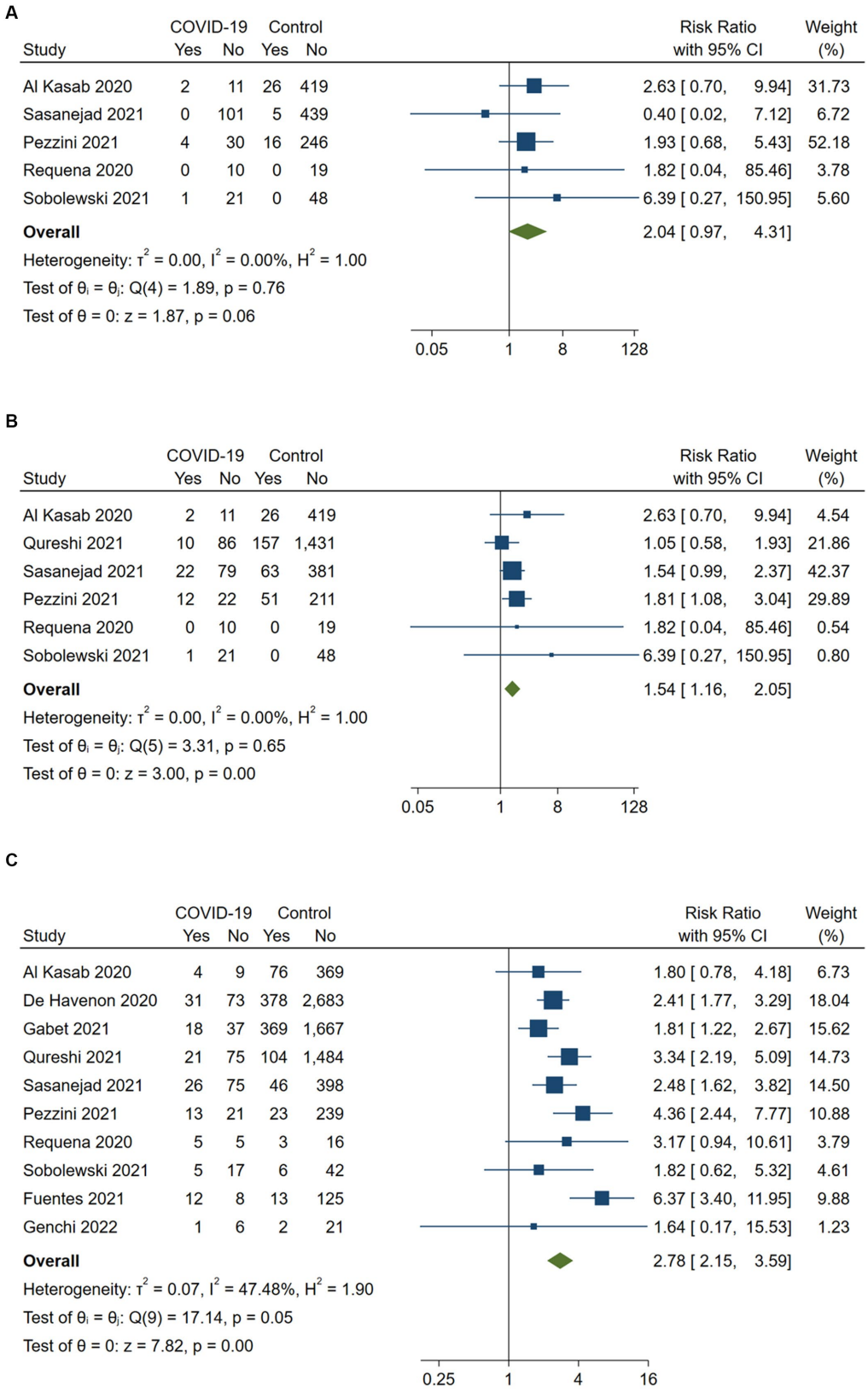

FIGURE 2
Pairwise meta-analysis of all available studies on **(A)** symptomatic intracerebral hemorrhage, **(B)** any intracerebral hemorrhage and **(C)** in-hospital mortality between COVID-positive and COVID-negative stroke patients receiving intravenous or endovascular therapy.

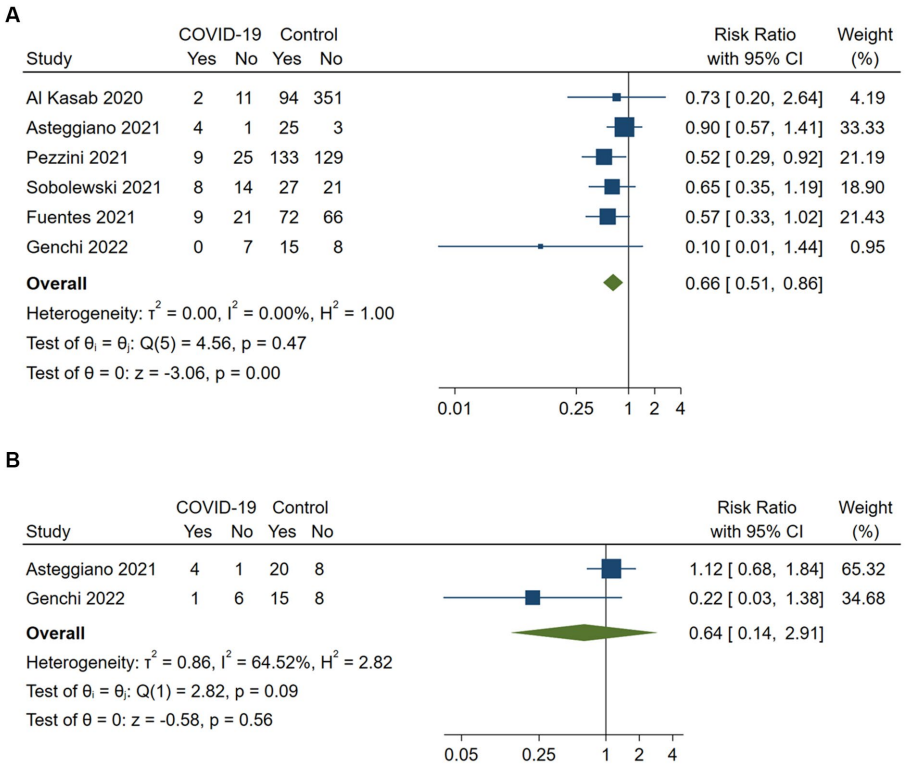

FIGURE 3
Pairwise meta-analysis of all available studies on favorable functional outcome **(A)** at discharge and **(B)** at 3 months between COVID-positive and COVID-negative stroke patients receiving intravenous or endovascular therapy.

by a value of $p > 0.05$ for Egger's test and the absence of funnel plot asymmetry. Supplementary materials also contain the results of the ROBINS-E quality control assessment for the 11 included studies.

Discussion

This systematic review and meta-analysis highlights a higher risk of any ICH and in-hospital death following reperfusion therapy in acute ischemic stroke patients with COVID-19 compared to those without COVID-19. However, there was no significant increase in the risk of symptomatic ICH among COVID-19 positive stroke patients. These findings might indicate that the increased mortality in these patients is likely attributable to COVID-19 and its associated complications rather than bleeding complications arising from reperfusion therapies.

Intracerebral hemorrhage is a significant complication that can occur after acute reperfusion therapy in acute ischemic stroke (26, 28). Current understanding indicates that ICH primarily results from tPA-related coagulopathy, blood–brain barrier disruption and hyperperfusion injury (29, 30). Nevertheless, hemorrhagic transformation of infarcted brain tissue, frequently detected through routine neuroimaging following reperfusion therapy, does not always have a negative impact on clinical outcomes (26, 30). Clinical significance becomes apparent when larger hematomas occur within the infarcted brain tissue and are accompanied by neurological deterioration, as indicated by an increase in the NIHSS score. Symptomatic intracerebral hemorrhages are strongly associated with unfavorable functional outcomes and increased mortality (28, 29). In our meta-analysis, COVID-19 positive patients with acute ischemic stroke displayed a heightened risk of any ICH following reperfusion therapy. Although the risk of symptomatic ICH was nearly doubled compared to COVID-19 negative patients, this association did not reach statistical significance and thus should be cautiously interpreted as potential indication of harm. In a recent multicenter study involving 853 COVID-19 positive ischemic stroke patients who received intravenous thrombolysis and/or EVT, a statistically significant 1.5-fold increased rate of sICH was observed compared to non-COVID-19 controls (9). This finding, which aligns with our analysis showing a nominally increased risk of sICH, could be attributed to the larger sample size utilized in the multicenter study compared to our data synthesis. Several factors have been identified as contributing to bleeding complications in ischemic stroke patients undergoing reperfusion therapy, including higher age, higher baseline NIHSS scores, elevated glucose levels, low platelet count and increased thrombin time at admission as well as inadequate blood pressure control (28, 29). Abstracted data from the included studies suggest that COVID-19 positive ischemic stroke patients had more severe strokes than COVID-19 negative patients (15, 20–23, 25). The risk of ICH in COVID-19 positive patients might be further enhanced due to pathophysiological mechanisms associated with COVID-19 including dysfunction of the renin-angiotensin system leading to reduced ACE2 expression, hypertension, elevated D-dimer and tPA plasma levels, as well as cerebral endothelial dysfunction caused by inflammatory factors (25, 31).

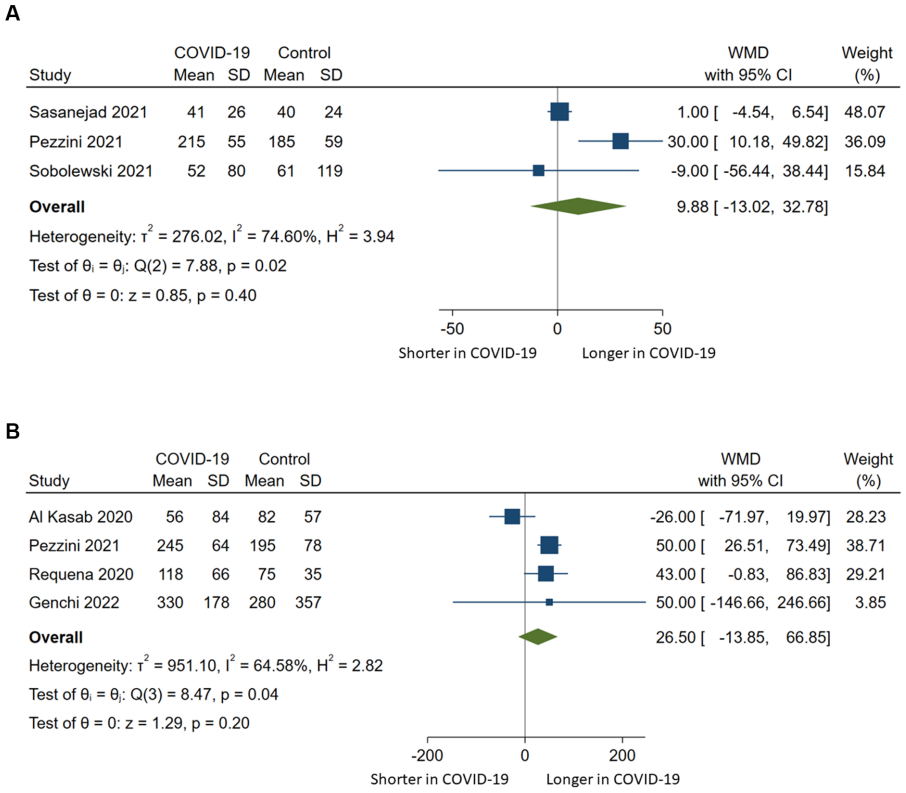

FIGURE 4
Pairwise meta-analysis comparing **(A)** door-to-needle times and **(B)** onset-to-groin or door-to-groin times among stroke patients with COVID-19 compared to those without COVID-19 who underwent intravenous or endovascular therapy. WMD indicates weighted mean difference.

Our data synthesis indicates that COVID-19 can lead to unfavorable outcomes in patients with acute ischemic stroke. COVID-19 is associated with common complications such as severe pneumonia, respiratory failure, kidney and hepatic dysfunction, dysregulated inflammatory response resulting in septic shock, and cardiac arrest (32). These complications may significantly contribute to poor outcomes following reperfusion therapy. Previous studies have consistently identified COVID-19 as a significant predictor of mortality in acute ischemic stroke patients, regardless of the treatment method (33). Moreover, in COVID-19 positive ischemic stroke patients who underwent reperfusion therapy, there is a higher likelihood of experiencing acute respiratory and kidney failure, septic shock, cardiac arrest, and requiring mechanical ventilation compared to COVID-19 negative patients (19, 34). Consistently, our pooled analysis of three studies showed an increased risk of ventilation dependency in COVID-19 positive ischemic stroke patients compared to COVID-19 negative patients. It is worth noting that COVID-19 positive stroke patients often have more severe strokes, as indicated by higher baseline NIHSS scores, which may have contributed to worse functional outcomes in this pooled patient population (35, 36). Lastly, cardiovascular risk factors commonly observed in patients with ischemic stroke have been shown to be associated with a higher risk of severe COVID-19 (37). This association may further diminish the chances of favorable outcomes in patients with ischemic stroke and COVID-19.

Based on the available data from the studies included in our meta-analysis, it appears that COVID-19 did not lead to a significant delay in starting reperfusion therapy. However, there was a notable finding in one study where a significant delay was observed in both door-to-needle and door-to-groin time for COVID-19 positive stroke patients when COVID-19 was suspected and confirmed with chest CT (24). These findings are surprising because one might expect treatment delays due to pre-clinical hygienic measures, prolonged intra-hospital processes through preventive measures, and swabbing for COVID-19 testing, which could potentially result in a missed therapeutic window, fewer implemented reperfusion therapies, and worse outcomes, as suggested by some studies (4, 19, 33, 35). Therefore, it is possible that the worse outcomes observed in COVID-19 positive ischemic stroke patients could be associated with pathophysiological aspects of COVID-19 disease itself rather than delays in reperfusion therapy.

Our meta-analysis demonstrates several strengths including an comprehensive literature review involving two independent reviewers, strict adherence to standardized methodological criteria guided by the PRISMA statement and the ROBINS-E tool for risk of bias assessment, and prior registration with PROSPERO. A significant contribution of our study is the inclusion of four studies that were not encompassed in a recently published meta-analysis on the same topic (38). This inclusion expands the existing body of knowledge regarding the safety and short-term efficacy of reperfusion therapies in acute ischemic stroke patients with COVID-19. Importantly, we implemented

rigorous measures to prevent potential overlap in patient samples within our analysis, addressing limitations identified in the previous meta-analysis where an overlap between two studies was observed (38–40). Furthermore, we excluded historical controls from our study considering that stroke outcomes during the pandemic could have been influenced by various factors, not only COVID-19 but also in-hospital cohorting and isolation strategies (4). Despite the differences in study selection, it is noteworthy that both meta-analyzes yielded comparable outcomes, underscoring the robustness of our findings.

Nevertheless, it is essential to acknowledge the limitations of our study. Firstly, the small sample size, particularly among ischemic stroke patients with COVID-19, restricts the generalizability of our findings to a broader population. Secondly, the absence of patient-level data on common confounding variables, such as age, baseline stroke severity, and the presence and location of large vessel occlusion, prevented us from performing meta-regression analysis. Additionally, the unavailability of patient-level data on COVID-19 severity hindered our ability to differentiate between unfavorable outcomes caused by the disease itself or complications arising from reperfusion therapy. Thirdly, due to possible impairment of consciousness in patients with severe COVID-19, it remains unclear how many patients eventually experienced asymptomatic or symptomatic ICH. Consequently, the actual symptomatic ICH rate could potentially be higher than reported. Fourthly, it is important to note that the majority of studies included in our meta-analysis recruited patients within the first year of the pandemic, aligning with the emergence of various SARS-CoV-2 variants, increasing vaccination rates and the availability of specific COVID-19 treatments. Our findings therefore may be prone to time-varying bias and may not necessarily be generalizable to current stroke patients with COVID-19. Lastly, the possibility of selection bias cannot be ignored, as patients may have been eligible for reperfusion therapy only if their treating physicians deemed the risk of bleeding complications to be low.

Conclusion

Our meta-analysis indicates that acute ischemic stroke patients tested positive for COVID-19 and undergo reperfusion therapy might be at higher risk of unfavorable outcomes compared to stroke patients without COVID-19. To optimize treatment strategies for COVID-19 positive stroke patients, further studies are necessary to explore the underlying mechanisms that contribute to these potential worse outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

IS, AK, and JB: conceptualization of study design and supervision. IS, AK, JB, and KB: data acquisition, analysis and interpretation, manuscript writing and revision. TS: supervision and manuscript revision. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1239953/full#supplementary-material

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Thrombectomy with and without computed tomography perfusion imaging for large-vessel occlusion stroke in the extended time window: a meta-analysis of randomized clinical trials

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Objective: In recent years, several studies have used computed tomography perfusion (CTP) to assess whether mechanical thrombectomy can be performed in patients with large-vessel occlusion (LVO) stroke in an extended time window. However, it has the disadvantage of being time-consuming and expensive. This study aimed to compare the impact of the CTP group with the non-CTP group [non-contrast CT (NCCT) ± CT angiography (CTA)] on the prognosis of this patient population.

Methods: A search of PubMed, EMBASE, and the Cochrane Library databases was conducted to collect randomized controlled trials (RCTs) comparing the two strategies. Outcome indicators and factors influencing prognosis were summarized by standardized mean differences, ratios, and relative risks with 95% confidence intervals using a random-effects model.

Results: A total of two RCTs were included in the combined analysis. There were no significant differences in the main outcome indicators (modified Rankin Scale score at 90 days, successful postoperative reperfusion rate) or the incidence of adverse events (90-day mortality and symptomatic intracranial hemorrhage) between the NCCT ± CTA and CTP groups. The time from the last puncture appeared to be significantly shorter in the NCCT ± CTA group than in the CTP group (SMD: −0.14; 95% CI: −0.24, −0.04). Among them, age (OR: 0.96; 95% CI: 0.94, 0.98), ASPECTS (OR: 1.18; 95% CI: 1.12, 1.24), NIHSS score (OR: 0.90; 95% CI: 0.89, 0.91), and diabetes (OR: 0.69; 95% CI: 0.54, 0.88) were associated with a 90-day independent functional outcome.

Conclusion: These findings suggest that the choice of NCCT ± CTA (without CTP) for the assessment of mechanical thrombectomy within 6–24 h after LVO in the anterior circulation is not significantly different from CTP; instead, the choice of NCCT ± CTA significantly reduces the time from onset to arterial puncture.

KEYWORDS

large-vessel occlusion stroke, NCCT, CTP, prognosis, meta-analysis

1. Introduction

Stroke is a widely prevalent disease that affects one-quarter of the population during their lifetime. As the second leading cause of death and the third leading cause of disability in adults worldwide, it has attracted the attention of many healthcare professionals (1). In patients with acute ischemic stroke, endovascular treatments such as mechanical thrombectomy and pharmacological thrombolysis have been shown to improve the functional outcome of stroke patients (2). Recent results from the DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) (3) and DEFUSE3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) (4) trials suggest that the use of perfusion imaging for endovascular treatment selection within an extended time window may be extremely beneficial for stroke patients. However, the two trials required all patients to only undergo computed tomography perfusion (CTP) or magnetic resonance imaging (MRI) of the brain. The importance of advanced perfusion imaging (CT perfusion or MRI) is reflected in the extended time window (6–24 h after stroke onset) by providing an assessment of ischemic tissue viability beyond an arbitrary clock time to allow physicians to select treatment modalities to resuscitate the patient (5). However, for low-level stroke centers, emergency MRI and CTP are not fully implemented (6). Therefore, a more pragmatic and resource-efficient approach to selecting patients is needed.

Multimodal CT imaging, which includes non-contrast CT (NCCT), CT angiography (CTA), and CT perfusion (CTP), is also crucial to the diagnosis and treatment of acute ischemic stroke (7). Previous studies have found no significant difference in the accuracy of NCCT-based Alberta Stroke Program Early CT Score (ASPECTS) and CTP in predicting lesion volume in the hyperacute phase of ischemic stroke (8). The use of ASPECTS in combination with different collateral scores, such as the National Institutes of Health Stroke Scale (NIHSS) to determine ischemic viability, provides an alternative to advanced imaging techniques within an extended time window. Previous studies have also demonstrated that CT may be more sensitive than CTP to detect irreversible damage during the extended time window (9). In addition, clinical outcomes have been observed in stroke patients selected by optimal CTP parameters, but this increased overall costs and prevented other patients from receiving care who would have benefited from it (10).

In this article, we review the different imaging modalities proposed in the literature and perform a meta-analysis of the utility and limitations of CT and CTP as endovascular treatment options. The feasibility and potential benefits of using only NCCT ± CTA in an extended time window were discussed.

2. Methods

This meta-analysis conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) regulatory process (11).

2.1. Search strategy

Two researchers identified all articles containing the terms through PubMed, EMBASE and Cochrane Library databases, "CT," "CTP," and "thrombectomy" in the title or abstract. We also checked reviews and references of other studies to avoid potentially missing studies. The searched articles were all published before November 2022.

2.2. Study selection

The inclusion criteria for the studies included in this article are as follows: (1) Participants: the study cohort included consecutive patients who met the following criteria: baseline NIHSS score of 6 or more, occlusion of the internal carotid artery or proximal middle cerebral artery (M1/M2 segments), pre-stroke modified Rankin Scale (mRS) score of 0 to 2, and time last seen well to treatment of 6 to 24 h. (2) Intervention: Compared with the control group, the experimental group used NCCT ± CTA instead of CTP in the selection of patients for endovascular treatment. (3) Outcome: The primary outcome was the distribution of the mRS score at 90 days (ordinal shift analysis). Secondary clinical outcomes included the rate of 90-day functional independence (mRS scores of 0–2), and successful reperfusion, defined as a grade 2b or 3 (>50% of the affected territory) on the modified Treatment in Cerebral Infarction scale. A standard approach to mRS assessment was used. Safety endpoints included post-procedural symptomatic intracranial hemorrhage (as defined in the European Cooperative Acute Stroke Study III: intracranial hemorrhage that is associated with deterioration in NIHSS $\geq$ 4 points and the main cause for neurological deterioration) and 90-day mortality. (4) Study design: RCT comparing the efficacy and safety of selecting acute large-vessel stroke patients for endovascular treatment between the NCCT ± CTA group and the CTP group in the extended time window.

2.3. Data extraction and quality assessment

We collected relevant data from various studies we needed, namely the article title, name of the first author, year of publication, country, study design, baseline characteristics of included studies, and change in the mean value of each quantitative indicator from baseline to endpoint. Two investigators critically checked the data for each study. If the data from the included studies were not publicly available, we searched the ClinicalTrails.gov database for the raw data. The risk of bias was evaluated through the Cochrane Collaboration's tool, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases.

2.4. Statistical analysis

R with the "meta" package was used to analyze the data. We visualized the aggregated results for each endpoint event using a forest plot diagram. The standardized mean difference

TABLE 1 Included studies and their characteristics.

Study	Unique identifier	Years	Site	Total patients	NCCT ± CTA/CTP
Nguyen et al. (12)	NCT04096248	2014–2020	Europe and North America	1,286	1:1.4
Nogueira et al. (6)	NCT02040259	2013–2017	North America, Europe, Asia	247	1:2.7

(SMD) with a 95% confidence interval (CI) was computed for the difference between baseline and endpoint in each indicator. The odds ratio (OR) with 95% CI values was calculated for adverse events. Cochrane's Q test and I^2 were used to calculate outcome heterogeneity. We used a fixed-effects model when heterogeneity was low ($I^2 < 50\%$, P-value > 0.10); otherwise, we used a random-effects model.

3. Results

3.1. Search results

Based on the search strategy, we retrieved 252 potentially relevant records, 14 of which were duplicates. After the screening, 222 articles were excluded for irrelevant content. Of the remaining 16 articles, only two RCTs were ultimately included in the meta-analysis based on the inclusion and exclusion criteria, and their main characteristics are shown in Table 1. The study by Nguyen et al. (12) included data from 1,286 patients in Europe and North America between 2014 and 2022, with a ratio of 1:1.4 patients undergoing NCCT ± CTA vs. those undergoing CTP. Another study included data from 247 patients in North America, Europe, and Asia between 2013 and 2017, with a ratio of 1:2.7 patients receiving NCCT ± CTA vs. CTP. The entire search flowchart is shown in Figure 1. A total of 1,533 eligible patients were included, including 602 in the NCCT ± CTA group and 931 in the CTP group. The age distribution of the two studies was 50–81 years. The proportion of women was slightly higher than that of men in both studies.

3.2. Quality assessment and risk of bias

The overall quality of the included studies was high. They consisted of RCTs registered on ClinicalTrials.gov. According to the risk of bias assessment, the *post-hoc* retrospective design of the two studies may lead to some selection bias, making it difficult to generalize the results. Neither study had an independent imaging assessment center, and there may be some variation in the interpretation of imaging results, selection of imaging modalities, and automated CTP processing software between providers, resulting in bias. Although both studies encouraged the consecutive enrollment of patients, they were not continuously monitored. Additionally, both studies were limited to patients with internal carotid artery occlusion or middle cerebral artery M1/M2 segment occlusion.

3.3. Assessment of the primary outcome

There was no significant difference in mRS scores between the NCCT ± CTA and CTP groups at 90 days of follow-up (RR: 0.98; 95% CI: 0.84, 1.15) in Figure 2A. Patients in the NCCT ± CTA group had a significantly shorter time from last seemed well to puncture than those in the CTP group (SMD: −0.14; 95% CI: −0.24, −0.04; Figure 2B). However, there was no significant difference in the successful postoperative reperfusion rate (mTICI ≥ 2b) between the two groups in Figure 2C (RR: 1.00; 95% CI: 0.97, 1.03). Pooling the results of the multivariate dichotomous mRS study (good outcome defined as a 90-day modified Rankin Scale score of 0 to 2) from the two RCT studies found no significant difference in the incidence of good prognosis between patients who chose CTP as their imaging modality and those who chose NCCT ± CTA as their imaging modality (OR: 0.90; 95% CI: 0.71, 1.16; Figure 3A). In addition, lower age (OR: 0.96; 95% CI: 0.94, 0.98; Figure 3B), higher ASPECTS (OR: 1.18; 95% CI: 1.12, 1.24; Figure 3C), lower NIHSS scores (OR: 0.90; 95% CI: 0.89, 0.91; Figure 3D), and non-diabetic patients (OR: 0.69; 95% CI: 0.54, 0.88; Figure 3E) were more likely to have a 90-day independent functional outcome. Moreover, the length of time from the last time the patient looked good to the puncture (OR: 1.00; 95% CI: 0.99, 1.01; Figure 3F) was not significantly correlated with a good prognostic outcome. The results of the 90-day ordinal mRS shift analysis were similar to the above findings, as shown in the Supplementary material.

3.4. Adverse events

There was no significant difference between the two groups in terms of 90-day mortality (RR: 1.09; 95% CI: 0.89, 1.33; Figure 4A) and the incidence of symptomatic intracranial cerebral hemorrhage (sICH) (RR: 1.41; 95% CI: 0.94, 2.12; Figure 4B).

4. Discussion

Our meta-analysis based on two large samples of randomized controlled studies (3, 4) suggests that more basic imaging modalities (NCCT ± CTA) replace advanced imaging to some extent during extended time windows (6, 12). Both studies analyzed the association between imaging modality and the 90-day mRS in an ordered (modified Rankin scale offset) and dichotomous (functionally independent, modified Rankin scale scores 0 ∼ 2) manner. To further validate our point, it was discussed whether a more inclusive selection paradigm could be used to allow a larger proportion of patients with extended time windows to be treated and whether they could still maintain significant benefits.

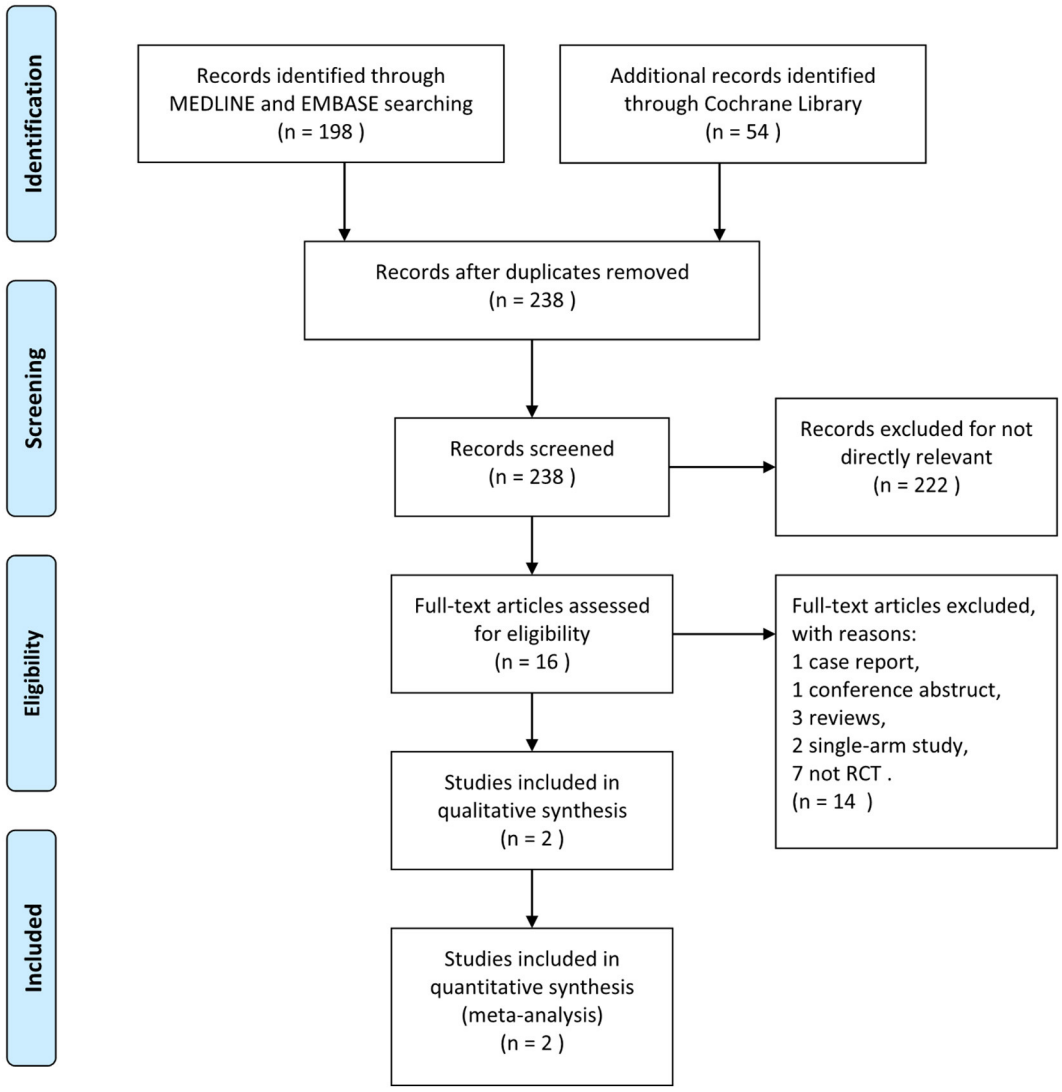

FIGURE 1
The PRISMA flow diagram.

The p imaging paradigm usually relies on the use of NCCT and CTA to simply predict ischemic core volume (9). In contrast, perfusion imaging provides a mismatched ratio to estimate the proportion of salvageable tissue for patient selection (13). Results from two landmark trials show that CTP is extremely beneficial for stroke patients undergoing endovascular treatment options within an extended time window. Nevertheless, the use of perfusion imaging is becoming increasingly controversial. In the SWIFT PRIME trial (10), perfusion imaging did not improve treatment efficacy and was associated with a potential time delay. Similarly, several other trials have shown no significant interaction between CTP mismatch and treatment effectiveness and no association with functional prognosis (14–16).

The first consideration is that acute CTP or MRI is not easily performed in many stroke centers around the world (6, 17). Advanced imaging resources are not readily available, and routine utilization of perfusion imaging with an extended time window does not correspond to reality (17). For the majority of patients who are not eligible for inclusion in the DAWN and DEFUSE3 trials, perfusion imaging is not performed. Moreover, from the standpoint of smaller hospitals, the full implementation of guideline recommendations for CTP/MRI in patients with suspected large-vessel occlusion is more problematic. It represents a triple challenge of technical, logistical, and economic conditions (18). Furthermore, accurate quantification of infarct tissue has been confirmed to have an impact on clinical outcomes in patients with acute ischemic stroke (19); it allows clinicians to determine the precise area affected by the occlusion and the embolic location (20). Currently, various automated CTP software such as RAPID, MIStar, F-STROKE, and Syngo.via, Spher, and Vitrea vary in their measurements of ischemic core volume and semi-dark zone volume, with overestimation or underestimation of infarct core occurring in each (21, 22). Underestimation of the infarct tends to allow the patient to be included in endovascular treatment to

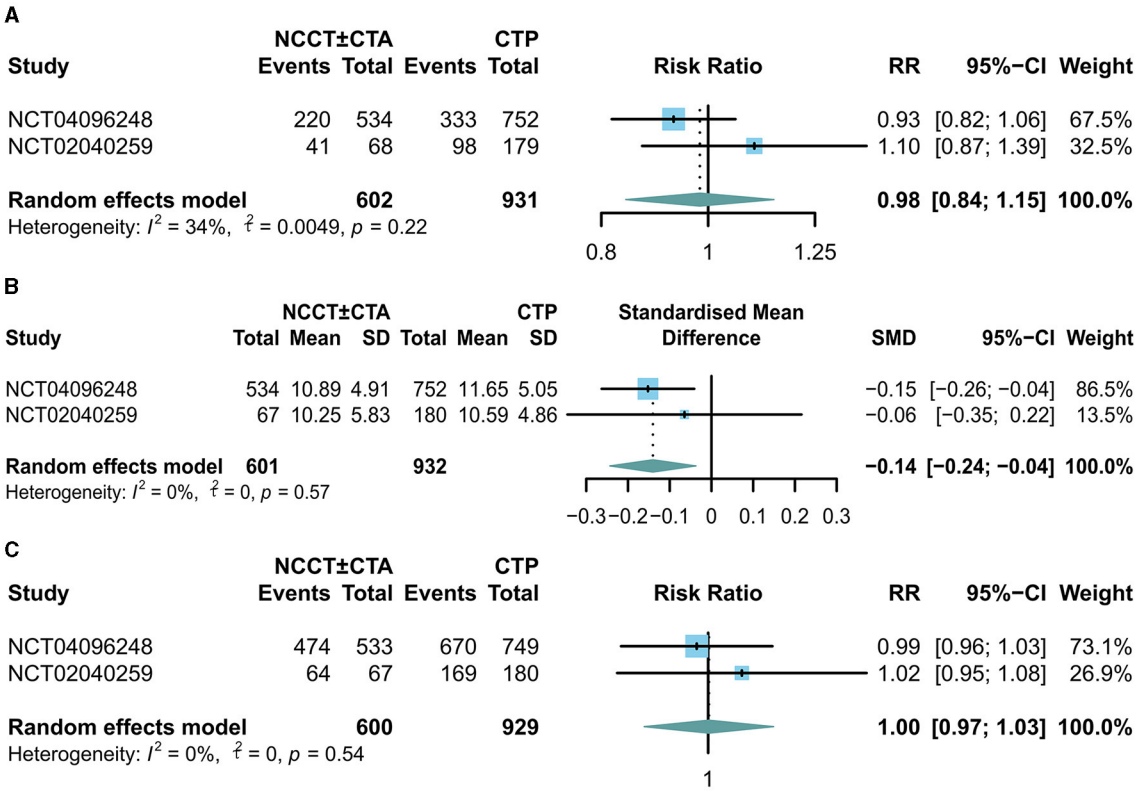

FIGURE 2
Forest plots for the odds of **(A)** good outcome (90-d mRS score 0-2), **(B)** time last seen well to puncture, and **(C)** successful postoperative reperfusion rate (mTICI ≥ 2b).

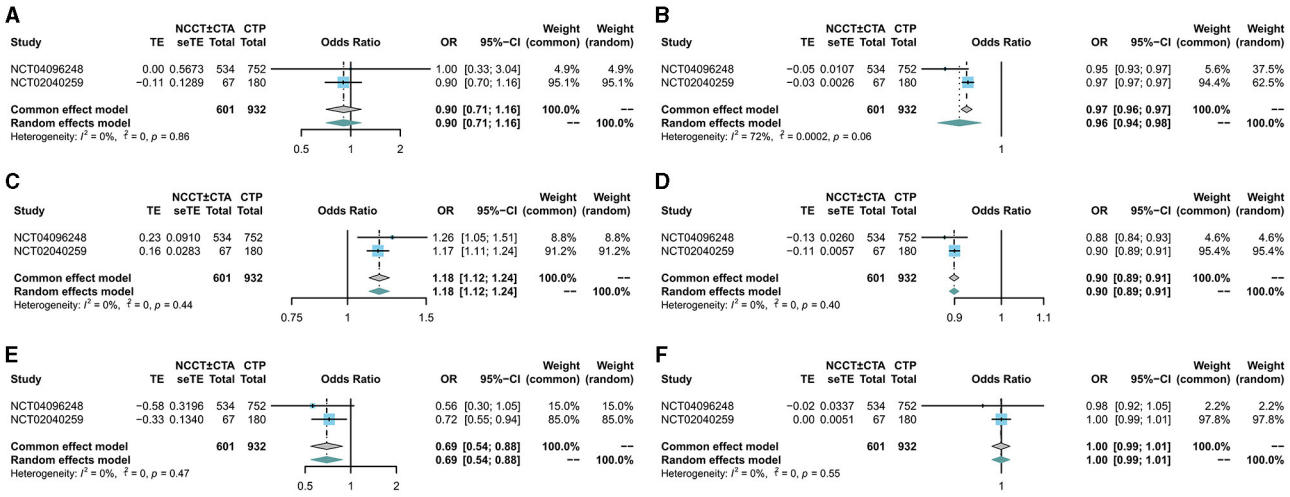

FIGURE 3
Forest plot for multivariate analysis of good prognosis. The diamond indicates the odds ratio (95% confidence interval) for all patients together. **(A)** CTP, **(B)** age, **(C)** ASPECTS score, **(D)** NIHSS score, **(E)** diabetes, **(F)** time last seen well to puncture.

restore lost neurological function but may increase the potential risk of reperfusion bleeding (23). In contrast, overestimating the final infarct core and selecting patients for reperfusion treatment based on the concept of CTP mismatch may exclude patients who may benefit from reperfusion (13, 24). Moreover, there remained discrepancies in the time-consuming image processing by various software, which may delay the time for patients to receive treatment (21, 22). A recent study showed that in up to 25% of cases, CTP may not detect an ischemic core at all, especially in isolated deep middle cerebral artery strokes (25).

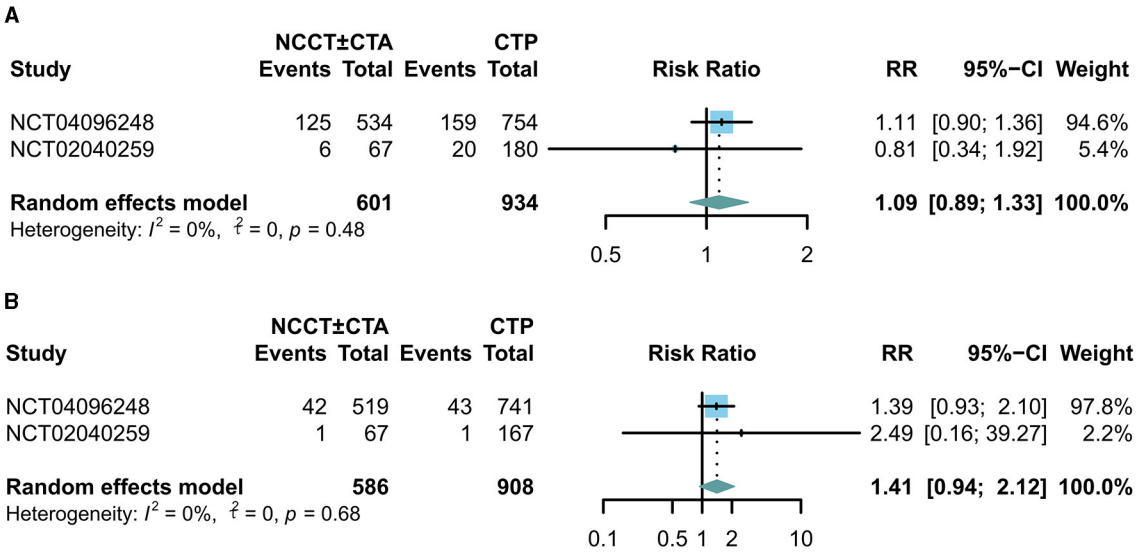

FIGURE 4
Forest plots for the incidence of adverse events. The diamond indicates the risk ratio (95% confidence interval) for all patients combined. **(A)** 90-day mortality, **(B)** incidence of symptomatic intracranial hemorrhage.

NCCT has become the first-line imaging method for acute stroke due to its wide applicability, short examination time, and low examination cost (9). NCCT ASPECTS is an easily accessible imaging metric to assess LVO in AIS (26). Although it may be difficult to detect early ischemic changes after stroke with a non-contrast CT, the sensitivity of non-contrast CT increases over time, and its predictive accuracy for irreversible injury may be higher than relative cerebral blood flow (9, 27). At cerebral blood flow <30%, CTP tends to depict larger infarct core volumes compared to NCCT and may underestimate the volume of potentially salvageable brain tissue, whereas NCCT ASPECTS is superior to CTP in correlating with the ischemic core at this time (28, 29). This means that one cannot rely too much on CTP imaging criteria alone for patient selection. Studies have shown that NCCT ASPECTS correlates with CTP core volume in delayed time windows (30). Combining NCCT ASPECTS with single- or multiphase CTA collateral scores can more accurately predict target zone mismatch (26). At the same time, ASPECTS scoring emphasizes the concern for population variability (31). In a recent large multicenter phase III trial, endovascular treatment selection for LVO stroke patients based on the presence or absence of CTA collateral flow was found to be effective and safe (32). Moreover, prospective studies of CTA-based artificial intelligence (AI) software for the detection of LVO stroke patients have also yielded favorable results (33). Of a total of 1,822 CTAs performed, 190 occlusions were identified, of which 142 were in the internal carotid artery terminal (ICA-T) and middle cerebral artery M1 and M2 sites. The detection rates of ICA-T, M1, and M2 occlusions were 100, 93, and 49%, respectively (34). With the continuous optimization of the algorithm, it is believed that clinicians can reduce the number of potentially salvageable patients missed by using AI as an auxiliary tool. The above evidence suggests that relying solely on NCCT ± CTA for endovascular treatment options for LVO patients is feasible and convenient for small stroke centers and, to some extent, superior to CTP (35).

The retrospective nature of most of the studies and some of the limitations associated with small sample sizes, in addition to the substantial heterogeneity of the reported data, require caution in interpreting our findings. Notably, the MR CLEAN LATE (Endovascular treatment of acute ischemic stroke in the Netherlands for late arrivals) and the RESILIENT-Extended (Randomization of Endovascular Treatment in Acute Ischemic Stroke in the Extended Time Window) trials are underway to provide more definitive evidence of simplified imaging protocols in extended time windows (36). In addition, as the algorithm has evolved, NCCT-based machine-learning models have been developed (37). In a recent study, an algorithm called Methinks was able to detect LVO from NCCT alone with reasonable accuracy (38). Meanwhile, another new technique, dCTA-perfusion, uses the existing ultra-fast three-phase trCTA acquisition to extract perfusion information and derive perfusion maps (39). Preliminary evidence suggests that the perfusion metrics obtained are comparable to those of CTP. The rapid results obtained with these new techniques help speed up treatment decisions compared with CTP evaluation. In addition, shorter scan times and fewer image acquisitions reduce radiation exposure (40). Most importantly, the low resource requirements allow for widespread use, benefiting stroke patients. In summary, the larger concern for healthcare practitioners is that whichever imaging selection paradigm is chosen, the goal is not to determine the maximum treatment benefit for the patient but to distinguish the population most likely to benefit from treatment.

5. Conclusion

These findings suggest that preoperative imaging evaluation of patients undergoing mechanical thrombectomy for anterior circulation large-vessel occlusion at 6–24 h after onset does not

differ significantly from the outcome of patients choosing the NCCT ± CTA modality compared with the CTP modality and significantly reduces the time from onset to arterial puncture. Our findings support the use of extended time window stroke imaging paradigms.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

ZZ and FG were the principal investigators, contributed to the writing of the article, designed the study, and developed the analysis plan. FG analyzed the data and prepared the plots. YJ and YZ revised the manuscript and polished the language. YG and ZW supervised the project. All authors have read and approved the final version of the paper.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1185554/full#supplementary-material

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A systematic review and meta-analysis of health utility values among patients with ischemic stroke

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Purpose: Ischemic stroke (IS) has a considerable impact on the health-related quality of life (HRQoL) of patients. A systematic review was conducted to summarize and synthesize the HRQoL reported from IS patients.

Methods: An electronic search was performed in PubMed, Web of Science, ScienceDirect, Embase, and Cochrane Library databases from inception to February 2022 for studies measuring utility values in IS patients. Basic information about the studies, patient characteristics, measurement of the utility values, and utility values were extracted and summarized. Utility values were pooled according to the time of evaluation, and disease severity was classified with modified Rankin Scale (mRS) scores. The quality of the studies was assessed according to key criteria recommended by the National Institute for Health and Care Excellence.

Results: A total of 39 studies comprising 30,853 participants were included in the study. Measured with EQ-5D-3L, the pooled utility values were 0.42 [95% confidential interval (CI): 0.13 to 0.71], 0.55 (95% CI: 0.43 to 0.68), 0.65 (95% CI: 0.52 to 0.78), 0.60 (95% CI: 0.43 to 0.78), and 0.67 (95% CI: 0.60 to 0.74) for patients diagnosed with IS within 1, 3, 6, 12, and 24 months or above among poststroke patients. Four studies reported utility values classified by mRS scores where synthesized estimates stratified by mRS scores ranged from 0.91 (95% CI: 0.85 to 0.97) for patients with an mRS score of 1 to−0.04 (95% CI:−0.18 to 0.11) for those with an mRS score of 5. As for the health dimension profiles, usual activity was the most impacted dimension, while self-care was the least impacted one.

Conclusion: This study indicated that the utility values in IS patients kept increasing from stroke onset and became relatively stabilized at 6 months poststroke. Health utility values decreased significantly as mRS scores increased. These results facilitate economic evaluations in utility retrieval and selection. Further exploration was required regarding the factors that affect the HRQoL of IS patients.

KEYWORDS

ischemic stroke, health-related quality of life, utility value, EQ-5D, systematic review

1. Introduction

Stroke continues to be one of the leading causes of death and disability worldwide; with 12.2 million strokes that occurred in 2019, ischemic stroke (IS) accounted for 62.4% (1). The disease burden of IS increases continuously in China, where the number of incident cases was estimated to reach 2.8 million in 2019 (2).

Despite the advances in early management and secondary prevention, deaths from stroke have increased by 43.0% over the last three decades (1, 3, 4). Additionally, patients who survive IS often experience long-term disability (5), cognitive impairment (6), and emotional problems (7), leading to compromised health-related quality of life (HRQoL).

HRQoL can be defined as how well a person functions in their life and his or her perceived wellbeing in physical, mental, and social domains of health and can be presented using utility (8), which ranges from 0 to 1, where 0 represents death and 1 represents perfect health, and a negative utility value represents health states that are worse than death (9). There are various methods to directly and indirectly measure utility values; these methods can be performed among patients, their caregivers, or the general public. Direct evaluation methods such as time trade-off (TTO), standard gamble (SG), and rating scale (RS) elicit values directly from respondents who make their assignment with respect to specific health states or are required to report their preferences toward some hypothetical scenarios. However, these evaluation methods take more time and may involve problems regarding cognitive understanding and interviewer effects (10, 11). Indirect valuation methods such as the EuroQol 5-dimensional (12) (EQ-5D), Short Form 6 Dimensions (13) (SF-6D), 15D (14), and Health Utility Value Index (15) (HUI) are questionnaires that are easier to administer and thus can be included as a part of clinical trials or routine follow-up without increasing respondent burden (16). In the questionnaires, respondents specify their health states in multiple dimensions, and the questionnaire responses are then converted to utility values by means of "tariffs" (17). The "tariffs" are obtained from previous studies in which values for possible health states were elicited from the general population using methods such as TTO (12, 17).

Utility can also be applied to estimate quality-adjusted life years (QALYs) gained for cost-effectiveness analysis by multiplying by the time of survival in a certain health state. With the launch of new medical techniques, the use of cost-effective analysis to compare the potential benefits, harms, and costs between new interventions and existing interventions is an important technique for healthcare decision-makers and has been widely adopted in many countries to help better allocate medical resources (18).

Given the important role of health utility values in summarizing HRQoL and supporting cost-effectiveness analysis, this systematic review aimed to identify and summarize studies reporting utility values in IS and provide the pooled utility values of the IS population at different times of measurement and disease severities.

2. Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (19).

2.1. Search strategy

The PubMed, Embase, Cochrane Library, Web of Science, and ScienceDirect databases were searched from inception to February 2022. Search terms included "ischemic stroke," "ischaemic stroke," "patient reported outcomes," "quality of life," "QoL" and "HRQoL." Detailed information on search items in the abovementioned database is shown in Supplementary Table 1.

2.2. Inclusion and exclusion criteria

According to the PICOS framework, both clinical trials and observational studies that reported outcomes on utility values in IS patients were included. There were no restrictions on interventions and comparators. In order to decrease the heterogeneity and uncertainty, studies were excluded if they met any of the following criteria: (a) only abstracts or studies with full-text unavailable; (b) systematic review; (c) economic evaluation; (d) not published in English; (e) reported utility values for a mixed cohort of patients with IS and hemorrhagic stroke; and (f) non-original study that did not provide additional information on health utility.

2.3. Data extraction

The characteristics of the included studies were extracted independently by two reviewers, with disagreements resolved through discussion or a third reviewer. The following data were extracted from the included studies: study characteristics (year of publication, country or region, study design, sample size, and intervention/grouping), demographic characteristics of patients (age and gender), methodology of HRQoL measurement (survey method, evaluation time, and tariff), and utility values.

2.4. Data analysis and synthesis

To observe the long-term changes in utility values in the IS population, mean utility values elicited with the EQ-5D were synthesized by meta-analysis according to the appropriate time of evaluation. Since few studies reported the mean utility values using EQ-5D-5L, only mean utility values measured using EQ-5D-3L were pooled. Considering the short duration of stay, days from discharge were regarded as days from poststroke. Additionally, the difference in synthesized utility values between each evaluation time was compared with minimally important differences (MIDs) in the EQ-5D-3L in stroke. The MID in the EQ-5D was 0.08 to 0.12 (20), and a 0.1-point increase or decrease in utility was considered an important change in our study. Furthermore, the utility values stratified by the modified Rankin Scale (mRS) were also pooled to describe utility weights for individuals with different mRS scores. The mRS is a commonly used clinician-reported scale that assesses changes in disability after stroke, with scores ranging from 0 to 6 (21).

Notably, this study aimed to synthesize utility values for IS population, and utility values derived from patients who entered the randomized controlled studies and received the specific treatments (e.g., intensive lipid rather than guideline lipid) or participated in some therapeutic programs (e.g., home rehabilitation program, which was a home-based exercise program

provided by a physical therapist) tend to generate better health states with higher utility values and could not represent the general population. Similarly, the utility values for IS patients with specific poststroke complications (e.g., spasticity) were not included. Pooled utility values of compared groups from clinical trials were also excluded. For multiple publications from the same study population, the article that reported utility values appropriate for meta-analysis or covered a larger sample size was included. For any study reporting utility values applying diverse tariffs from multiple countries, to eliminate the additive effect, only the utility value calculated using investigators' country-specific tariff was included in the meta-analysis.

If the standard deviation (SD) around the mean utility value was not available in the article, estimations from the standard error or 95% confidential interval (CI) were applied. The heterogeneity among the included studies was assessed using the I^2 statistic, and fixed effects models were employed if the value of I^2 was smaller than 50%; otherwise, random effects models were used. The meta-analysis was conducted in R software version 4.2.1 using the "meta" package.

2.5. Quality assessment

Since there were no agreed criteria specific for assessing the quality of utility studies, we assessed the quality of the included studies based on the criteria recommended in the National Institute for Health and Clinical Excellence guidance on a systematic review of utility values (22) and additional two criteria (uncertainty measurement and appropriateness of tariff) applied in the study by Mok et al. (23).

3. Results

3.1. Study selection

The flowchart of study selection and the inclusion process is presented in Figure 1. Our search initially identified 4,106 references. After removing duplicates, 1,911 records were further screened by titles and abstracts. Finally, 91 articles were subject to full-text screening, where 55 were excluded mostly because they did not involve utility evaluation. Three additional studies were identified from the reference lists of relevant publications. A total of 39 studies were included, and 17 studies were selected for meta-analysis.

3.2. Basic characteristics of the included studies

The basic characteristics of the included studies are summarized in Table 1. A total of 39 identified studies were published between 1999 (24) and 2022 (25), with most of studies (n = 8) (26–33) published in 2017. The included studies covered different regions around the world. Five of the studies were multinational (26, 31, 34–36), 18 studies in Europe (24, 27, 28, 30, 32, 33, 37–48), 8 studies in Asia (25, 49–55), 7 studies in North America (29, 56–61), and 1 study in Australia (62). In terms of study design, 22 of the 39 (56.4%) studies were observational, while the rest were randomized controlled studies to assess the effectiveness of treatment. In the randomized controlled studies, endovascular treatment (EVT) was the most common therapy (25, 28, 31–33, 35, 43, 54). Other treatments included a rehabilitation program, alteplase, citicoline, intravenous tissue plasminogen activator (t-PA), lipid management, and blood pressure management. Studies included 30,853 participants (adjustment has been made for the overlapping populations), and the sample size ranged from 11 to 4,016. The average or median age of the study population was >60 years in most of the studies. The proportion of males ranged from 36.0 to 81.6%.

3.3. Utility score evaluation methods

The evaluation methods are presented in Table 2. For methods applied, three studies (40, 42, 46) did not specify the survey method, while nine studies (25, 28, 34, 36, 44, 45, 53, 54, 61) used more than one method. The survey methods included telephone interviews (n = 16, 41.0%), face-to-face interviews (n = 11, 28.2%), questionnaires during the follow-up visit (n = 10, 25.6%), and postal questionnaires (n = 4, 10.3%). As for the respondents, only one study involved a normal population (24), in which they were asked to imagine their preference for certain scenarios as IS survivors. Among the studies that reported specific information on respondents, the percentage of proxies in the reported studies ranged from 12 to 56%. Regarding the utility score elicitation method, only one study used direct methods where TTO, SG, and RS were adopted simultaneously (24). For the indirect methods, the vast majority of studies (n = 37) used the EQ-5D, most of which (n = 31) used the EQ-5D-3L, 4 studies used EQ-5D-5L, and 2 studies did not mention the EQ-5D-3L/EQ-5D-5L version. In addition, the time point of evaluation for IS patients in the included studies ranged from the stroke onset to 7 years poststroke. A total of 3, 6, 12, and 24 months after stroke/discharge were the most frequently adopted evaluation time points. For tariffs to calculate utility values, 20 studies did not specify the tariffs, and 2 of 5 multinational studies (26, 34) used tariffs from multiple countries of the study population.

3.4. Utility results

3.4.1. Utility values classified by the time of evaluation

We synthesized the utility values by the baseline (within 1 month after stroke/discharge), 3, 6, 12, and 24 months or above among poststroke patients, as illustrated in Figure 2. For patients at the baseline of stroke onset, the utility values were reported in five studies, ranging from−0.11 to 0.67. Accordingly, the pooled estimate as utility value for the acute stroke phase was 0.42 (95% CI: 0.13 to 0.71), with significant heterogeneity (I^2 = 100%), as presented in Figure 2A. When measured at 3 months after stroke, the utility values were increased and ranged from 0.34 to 0.71 in six studies. The synthesized utility value was 0.55 (95% CI: 0.43 to 0.68). When measured at 6 months after stroke, the utility values

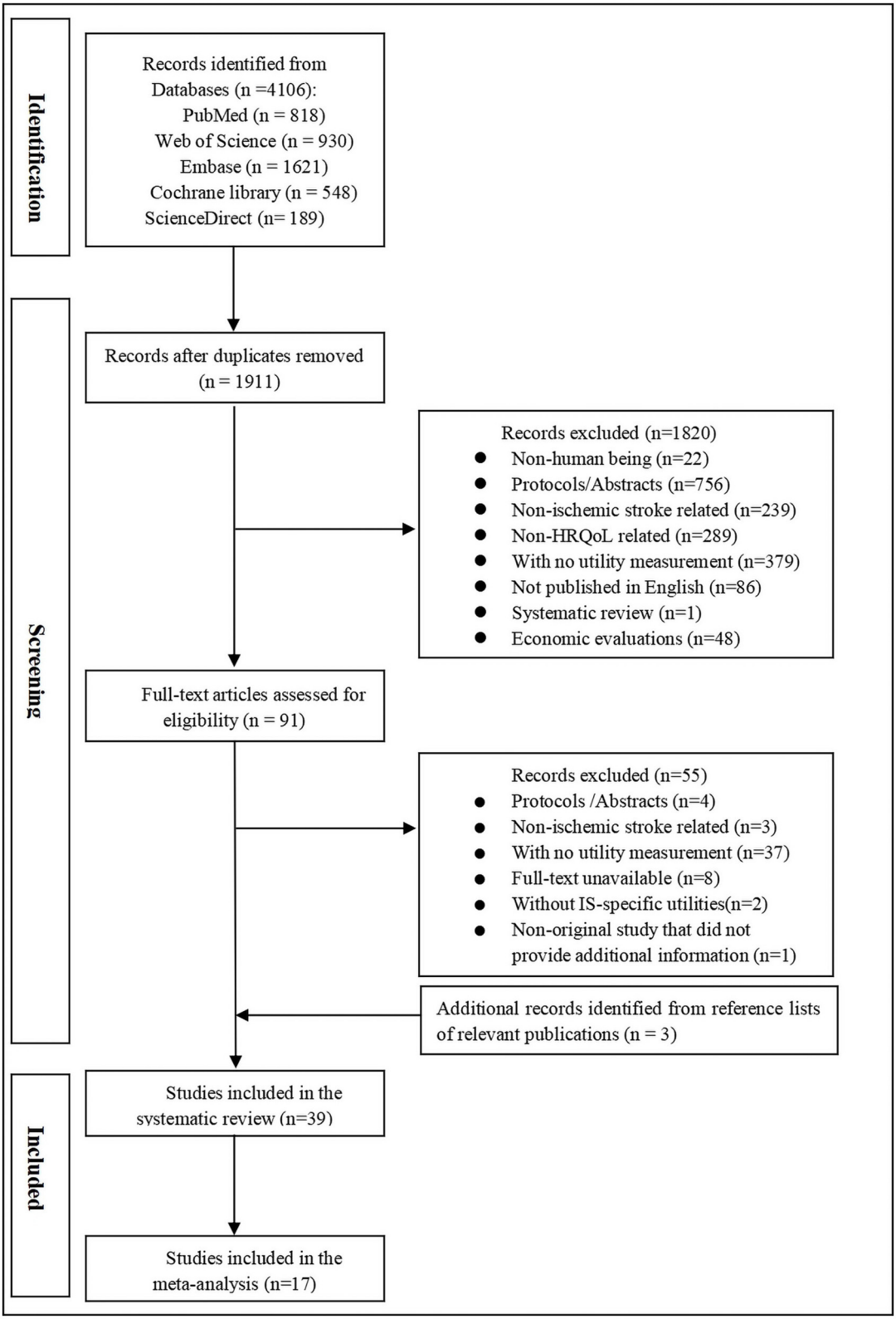

FIGURE 1
Flowchart of the study inclusion process.

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TABLE 1 Basic characteristics of the included studies.

Study	Country/ region	Study design	Intervention/ grouping	Sample size	Male (%)	Age (mean ± sd)
Hallan et al. (24)	Norway	Obs	a: minor stroke b: major stroke	158	47.0	NR
Pickard et al. (56)	Canada	Obs	NR	124	53.0	68.3 ± 14.6
Haacke et al. (37)	Germany	Obs	NR	54	48.0	NR
Chaiyawat et al. (49)	Thailand	RCT	a: home rehabilitation program b: usual care	a: 30 b: 30	a: 47.0 b: 43.0	a: 67.0 ± 10.0 b: 66.0 ± 11.0
Lee et al. (50)	Taiwan	Obs	a: lacunar infarction b: non-lacunar infarction	a: 170 b: 263	a: 62.9 b: 63.5	a: 67.7 ± 10.4 b: 63.7 ± 13.1
Chiayawat et al. (51)	Thailand	RCT	a: home rehabilitation program b: usual care	a: 30 b: 30	a: 47.0 b: 43.0	a: 67.0 ± 10.0 b: 66.0 ± 11.0
Naess et al. (38)	Norway	Obs	NR	328	63.0	67.7
Luengo-fernandez et al. (39)	UK	Obs	NR	404	NR	NR
The IST-3 group (34)	Multinational	RCT	a: alteplase + standard care b: standard care	a: 1,169 b: 1,179	a: 49.0 b: 49.0	NR
Bushnell et al. (58)	USA	Obs	NR	1,370	53.7	65.0*(56.0–75.0)#
Kelly et al. (57)	USA	Obs	Hemicraniectomy	11	36.0	55.0*(42.0-62.0)#
Gillard et al. (59)	USA	Obs	a: patients with spasticity b: patients without spasticity	a: 54 b: 274	a: 54.0 b: 51.0	a: 59.7 ± 14.1 b: 67.1 ± 13.5
Alvarez-Sabín et al. (40)	Spain	RCT	citicoline/usual treatment	163	50.9	67.5 ± 10.7
Chang et al. (52)	Korea	Obs	NR	2,289	62.2	65.7 ± 12.4
Rangaraju et al. (35)	Multinational	RCT	EVT + intravenous t-PA/intravenous t-PA alone	423	NR	NR
Sand et al. (41)	Norway	Obs	a: with vision problem b: with normal vision	a: 83 b: 244	a: 55.4 b: 65.2	a: 71.8 ± 14.3 b: 66.5 ± 12.4
Ali et al. (26)	Multinational	RCT	NR	3,858	NR	67.5 ± 12.5
Bath et al. (27)	UK	RCT	a: intensive lipids b: guideline lipids	a: 39 b: 38	a: 76.9 b: 81.6	a: 74.2 ± 6.4 b: 74.4 ± 6.9
Dávalos et al. (28)	Spain	RCT	a: EVT + medical treatment b: medical treatment	a: 103 b: 103	a: 53 b: 52	a: 65.7 ± 11.3 b: 67.2 ± 9.5
Katzan et al. (29)	USA	Obs	NR	3,283	54.0	63.5 ± 14.4
Persson et al. (30)	Sweden	Obs	NR	248	66.0	64.0 ± 11.0
Rangaraju et al. (31)	Multinational	RCT	EVT + intravenous t-PA/intravenous t-PA alone	423	NR	64.0 ± 13.0
Schreuders et al. (32)	Netherlands	RCT	a: EVT + usual care b: usual care	457	41.1	66.0*(56.0-76.0)#
van den berg et al. (33)	Netherlands	RCT	a: EVT + usual care b: usual care	a: 194 b: 197	a: 57.2 b: 59.9	a: 65.9*(55.8–76.2)# b: 65.5*(56.6–76.6)#
Chung et al. (53)	Korea	Obs	NR	991	65.6	64.3 ± 12.0
Dijkland et al. (43)	Netherlands	RCT	a: EVT + usual care b: usual care	a: 233 b: 267	a: 58.0 b: 59.0	a: 65.8*(54.5–76.0)# b: 65.7*(55.5–76.4)#
Winter et al. (42)	Germany	Obs	a: with poststroke epilepsy b: without poststroke epilepsy	a: 23 b: 351	a: 56.2 b: 57.0	a: 67.0 ± 8.4 b: 69.0 ± 4.9
Dewilde et al. (44)	Belgium	Obs	NR	539	58.9	68.7 ± 12.9
Oemrawsingh et al. (45)	Netherlands	Obs	NR	1,022	57.0	74.0*(64.0–82.0)#
Chen et al. (36)	Multinational	RCT	Standard-dose/low-dose rt-PA/intensive BP lowering/guideline-recommended BP lowering	4,016	62.4	66.1

(Continued)

TABLE 1 (Continued)

Study	Country/ region	Study design	Intervention/ grouping	Sample size	Male (%)	Age (mean ± sd)
Jarosławski et al. (46)	Poland	Obs	NR	171	47.7	70.5
Willeit et al. (47)	Austria	RCT	a: STROKE-CARD care b: standard care	a: 1,438 b: 711	a: 59.0 b: 59.0	a: 69.0 ± 14.0 b: 70.0 ± 13.0
Yang et al. (54)	China	RCT	a: EVT b: alteplase + EVT	a: 327 b: 329	a: 57.8 b: 55.0	a: 69.0* (61.0–76.0)# b: 69.0* (61.0–76.0) #
Parameshwaran et al. (62)	Australia	Obs	EVT	145	57.0	70.0 ± 13.3
Romano et al. (60)	USA	Obs	NR	1,765	58.0	65.0 ± 14.0
Schneider et al. (48)	Estonia	Obs	NR	352	63.1	48.8*
She et al. (55)	China	RCT	NR	1,714	63.4	61.4 ± 9.7
Sucharew et al. (61)	USA	Obs	NR	294	48.0	70.0* (60.0–79.0)#
Zhang et al. (25)	China	RCT	a: with anxiety/depression b: without anxiety/depression	a: 289 b: 226	a: 61.3 b: 51.8	a: 66.8 ± 11.5 b: 67.5 ± 12.7

*Median; #Interquartile range. Obs, observational; RCT, randomized controlled trial; sd, standard deviation; EVT, endovascular treatment; t-PA, tissue plasminogen activator; BP, blood pressure; NR, not reported.

ranged from 0.34 to 0.82 in six studies, and the pooled utility value was 0.65 (95% CI: 0.52 to 0.78). A slight decrease could be observed at 12 months poststroke, where the estimated utility values were 0.60 (95% CI: 0.43 to 0.78). The synthesized utility values were 0.67 (95% CI: 0.60 to 0.74) at 24 months and above poststroke, indicating a relatively steady HRQoL among patients. Health utility values kept increasing from stroke onset to 6 months poststroke, and MID could be observed between the baseline and 3 months as well as 3 and 6 months. Therefore, it is concluded that the utility values reached a relatively stable level after 6 months poststroke. The utility values after 6 months were further combined and estimated to be 0.66 (95% CI: 0.59 to 0.72), as presented in Supplementary Figure 1. The trend of change in utility values was similar to that of most of the included longitudinal studies (Figure 3).

3.4.2. Utility values classified by mRS

Eight studies reported utility values stratified by mRS scores (as shown in Table 3), of which three reported utility values for dichotomized mRS scores (24, 37, 62) (classified as "independence" and "severe disability") and one study reported the utility index as median values (31). Thus, these four studies were excluded, and the other four studies reported mean values (26, 36, 43, 44) were included in the pooled analysis. With considerable heterogeneity, the pooled effect estimates for mRS scores from 0 to 5 were 0.91, 0.85, 0.73, 0.54, 0.26, and−0.04, respectively, as shown in Figure 4. The MID in utility values was seen between all mRS levels except mRS 0 and mRS 1.

3.4.3. Utility values for subgroups

The utility of the IS population is affected by many factors. Some of the studies reported utility values for specific subgroups of IS populations. For example, four studies reported utility values for male and female IS patients, and all suggested that men had better HRQoL as measured by the EQ-5D-3L than women (37, 40, 55, 58). In addition, one study reported utility values stratified by National Institutes of Health Stroke Scale (NIHSS) scores, which was another scale for disease severity. It was indicated that utility values at 3 months for NIHSS 0–4, NIHSS 5–11, NIHSS 12–19, and NIHSS ≥ 20 were 0.86, 0.77, 0.59, and 0.52, respectively (35).

Poststroke complications also played an important role in affecting utility values, and it was reported that IS patients with poststroke spasticity had lower scores on the EQ-5D (0.63 vs. 0.71) (59). Similarly, patients with poststroke epilepsy reported worse HRQoL in the long term (42).

Moreover, the utility values were affected by the valuation instrument. In four studies that reported instrument-specific utility values, the utility values elicited by EQ-5D were lower than those elicited by 15D (38, 41) but higher than those elicited by HUI3 (37, 56). Additionally, the utility was mediated by respondents due to differences in the perception of HRQoL between patients and their proxies, in two studies that reported the utility of specific respondents, both suggested that the utility was slightly lower for proxies than for patient self-assessments (56, 61).

3.5. Responses to EQ-5D dimensions

Nine studies (16 groups) reported the responses to EQ-5D dimensions. The overall information on responses to five dimensions is illustrated in Figure 5. Given the differences in baseline characteristics, disease severity of the study population, and evaluation time, the proportion of patients reporting "no problems" in each dimension varied greatly. Nevertheless, by comparing the dimensions, 12 groups suggested that the proportion of patients who reported "no problems" in the self-care dimension was higher than that of other dimensions. Additionally, six groups showed that the proportion of patients who reported "no problems" in the usual activity dimension was lower than that of other dimensions. In general, the most impaired health dimension

TABLE 2 Utility evaluation methods and results.

Study	Survey method	Valuation instrument	Tariff	Valuation time	Respondents	Utility values	EQ-VAS
Hallan et al. (24)	Interview (supported by an interactive computer program)	SG, TTO, Direct scaling	NA	NR	Healthy people: 42% Non-stroke patients: 32% Stroke survivors: 26%	SG: a: 0.91*, b: 0.61* TTO: a: 0.88*, b: 0.51* Direct scaling: a: 0.71*, b: 0.31*	NA
Pickard et al. (56)	Self-administered questionnaire	EQ-5D-3L, HUI3	UK	Baseline (after the acute phase but before discharge) 1 month, 3 months, 6 months	Patients and proxies answered questionnaires separately	Patients: EQ-5D-3L: 0.31 ± 0.38; HUI3: 0.21 ± 0.30 EQ-5D-3L: 0.55 ± 0.36; HUI3: 0.42 ± 0.36 EQ-5D-3L: 0.61 ± 0.30; HUI3: 0.45 ± 0.34 EQ-5D-3L: 0.62 ± 0.34; HUI3: 0.44 ± 0.37	61 ± 17 64 ± 19 69 ± 17 70 ± 18
Haacke et al. (37)	Face-to-face interview	EQ-5D-3L, HUI2, HUI3	NR	4 years after stroke	Patients	EQ-5D-3L:0.68 ± 0.33 HUI2: 0.61 ± 0.24 HUI3: 0.36 ± 0.38	56.74 ± 22.10
Chaiyawat et al. (49)	Face-to-face interview	EQ-5D-3L	NR	Baseline 3 months after stroke	Patients	a:−0.14 ± 0.08; b:−0.11 ± 0.13 a: 0.88 (SE 0.02); b:0.53 (SE 0.02)	NR
Lee et al. (50)	Interview	EQ-5D-3L	USA, UK	4.0 to 5.1 years after stroke	Patients	a: 0.8 ± 0.2 b: 0.7 ± 0.3	NR
Chiayawat et al. (51)	Face-to-face interview	EQ-5D-3L	NR	2 years after stroke	Patients	a: 0.9 ± 0.02 b: 0.7 ± 0.04	NR
Naess et al. (38)	Postal survey	EQ-5D-3L 15D	NA	at least 6 months after stroke	Patients: 80% Proxy: 20%	EQ-5D-3L: 0.70 ± 0.30 15D: 0.82 ± 0.14	66 ± 21
Luengo-fernandez et al. (39)	Interview	EQ-5D-3L	UK	1 month, 6 months 1 year, 2 years, 5 years	Patients	0.64 ± 0.33 0.70 ± 0.29 0.70 ± 0.27 0.66 ± 0.29 0.67 ± 0.31	NR
The IST-3 group (34)	Telephone interview, Postal survey	EQ-5D-3L	UK and other European tariff	18 months after stroke	Patients: 44% Proxy: 56%	a: 0.55 (SE 0.015) b: 0.50 (SE 0.016)	NR
Bushnell et al. (58)	Telephone interview	EQ-5D-3L	USA	3 months post-discharge 1 year post-discharge	Patients	0.83* (0.76–1.00)# 0.83* (0.74–1.00)#	NR
Kelly et al. (57)	Self-administered questionnaire	EQ-5D-3L	NR	3 months after hemicraniectomy 9 months post-hemicraniectomy	Patients without assistance: 45% Patients with assistance: 55%	0.33* (0.12–0.51)# 0.69* (0.40–0.71)#	NR
Gillard et al. (59)	Telephone interview	EQ-5D-3L	USA	3 months after stroke 1 year after stroke 2 years after stroke	Patients	a: 0.59 (SE 0.03) b:0.71 (SE 0.11) a: 0.60 (SE 0.03) b:0.73 (SE 0.01) a: 0.64 (SE 0.04) b:0.72 (SE 0.02)	NR
Alvarez-Sabín et al. (40)	NR	EQ-5D-3L	NR	2 years after stroke	Patients	0.63 ± 0.28	64.4 ± 25

(Continued)

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TABLE 2 (Continued)

Study	Survey method	Valuation instrument	Tariff	Valuation time	Respondents	Utility values	EQ-VAS
Chang et al. (52)	Face-to-face interview	EQ-5D-3L	NR	6 months after stroke	Patients	0.82 ± 0.19	NR
Rangaraju et al. (35)	Self-administered questionnaire	EQ-5D-3L	USA	3 months after randomization	Patients	NIHSS 0-4: 0.86 ± 0.16 NIHSS 5-11: 0.77 ± 0.18 NIHSS 12-19: 0.59 ± 0.26 NIHSS ≥20: 0.52 ± 0.26	NR
Sand et al. (41)	Postal survey	EQ-5D-3L,15D	NR	At least 6 months poststroke	Patients	EQ-5D-3L: a: 0.62*(0.23–0.73)#, b:0.80*(0.69–1)# 15D: a: 0.73*(0.63–0.82)#, b: 0.89 (0.79–0.95) #	NR
Ali et al. (26)	Self-administered questionnaire	EQ-5D-3L	12 countries	3 months after stroke	Patients: 76.4% Proxy: 21.8%	Utility values were reported based on mRS score.	NR
Bath et al. (27)	Telephone interview	EQ-5D-3L	NR	Baseline (3–7 months poststroke event), around 2 years after randomization	Patients	Baseline: 0.8 ± 0.2 (all) 2 years after randomization: a: 0.8 ± 0.2, b:0.7 ± 0.2	Baseline: 72.9 ± 17.6 Follow-up: a:69.0 ± 22.0 b:73.2 ± 14.5
Dávalos et al. (28)	Face-to-face interview, telephone interview	EQ-5D-3L	Spanish	3 months after stroke 6 months after stroke 1 year after stroke	3/6/12 months: Patients: a:82.1%; 63.4%; 83.5% b:82.8%; 65.9%; 77.9%	a: 0.44 ± 0.36, b: 0.34 ± 0.34 a: 0.45 ± 0.36, b: 0.34 ± 0.34 a: 0.46 ± 0.38, b: 0.33 ± 0.33	3 months: a: 60.0 ± 22.0 b:52.2 ± 23.8 6 months: a:59.9 ± 22.8 b:52.3 ± 24.1 1 year: a:63.0 ± 23.9 b:57.0 ± 23.8
Katzan et al. (29)	Self-administered questionnaire	EQ-5D	NR	58*(32-258)# days after stroke	Patients	0.79* (0.68-0.84)#	NR
Persson et al. (30)	Self-administered questionnaire	SF-6D	UK	7 years after stroke	Patients	0.70 ± 0.12	NA
Rangaraju et al. (31)	Self-administered questionnaire	EQ-5D-3L	USA	3 months after randomization	Patients	0.73 ± 0.24	NR
Schreuders et al. (32)	Telephone interview	EQ-5D-3L	Dutch	3 months after stroke	Patients	a: 0.57* b: 0.39*	NR
van den berg et al. (33)	Telephone interview	EQ-5D-3L	NR	2 years after stroke	Patients	a: 0.48 ± 0.40 b: 0.38 ± 0.39	NR
Chung et al. (53)	Self-administered questionnaire, telephone interview	EQ-5D-3L	NR	Baseline (discharge or within 1 month after discharge) 3 months after discharge 6 months after discharge	Patients	0.67 ± 0.21 0.72 ± 0.18 0.73 ± 0.16	69.25 ± 17.52 74.38 ± 13.85 76.54 ± 13.35
Dijkland et al. (43)	Face-to-face interview	EQ-5D-3L	Dutch	3 months after stroke	Patients: 62% Proxy: 38%	Overall: 0.45 ± 0.32 a: 0.50 ± 0.33 b: 0.41 ± 0.31	NR

(Continued)

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TABLE 2 (Continued)

Study	Survey method	Valuation instrument	Tariff	Valuation time	Respondents	Utility values	EQ-VAS
Winter et al. (42)	NR	EQ-5D-3L	German	Admission 6 months 1 year 2 years	Patients	a: 0.55 ± 0.27, b: 0.59 ± 0.29 a: 0.62 ± 0.36, b: 0.69 ± 0.37 a: 0.51 ± 0.23, b: 0.65 ± 0.19 a: 0.52 ± 0.31, b: 0.66 ± 0.24	a:51.84 ± 10.83 b:54.84 ± 17.93 a:58.34 ± 27.49 b:67.42 ± 20.17 a:56.38 ± 11.24 b:64.77 ± 14.51 a:55.27 ± 10.74 b:64.24 ± 11.44
Dewilde et al. (44)	Self-administered questionnaire, telephone interview	EQ-5D-3L	European	3–36 months after stroke	Patients: 70% Proxy: 30%	Utility values were reported based on mRS score	NR
Oemrawsingh et al. (45)	Face-to-face interview, telephone interview	EQ-5D-5L	Dutch	3 months post-discharge	Patients or proxies	0.65* (0.1-0.83) #	NR
Chen et al. (36)	Face-to-face interview, telephone interview	EQ-5D-3L	UK	3 months after stroke	Patients: 63% Proxy: 37%	0.72 ± 0.37	NR
Jarosławski et al. (46)	NR	EQ-5D-3L	UK, Poland	6-18 months after stroke	Patients	UK standard: 0.51 Polish standard: 0.68	54.4
Willeit et al. (47)	Self-administered questionnaire	EQ-5D-3L	European	12 months after discharge	Patients	a: 0.78* (0.69–1.00) # b: 0.78* (0.57–1.00) #	NR
Yang et al. (54)	Face-to-face interview, telephone interview	EQ-5D-5L	NR	3 months after stroke	Patients	a: 0.84* (0.48–0.95) # b: 0.85* (0.26–1.00)#	NR
Parameshwaran et al. (62)	Telephone interview	EQ-5D-3L	NR	12 months after EVT	Patients	Utility values were reported based on mRS score	NR
Romano et al. (60)	Telephone interview	EQ-5D-5L	NR	3 months after stroke	Patients: 76% Proxies: 12% Undocumented: 12%	0.85 ± 0.17	77 ± 19
Schneider et al. (48)	Postal survey	EQ-5D-3L	Poland	5.7 years after stroke	Patients	0.71 ± 0.28	NR
She et al. (55)	Face-to-face interview	EQ-5D-3L	China	Within 2 weeks after hospitalization	Patients	0.75 ± 0.23	72.7 ± 15.8
Sucharew et al. (61)	EMR, Telephone interview	EQ-5D	USA	3 months after stroke 6 months after stroke	3/6 months: Patients: 66/72% Proxy: 34%/28%	EMR reviewer: 0.78* (0.60–0.83)#, Telephone interviews: 0.81*(0.60–0.85) # EMR reviewer: 0.78* (0.69–0.84), Telephone interviews: 0.83* (0.71–1.00) #	NR
Zhang et al. (25)	Face-to-face interview, telephone interview	EQ-5D-5L	NR	3 months after stroke	Patients	a:0.96* (0.78–1.00)# b:0.57* (0.06–0.85)#	NR

The version of EQ-5D in studies that were published before 2011 and was considered EQ-5D-3L (63). *Represents median. #Represents interquartile range. SG, standard gamble; TTO, time trade-off; EQ-5D, EuroQol 5-dimensional; HUI2, Health Utilities Index Mark 2; HUI3, Health Utilities Index Mark 3; NA, not applicable; NR, not reported; SE, standard error; NIHSS, National Institutes of Health Stroke Scale; EMRs, electronic medical records.

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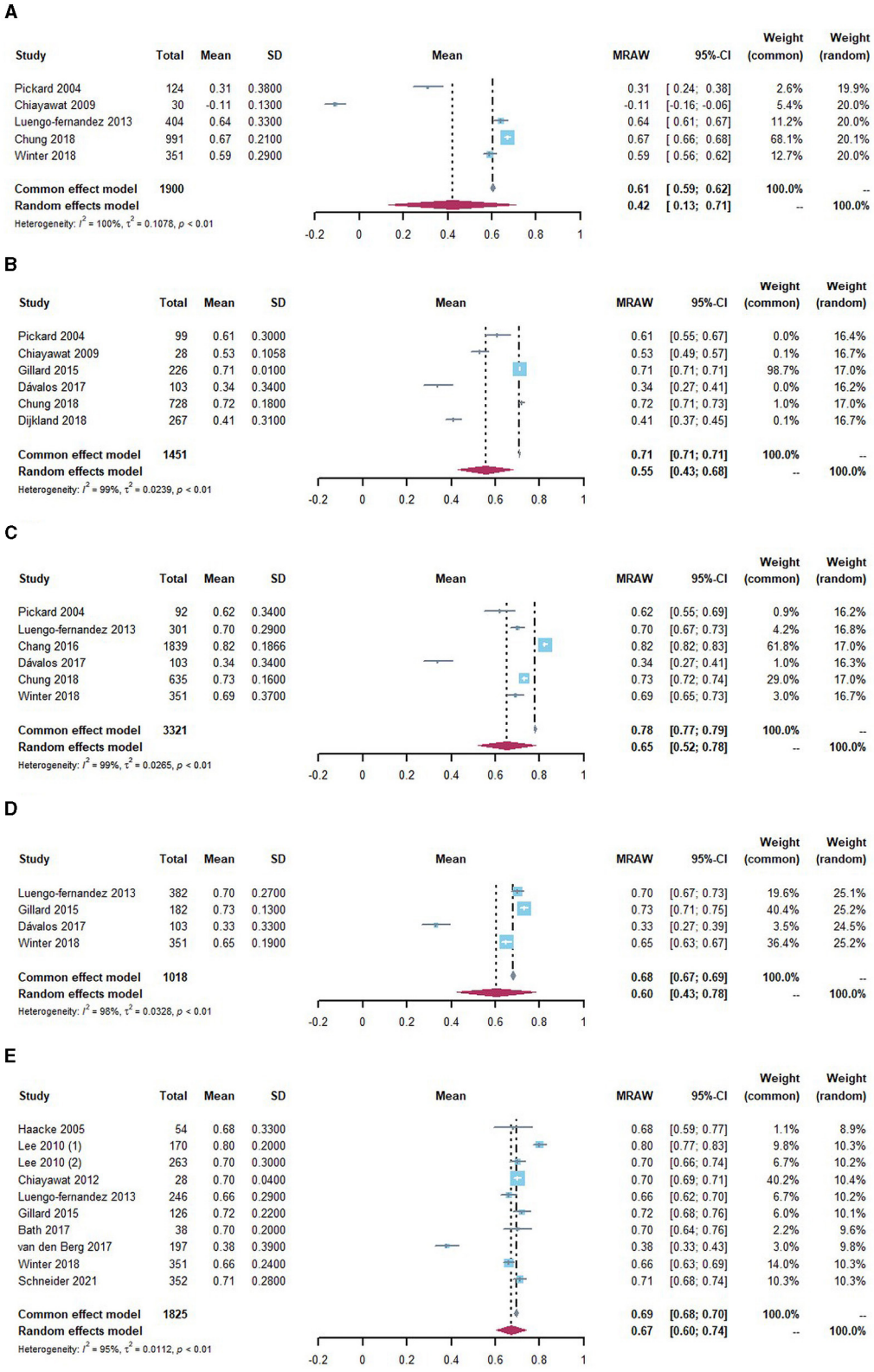

FIGURE 2
Utility values stratified by evaluation time for IS population **(A)** within 1 month of poststroke, **(B)** at 3 months of poststroke, **(C)** at 6 months of poststroke, **(D)** at 12 months of poststroke, and **(E)** 24 months and above of poststroke.

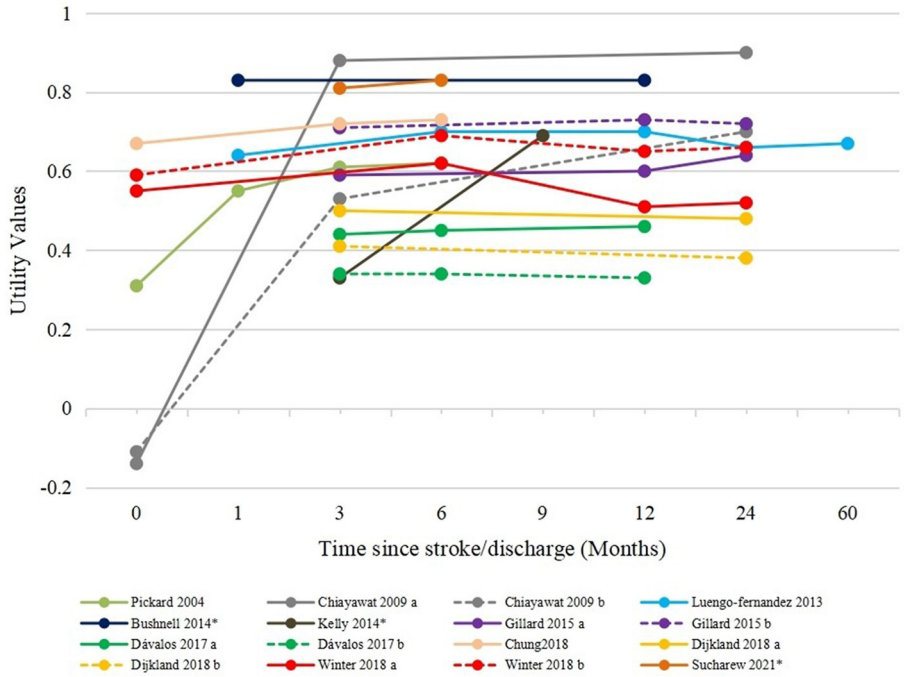

FIGURE 3
Utility values in longitudinal studies. Chiayawat 2009 a, rehabilitation program; Chiayawat 2009 b, usual care; Gillard 2015 a, patients with spasticity; Gillard 2015 b, patients without spasticity; Dávalos 2017 a, endovascular treatment + medical treatment; Dávalos 2017 b, medical treatment; Dijkland 2018 a, EVT + usual care; Dijkland 2018 b, usual care; Winter 2018 a, patients with poststroke epilepsy; Winter 2018 b, patients with poststroke epilepsy. *Utility values were reported as median values in these studies.

TABLE 3 Utility values classified by the modified Rankin Scale.

Study	mRS = 0	mRS = 1	mRS = 2	mRS = 3	mRS = 4	mRS = 5	mRS = 6
Hallan et al. (24)	NR	NR	mRS 2-3: 0.91*		mRS 4-5: 0.61*		NA
Haacke et al. (37)	mRS 0-2 (independence): 0.86			mRS 3-6 (severe disability): 0.44			
Ali et al. (26)	0.90	0.82	0.70	0.53	0.20	−0.15	NA
Rangaraju et al. (31)	1.00*	0.84*	0.78*	0.71*	0.44*	0.18*	NA
Dijkland et al. (43)	0.95	0.93	0.83	0.62	0.42	0.11	0.00
Dewilde et al. (44)	0.83	0.77	0.65	0.44	0.25	0.08	NA
Chen et al. (36)	0.97	0.89	0.75	0.58	0.19	−0.17	NA
Parameshwaran et al. (62)	mRS 0-2: 0.863*			mRS 3-5: 0.324*			NA

*Median. mRS, modified Rankin Scale; NA, not applicable.

was usual activity, while self-care was the least impacted dimension. Anxiety/depression, pain/discomfort, and mobility dimensions were moderately affected.

3.6. Quality assessment

The quality assessment of the included studies is presented in Supplementary Table 2. Many studies did not provide sufficient information on evaluation methodology or utility results to be assessed by several criteria, such as response rates to instruments and missing data. More specifically, in terms of sample size, the utility values were elicited from fewer than 100 participants in five studies (27, 37, 49, 51, 57). The sample size was smaller within the studies focused on specific patients such as those who underwent hemicraniectomy or who had specific complications. The recruitment and inclusion criteria were given in most of the included studies, and since most of the studies applied restrictions on age, disease severity, medical history, and so on and excluded the most severe patients, an overestimate of utility may be induced.

Regarding the results reporting, 22 studies (56.4%) reported their response rates to utility instruments, and none of them were lower than 60%. In addition, in eight included longitudinal studies, only one study (42) did not report information on lost follow-up. However, it remained unclear whether patient characteristics with lost follow-up were similar to those of

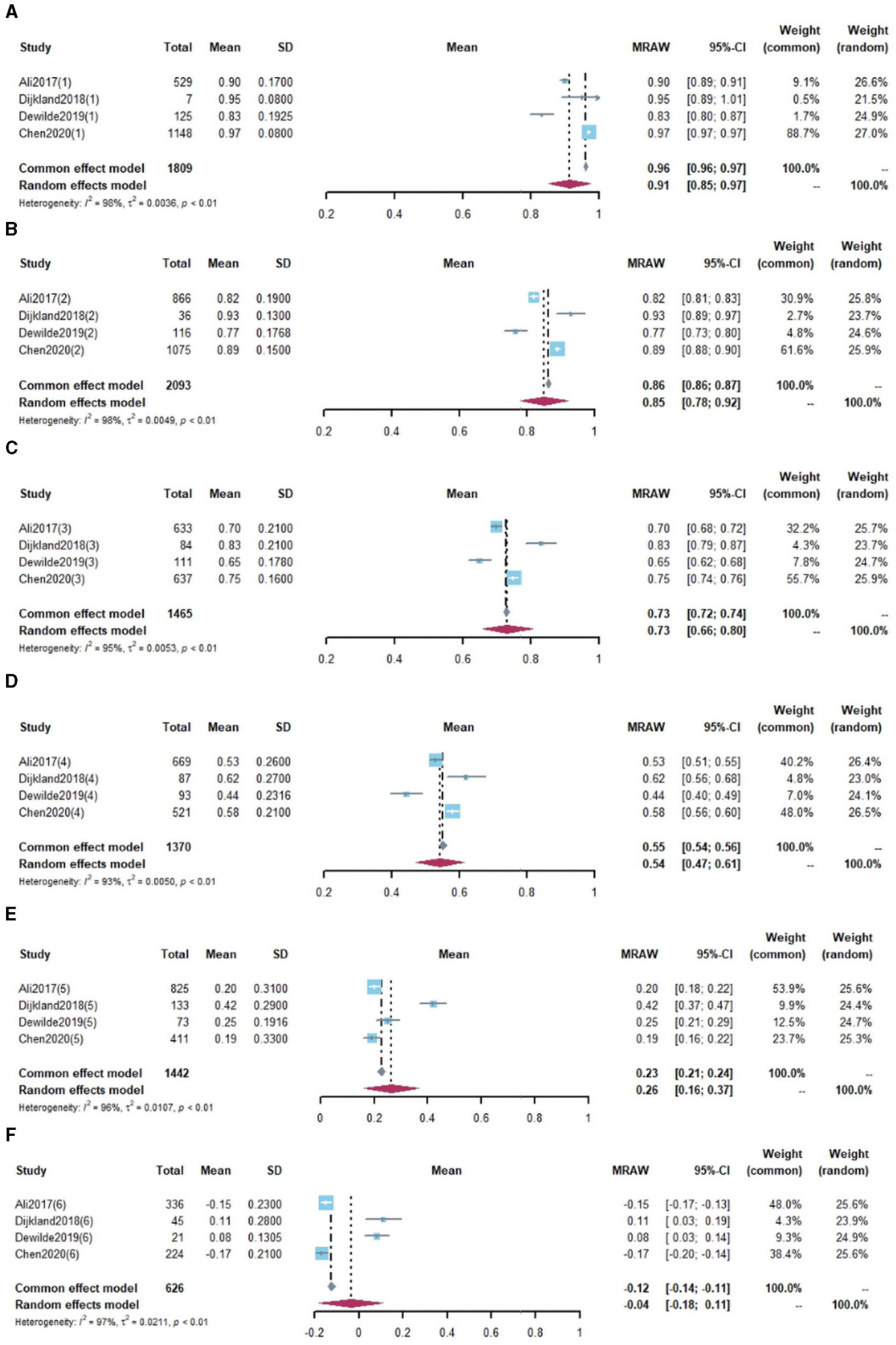

FIGURE 4
Utility values by modified Rankin Scale for IS population. **(A)** mRS = 0, **(B)** mRS = 1, **(C)** mRS = 2, **(D)** mRS = 3, **(E)** mRS = 4, **(F)** mRS = 5.

patients followed up for the rest of the studies indicating a potential risk of bias. Information on missing data was reported in a limited number of studies (n = 12), and eight of them stated the techniques of handling missing data, such as multiple imputation (39, 45) and analysis based on only complete data (52, 58). The studies that did not report missing

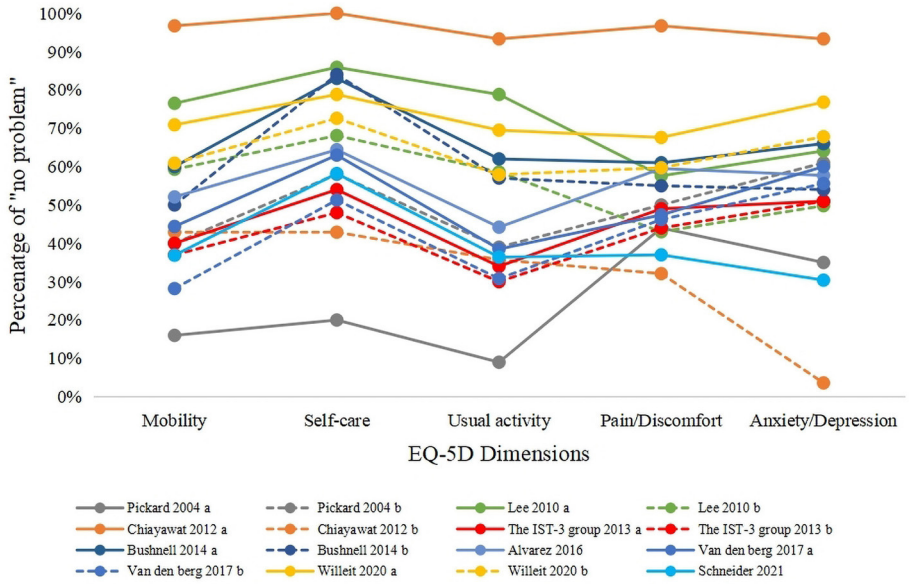

FIGURE 5
Responses to EQ-5D dimensions. Pickard 2004 a, within 2 weeks of stroke (baseline); Pickard 2004 b, 6 months after baseline; Lee 2010 a, lacunar infarction; Lee 2010 b, non-lacunar infarction; Chiayawat 2012 a, rehabilitation program; Chiayawat 2012 b, usual care; The IST-3 group a, alteplase + standard care; The IST-3 group b, standard care; Bushnell 2014 a, male; Bushnell 2014 b, female; Van den berg 2017 a, endovascular treatment plus usual care; Van den berg 2017 b, usual care.

data or the corresponding solution could also cause potential biased estimates.

The measures to elicit utility values were all considered valid in all included studies because they all used well-established instruments. For the uncertainty measurements, most of the studies reported SD or interquartile range (IQR) as uncertain estimates, and only two studies (31, 62) reported median utility values without uncertain estimates. Information on tariffs remained unclear in more than 35% of the included studies, and three studies (48, 50, 56) might apply inappropriate tariffs that did not match the country/region of origin of the HRQoL respondents mainly because localized tariffs were not established at the time their studies were conducted.

4. Discussion

HRQoL plays an important role in measuring and assessing the total wellbeing of poststroke patients. This study aimed to summarize the HRQoL among patients with IS by a systematic review of previous studies. It could be found that EQ-5D-3L was still the most frequently used tool for measuring HRQoL in IS. Additionally, the meta-analysis was performed according to different times of evaluation poststroke and mRS scores. Thereafter, the results could not only observe and discuss the long-term changes in preference-based HRQoL of IS but also provide utility within each mRS level, both of which could be applied in future economic evaluations. When pooling according to the time of evaluation, the results showed that the mean utility values across the included studies increased gradually over time and then reached a stable level at 6 months poststroke. This made sense because the health condition of patients was expected to be improved after the treatment even though IS could make them suffer from long-term disability. However, the utility values were consistently lower than the matched non-stroke population in the long-term observation (30, 48). When stratified by mRS levels, the utility estimates significantly declined by increasing the mRS levels, and the utility for mRS 5 was negative in our review, suggesting that patients had health states that were worse than death. The summary of utility values for specific groups and the response to EQ-5D dimensions might also provide additional information to researchers. Specifically, female patients and patients with poststroke complications had worse HRQoL, which suggested that more attention should be paid to these patients in disease management. Moreover, since self-care dimension was relatively less impacted, efforts to improve patients' HRQoL should focus on usual activity, anxiety/depression, pain or discomfort, and mobility dimensions.

While there have been numerous studies of HRQoL in patients with IS, to the best of our knowledge, very few studies have reviewed utility values regarding IS. Previous reviews included hemorrhagic stroke and were published almost 2 decades ago (64–66), which might not be representative of the current perception in HRQoL. The recently published review (67), focusing on observational studies, synthesized utility values by the evaluation time points and found that a great increase in utility values between acute care and <4-month follow-up, which was consistent with our findings. Moreover, we used an additional time point (2 years and above) for pooled utility values because economic evaluations of cardiovascular disease often include health states for 2-year poststroke (68, 69). In comparison with this review, the present systematic review focuses on a certain type of stroke without

much restriction on the study design and therefore provides more applicable evidence. Moreover, our findings serve as an update for a current assessment of the evidence on the HRQoL in IS patients.

The study also has several limitations to be considered. First, there was a significant heterogeneity in reported utility values although we followed a rational approach to pool comparable studies that applied EQ-5D-3L to similar evaluation time or disease severity and employed random effects models. Heterogeneity in utility may be induced by the differences in characteristics of participants, including age, gender, and complications. Treatments that were assigned to patients, evaluation methods, and tariffs would also contribute to heterogeneity. Second, there was a poor representation of studies from Central and South America, so it could affect the generalizability of the combined results for these regions. Third, our study may be subject to selection bias since the included studies were limited to those published in English. However, given that English is widely used and well accepted around the world, such influence may be mitigated. Fourth, with limited applicable mean utility values measured with EQ-5D-5L, only mean values measured with EQ-5D-3L were included in the meta-analysis. Furthermore, with a limited number of studies assessing the utility values for subgroups, subgroup analysis was not feasible.

There are some arrears that require further investigation in future research. For instance, utility values stratified by time since IS were important to economic evaluations of cardiovascular disease, our findings might be useful when there were no suitable or appropriate sources, and future evidence on long-term changes in utility values among IS patients from longitudinal studies could be more reliable. Additionally, utility estimates for IS patients with complications needed further explanation since poststroke complication has a negative influence on utility, but few studies have investigated on this. Furthermore, few studies have focused on the impact of IS on utility for caregivers or families, which has been evidenced as a source of significant burden (70). Finally, future HRQoL studies would be more informative if considering the appropriate sample size, evaluation method, reporting the missing data, uncertainty around utility results, and so on. These could facilitate future research studies, health decision–making, and improvement of health policies by providing high-quality data and evidence.

5. Conclusion

IS has a substantial effect on patients' HRQoL. This study provided a comprehensive summary of the characteristics of HRQoL research in IS, synthesized health utility values both at different time poststroke and mRS levels, and assessed the quality of studies. The findings from this study will be informative for HRQoL research, economic evaluations, and health decision-making.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

LW and AM contributed to the conception of the study. LW and JZ completed the database search. JZ, QW, HH, and WL conducted the screening, data extraction, and quality assessment, under the guidance of LW, XG, and AM. JZ and LW performed the meta-analysis and interpreted the data. JZ, QW, and LW contributed to the writing and revised the manuscript. All authors approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1219679/full#supplementary-material

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Spontaneous cervical artery dissection: is it really a connective tissue disease? A comprehensive review

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Background: Spontaneous cervical artery dissection (sCeAD) is an important cause of stroke in young adults. The underlying pathophysiology remains unclear, without validated biomarkers to identify subjects at risk. Previous studies suggested the role of abnormalities in the connective component of the arterial wall.

Purpose: To assess dermal ultrastructural aberrations of connective tissue by skin biopsy and genetic variations in sCeAD patients.

Method: We searched the PubMed and Scopus databases until August 2023 with PRISMA guidelines. Original articles assessing skin biopsy in sCeAD patients were included. Two reviewers independently conducted the screening.

Findings: We included 16 studies compromising 459 patients. Thirteen studies assessed ultrastructural changes and found aberrations of collagen and elastic fibers, described as irregular contours and calibers of collagen fibrils, composite flower-like fibrils, fragmented moth-eaten elastin, and microcalcifications, cumulatively in 50.5% of patients. Seven studies showed no causative mutations in collagen type I, III, V, or elastin genes. One study showed linkage between connective tissue alterations and mutation on chromosomes 15q2 and 10q26 using genome-wide linkage analysis, while another study found significant copy number variant enrichments in genes involved in extracellular matrix (COL5A2/COL3A1/SNTA1) and collagen fibril organizations (COL5A2/COL3A1). Finally, differential expression of extracellular proteins was linked to connective tissue disorder in patients with recurrent sCeAD using a quantitative proteomics approach.

Conclusion: Current literature supports the hypothesis that an underlying, subclinical connective tissue disorder, likely genetically determined, may predispose to arterial wall weakness and sCeAD. Further studies with larger sample sizes and robust methodology are needed to better define the role of connective tissue in sCeAD pathogenesis.

KEYWORDS

cervical artery dissection, skin biopsy, connective tissue disorder, genetics, stroke

1. Introduction

Being responsible for up to 25% of brain infarcts in young adults, cervical artery dissection (CeAD), a clinical condition biologically characterized by bleeding within the wall of the cervical arteries, is the most common cause of stroke at young age (1).

The craniocervical arterial wall consists of three layers: (i) the tunica intima, the innermost layer with endothelial cells; (ii) the tunica media, a thick muscular middle layer that is composed of vascular smooth muscle cells and extracellular matrix (ECM); and (iii) the tunica adventitia, the outermost layer that is an ECM coating (2). The two major components of the ECM are elastic fibers and collagen fibers. Elastic fibers comprise a diverse range of ECM species, among which elastin is the most represented. Elastin is attributed to providing distensibility in the vessels and distributing stress onto collagen. Collagen fibers are comprised of bundles of collagen fibrils, which are formed from collagen triple helix bundles (each collagen triple helix is made up of three collagen chains). In arteries, collagen is the greatest facilitator of the contractile changes that occur and is attributed to defining the stiffness of vessels. CeAD is a sudden tear most commonly within the intima with subsequent bleeding into subintimal space (3). This tearing results in the separation of the vessel wall and allows blood to flow into to intimal layer of the vessel, thus resulting in a false lumen and intramural hematoma, which may cause significant stenosis or occlusion of the artery and may lead to a transient ischemic attack or ischemic stroke (4–6). Most CeADs are either spontaneous (sCeAD) or occur in settings of mild non-penetrating trauma. Unfortunately, the underlying pathophysiology of sCeAD remains largely unknown, and it is unclear why some people develop the disease while most of the population does not.

Several risk factors, such as hypertension and migraine, have been associated with increased risk of CeAD (7). On the other hand, known nosographic entities, such as hereditary connective tissue disorders (HCTD, i.e., Marfan's syndrome, Ehlers-Danlos syndrome type IV or Loeys-Dietz disease), have been documented to cause sCeAD in some affected individuals (7–10), while recent studies showed subtle or subclinical connective tissue aberrations in patients with sCeAD (11). Isolated mild, clinically detectable, connective tissue abnormalities in skeletal, ocular, and skin systems (i.e., joint hypermobility or multiple dislocations, easy bruising, poor wound healing) are frequently observed in patients with sCeAD (50%–96%) (11). Therefore, the prevailing idea is that the disease might be the end phenotype of an underlying, inherited, subclinical, systemic connective tissue disorder, leading to an arterial wall weakness. However, since no reliable biomarker has been identified to detect such subclinical abnormalities, the "*connective hypothesis*" in sCeAD pathogenesis remains not definitively proven and, in clinical practice, there are currently no tools to predict which individuals are at risk of disease occurrence. Several previous analyses of skin samples taken by biopsy in patients with sCeAD examined ultrastructural connective tissue abnormalities such as aberrations of collagen and elastic fibers that are usually found in HCTD (12, 13), while other studies attempted to identify genetic aberrations, particularly in genes involved in the extracellular matrix and collagen fibril organization, based on the familial clustering of sCeAD in some cases (7). These histologic and ultrastructural, as well as genetic findings, may provide relevant information on disease pathogenesis. Therefore, we conducted a systematic review of studies exploring the hypothesis that connective tissue abnormalities might play a role in sCeAD pathogenesis through a search for dermal connective tissue aberrations. We also summarized the results of genetic analyses, if performed in the included studies.

2. Methods

A systematic search was conducted using the PubMed and Scopus databases, by Nested Knowledge systematic review software,[1] with the following search keywords: "Cervical artery dissection" or "Intracranial Dissection" or "Carotid dissection" or "Vertebral Dissection" and "Skin biopsy." We included studies from the inception to August 2023. We also conducted a manual search and requested expert recommendations to further identify any other potential articles.

We included all original articles written in English that reported the skin biopsy assessments in patients with sCeAD. We excluded the following articles: (1) case reports, (2) not sCeAD diagnosis, (3) no skin biopsy performed, (4) animal studies, (5) non-English literature, (6) review articles, (7) letters to the editor and editorial, and (8) duplicate records. Two authors (MEG and ZK) screened the titles and abstracts using these predefined criteria. The discrepancies were assessed by all authors with the full text of the articles.

After the screening and review of the articles, we extracted the most significant data to evaluate the results of these studies. The following variables were extracted from the included articles when available: study and control population, type of dissection, mean age, time since event/stroke, primary skin biopsy outcomes, and their main results.

3. Results

The results of the systematic search and summary of the screening process are available in Figure 1 as a PRISM statement flow diagram (14). Our literature search identified 255 studies from PubMed and Scopus. We excluded 241 articles based on a review of the title and abstract with the criteria listed above. Two additional studies were identified with an expert recommendation. The remaining 16 articles were assessed with full text and included in this review.

3.1. Demographics and clinical features

Fifteen of the studies included were case–control (15–22) and case-series studies (12, 13, 23–27) and one study was a cohort study (28). The demographic and clinical characteristics of subjects included in these 16 studies are summarized in Tables 1, 2. The aggregate number of patients included in this review was 459 (range, 3–126). All studies included sCeAD adult patients with single vessel, bilateral or multivessel involvement, and they were compared to healthy controls, other than two studies without a control group (12, 24). Fifteen studies reported ages ranged from 18–70, but most of the patients were young adults with a mean age of 41.5 ± 9.3 years. The time since the event/

1 https://nested-knowledge.com/

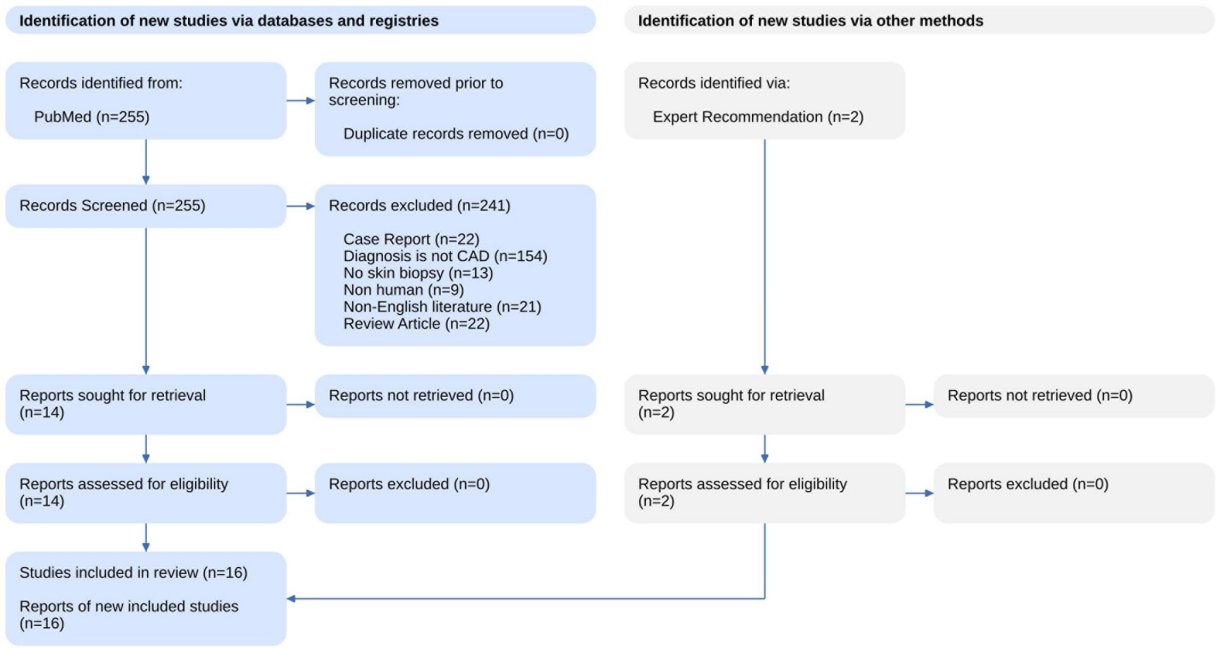

FIGURE 1
Literature search flow chart.

stroke was mostly not reported. All studies evaluated possible underlying connective tissue disorders by analysis of skin samples obtained from biopsy, in which histologic and/or ultrastructural changes were searched for, as well as by genetic analysis for possible gene involvement. Three studies investigated families with sCeAD patients, for a total of 11 families with 19 sCeAD patients (24–26).

3.2. Structural aberrations in connective tissue

Table 1 summarizes the findings from ten studies (12, 13, 16, 19–21, 24–28) that evaluated the connective tissue morphology showed ultrastructural aberrations, in the absence of clinical manifestations, such as alteration of the collagen and elastic fiber networks (12), significantly thinner dermis (19), smaller collagen fibrils diameter in the skin (20, 27), abnormal collagen fibril structures with faint and absent banding pattern (21, 24, 27), aberrations in numerous composite fibrils within mid-dermal collagen bundles with enlarged diameters of composite fibrils (13, 24) (very similar to the aberrations seen in patients affected by EDS-II or III (12, 16)) and elastic fiber abnormalities with mini calcifications and fragmentation (16). All of these studies were consistent in showing aberrations of the connective tissue, in a cumulative number of 149 out of 295 (50.5%) patients.

3.3. Genetic analyses

Besides the morphological evaluation, molecular analyses that were performed in 10 out of the 15 studies did not detect any causative mutations in genes encoding for collagen type I, III, V, and elastin and sCeAD (15, 17, 18, 22–26, 28). Table 2 summarized the findings of genetic analyses from skin biopsy studies.

Notwithstanding, the linkage analysis of a large family with sCeAD-associated connective tissue alterations suggested the presence of a candidate locus on chromosome 15q2 or on chromosome 10q26 (26), while other studies revealed copy number variants (CNV) enrichment in genes involved in extracellular matrix organization (COL5A2, COL3A1, SNTA1), collagen fibril organization (COL5A2, COL3A1), smooth cell functions (MHY11) and possibly in genes involved in transforming growth factor beta (TGF)-beta receptor signaling pathway (COL3A1, DUPS22) (22, 27). Finally, Mayer-Suess and co-workers, based on the analysis of the extracellular matrix proteins by the proteomics approach, showed different expressions of 25 proteins, 13 of which were linked to connective tissue disorders, in patients with recurrent sCeAD (28).

Overall, although the results of the genetic analyses included in this systematic review do not allow for definitive conclusions, they seem to support the hypothesis of a potential involvement of "connective genes" in sCeAD pathogenesis.

4. Discussion

In this review, we summarized the results of the studies examining connective tissue abnormalities through the analysis of samples obtained by skin biopsy in patients with sCeAD. Given the lack of biologic or molecular markers specifically linked to the disease, histologic and ultrastructural connective tissue abnormalities detected by the analysis of skin samples potentially represent a useful tool to indirectly support the hypothesis that structural and functional alterations of the arterial connective

TABLE 1 Summary of studies assessing structural aberrations in connective tissue.

References	Type of article	Sample Size	Type of dissection	Control	Age (Mean)	Primary Outcomes	Main Results
Brandt et al. (13)	Case series	25 sCeAD	ICA (14), Bilateral ICA (2), VA (8), Bilateral VA (1)	10 healthy controls	42	Blinded qualitative light and electron microscopy analysis	Collagen aberrations in 15 patients; composite fibrils with a variable diameter and a flower-like cross-section
Brandt et al. (16)	Case control	65 sCeAD	ICA (29), VA (7), Multivessel (22), Recurrent (7)	10 healthy controls	41	Ultrastructural morphology by transmission electron microscopy	- Ultrastructural aberrations in 55% of patients - Only 5% had clinical manifestations - Recurrent sCeAD correlated with connective tissue aberrations.
Grond-Ginsbach et al. (24)	Case series	6 family members of 1 sCeAD patient	Left ICA	No control	Index patient: 48	Ultrastructural morphology by electron microscopy	Index patient and 3 children with connective tissue aberrations of collagen and elastic fibers.
Hausser et al. (19)	Case control	126 sCeAD	Not reported	29 healthy controls	Not reported	Connective tissue morphology by electron microscopic	Aberrant morphology of collagen and elastic fibers in 57% of patients
Ulbricht et al. (12)	Case series	7 sCeAD	ICA (6), VA (1)	No control	39	Ultrastructural morphology	Alterations of the collagen and elastic fibers in 6 patients
Martin et al. (25)	Case series	7 families with 15 sCeAD patients	ICA (10), VA (5)	No control	36.2	Connective tissue morphology	EDS-III and IV-like changes in 4 patients, normal in 9 patients.
Wiest et al. (26)	Case series	Families of 3 sCeAD patients	ICA (3)	No control	48	Connective tissue phenotypes by electron microscopic	All 3 families with same EDS-III like connective tissue alterations with "flower-like" composite fibrils in some collagen bundles and with fragmentation of the elastic fibers.
Völker et al. (20)	Case control	20 sCeAD	ICA (10), VA (6), ICA + VA (4)	18 (14 healthy, 4 autopsy)	41	Connective tissue morphology	- Significantly smaller mean diameter of collagen fibrils in sCeAD patients - No significant difference in fibril density and relative fibril area
Uhlig et al. (21)	Case control	31 sCeAD	ICA (18), Bilateral ICA (1), VA (7), Bilateral VA (2), Multivessel (3)	17 healthy controls	40.8	Collagen fibril abnormalities by transmission electron microscopy	20% of sCeAD patients showed collagen fibril alterations; irregularly contoured surfaces and increased diameters, often associated with a faint or absent banding pattern
Erhart et al. (27)	Case series	4 sCeAD patients with additional dissection in other vasculature beds	1. Right ICA, aorta type B 2. Bilateral ICA, left VA, aorta type B 3. Left ICA, aorta type A 4. Right ICA, aorta type B	No control	41.7 ± 5.1	Ultrastructural morphology by electron microscopy	3 patients had morphologic alterations of the dermal connective tissue (small-caliber and composite/abnormal collagen fibrils)

ICA, internal carotid artery; VA, vertebral artery; EDS: Ehlers-Danlos syndrome.

component may play a crucial role in the pathogenesis of sCeAD. This is made even more biologically plausible when we consider that these connective tissue elements provide mechanical stability and are responsible for most of the functional properties of the arterial wall.

4.1. Evidence from the analysis of skin biopsies

Our review showed that alterations of the collagen and elastic fiber networks are frequent findings in patients with sCeAD as opposed to

what is observed in subjects without sCeAD. Such dermal connective tissue aberrations include irregular (flower-like) contours with variable diameters of collagen fibrils, and fragmented, moth-eaten-like appearance and microcalcifications of elastic fibers. These alterations are similar to those that may be found in classic HCTD such as in Ehlers–Danlos syndrome type IV or pseudoxanthoma elasticum, a further argument in favor of the "connective hypothesis" of sCeAD.

4.2. Evidence from the genetic analyses

Over the last decades, it has been repeatedly emphasized that classical HCTD, such as EDS type IV and Marfan syndrome, or other more recently identified nosographic entities, such as the Loeys-Dietz syndrome (LDS) comprise sCeAD in their phenotypic spectrum. However, diagnostic criteria for HCTD are met in only 1%–5% of sCeADs patients (10, 29). This implicates that there might be other unrecognized connective tissue abnormalities predisposing the vessel wall to dissection. The results of the studies included in the present review support this hypothesis. First, a family history of CeAD in some cases indirectly suggests that genetic factors might be operant in the pathogenesis of the disease. This hypothesis was further supported by the observation that dermal ultrastructural connective abnormalities not fulfilling the diagnostic criteria for known HCTD (26) aggregate in familial groups in some cases, where they follow an autosomal-dominant pattern of inheritance.

Second, besides searching for morphological aberrations, molecular analyses were also conducted in some of the studies included in our systematic review. The majority of these studies focused on the genes of collagen type I (COL1A1) (25), type III (COL3A1) (15, 17, 25), type V (COL5A1, COL5A2) (23, 25) as well as elastin (ELN) (23), but they were unable to identify any causative mutations in sCeAD. Although collagen type III was particularly an area of interest as the mutation in this gene is related to EDS type IV (the "vascular" subtype of EDS), none of these studies identified causative mutations in this gene among patients with sCeAD other than the missense mutation G157S in two patients from the same family. The major limitation of these studies is inherent in their nature of small case series, which makes them not fully adequate for determining the prevalence of such causative mutations among sCeAD patients.

Similarly, most of the studies in which a genetic linkage analysis was performed gave negative results, with the only exception of one study suggesting a linkage between connective tissue alterations and mutations in genes involved in extracellular matrix and collagen fibril organization, especially in patients with recurrent sCeAD, in whom a greater pathogenic impact of structural vessel wall alterations is assumed.

More advanced methods such as whole-exome and whole-genome sequencing have been recently used to investigate patients with sCeAD. One study performed a genome-wide linkage analysis and found suggestive linkage between CAD-associated connective tissue alterations and mutation of the locus on chromosome 15q2 and chromosome 10q26 (26). This approach identified several promising candidate genes such as CSPG2, LOXL1, and FGFR2, all already known to be involved in aortic dissections and aneurysms formation.

Another study searched for rare genetic deletions and duplications that predispose to sCeAD based on the analysis of CNV (22). This study showed significant CNV enrichments in genes involved in extracellular matrix organization (COL5A2, COL3A1, SNTA1) and collagen fibril organization (COL5A2, COL3A1). Interestingly, none of these rare CNV enrichments were found in more than one patient, which indicated that the underlying genetic variation is a complex and heterogeneous process that cannot be explained with simple monogenetic variations. Furthermore, one small study performed whole-exome sequencing and CNV analysis in patients with independently occurring dissections in both the aorta and cervical arteries, and similarly identified pathogenic CNV in COL3A1, COL5A2, and MYH11 genes, which all involved in arterial connective tissue functions (27).

Finally, a recent study used a cutting-edge quantitative proteomics approach to identify extracellular protein aberrations in sCeAD patients and identified 25 proteins expressed differently only in patients with recurrent sCeAD (28). The Authors also identified two main protein clusters; (1) desmosome-associated cluster with four proteins and (2) collagen and elastin cluster with eight proteins, suggesting a more complex pathophysiology of sCeAD and possibly more evident aberrations at the proteome level. These results suggest underlying pathological genetic variants, particularly in patients with recurrent and multiple territory dissections.

4.3. Further indirect evidence of relationship between sCeAD and connective tissue disorder

The literature suggests further arguments in favor of the "connective hypothesis" in the pathogenesis of sCeAD.

First, echocardiographic studies assessing cardiac manifestations of connective tissue disorder showed that valvular abnormalities such as mitral valve prolapse, mitral valve dystrophy, aortic valve dystrophy as well as the enlarged diameter of the aortic root were observed more frequently in sCeAD patients (56%) compared to controls (15%) (30). One study, in particular, showed that aortic root dilatation, one of the classical signs of HCTD, particularly seen in Marfan syndrome or Ehlers-Danlos syndrome, was strongly associated with sCeAD.

Second, studies investigating arterial wall biomechanical proprieties in sCeAD patients found altered arterial distensibility. Guillon and co-workers, in an ultrasound study focusing on common carotid artery diameter and diameter changes during the cardiac cycle showed that the diameter changes were more pronounced in sCeAD, reflecting less elastic properties of the arterial wall (31). Similarly, in another study Calvet and co-workers assessed the elastic properties of the carotid wall in sCeAD patients using noninvasive high-resolution echo tracking systems and showed that sCeAD patients had higher circumferential wall stress and stiffness (32). Besides, this study also showed that Young's modulus, a direct measure of elasticity proprieties of the vessel, was significantly higher (indicating stiffer arterial wall), and associated with an up to the 8-fold increased risk of sCeAD. Lucas and co-workers assessed endothelial function and reactivity using high-resolution ultrasonography and showed that the brachial artery flow-mediated vasodilatation was significantly reduced in patients with sCeAD compared to controls, indicating impaired endothelial-dependent vasodilation (33).

Third, weakened arterial structure caused by connective aberrations may also predispose to vascular deformities, such as

TABLE 2 Summary of studies with genetic analyses from skin biopsy.

References	Type of article	Sample size	Type of dissection	Control	Age (mean)	Primary outcomes	Main results
van den Berg et al. (15)	Case control	16 sCeAD	ICA (10), Bilateral ICA (3), VA (3)	41 healthy controls	40.7	Protein analysis of type III collagen	No mutation in the gene of type III collagen was demonstrated.
Grond-Ginsbach et al. (23)	Case series	10 sCeAD	ICA (5), VA (2), Recurrent (3)	1 healthy control	44	Gene encoding tropoelastin (ELN) sequence analysis	No mutations in the whole coding region of the ELN gene
von Pein et al. (17)	Case control	12 sCeAD	Partially reported	50 healthy controls	42.5	Sequence analysis of the COL3A1 gene	No disease-causing mutations in the COL3A1 in gene.
Morcher et al. (18)	Case control	12 sCeAD	Partially reported	25 healthy controls	38.8	Genomic sequencing of the ABCC6 gene	No changes in ABCC6 gene.
Martin et al. (25)	Case series	7 families with 15 sCeAD patients	ICA (10), VA (5)	203 healthy subjects	36.2	Coding sequences of COL3A1, COL5A1, COL5A2, and COL1A1	Only a missense mutation in the COL3A1 gene.
Wiest et al. (26)	Case series	Families of 3 sCeAD patients	ICA (3)	No control	48	Genome-wide linkage analysis	- Linkage between sCeAD-associated connective tissue alterations and chromosome 15q2 and 10q26 mutations - Locus heterogeneity in connective tissue phenotype of sCeAD patients
Uhlig et al. (21)	Case control	31 sCeAD	ICA (18), Bilateral ICA (1), VA (7), Bilateral VA (2), Multivessel (3)	17 healthy controls	40.8	Collagen fibril abnormalities by transmission electron microscopy	20% of sCeAD patients showed collagen fibril alterations; irregularly contoured surfaces and increased diameters, often associated with a faint or absent banding pattern
Grond-Ginsbach et al. (22)	Case control	70 sCeAD	Not reported	403 controls	42.5 ± 9.8	CNVs screening and Gene Ontology analysis	Significant CNVs enrichments for genes involved in Extracellular matrix (COL5A2, COL3A1, SNTA1) and collagen fibril (COL5A2, COL3A1) organizations
Mayer-Suess et al. (28)	Cohort Study	38 sCeAD	Single vessel (19), Multivessel (13), Recurrent (6)	12 healthy controls	49.1	Extracellular Matrix Protein analysis from skin punch biopsies using quantitative proteomics approach	- No difference in single-vessel or multiple-vessel dissections between each other or compared to healthy controls - Recurrent sCeAD showed significantly different expression of 25 proteins compared to the other groups combined. 13 proteins were linked to connective tissue disorders.
Erhart et al. (27)	Case series	4 sCeAD patients with additional dissection in other vasculature beds	1. Right ICA, aorta type B 2. Bilateral ICA, left VA, aorta type B 3. Left ICA, aorta type A 4. Right ICA, aorta type B	No control	41.7 ± 5.1	Whole-exome sequencing and CNV analysis	3 patients carried pathogenic variants in COL3A1, COL5A2, and/or MYH11 genes

ICA: Internal carotid artery, VA: Vertebral artery, CNV: copy number variant.

tortuosity. Higher arterial tortuosity was associated with connective tissue diseases, particularly Marfan syndrome and Loeys-Dietz syndrome (34, 35). In a study using magnetic resonance angiography Giossi and co-workers showed that tortuosity indexes in sCeAD patients were significantly higher compared to those of matched controls (36). These findings are indirectly supported by the

observation that aortic dissection in patients affected by Marfan syndrome correlates with arterial tortuosity of the aorta (37).

Fourth, Brandt and co-workers showed that the ultrastructural connective tissue abnormalities in collagen and elastin fibrils of patients with sCeAD were related to disease recurrence (16). They also showed that these aberrations were more commonly seen in male patients but were not associated with age and vascular risk factors.

Fifth, indirect evidence in favor of the connective hypothesis also comes from studies investigating clinically detectable connective signs in sCeAD patients. Dittrich and co-workers assessed the clinical connective tissue phenotype of sCeAD patients using a standardized examination containing 25 clinical items that mainly included signs found in Marfan and Ehlers-Danlos syndromes (38). Presumably due to the fact that the sample size was relatively small to detect small clinical changes, they found no significant difference in clinically detectable connective tissue abnormalities in patients with sCeAD compared with the non-sCeAD group. Conversely, another more recent study with a larger sample size assessed clinically detectable connective tissue abnormalities with a more extensive standardized examination protocol including 68 items found in HCTD (11) and showed a higher prevalence of connective tissue abnormalities in sCeAD patients, further supporting the connective hypothesis. Interestingly, the low prevalence of these clinically detectable signs in patients with traumatic CeAD contrary to sCeAD further supports this hypothesis. Similarly to previous studies discussed in this review, these patients were not diagnosed with a definite HCTD, implicating that sCeAD may represent a multifactorial disease that is the result of the combination of triggering factors in settings of an underlying subclinical connective tissue disorder.

5. Conclusion and future directions

Data reported in this review support the presence of an underlying subclinical, likely genetically determined, connective tissue disorder predisposing to arterial wall weakness and sCeAD. Our current knowledge is limited by the small sample size, the specific design of some studies, the cost-resource requirements of these methods, as well as by the characteristics of the disease itself, the pathogenesis of which is likely to be complex. Further studies with larger sample sizes and robust methodology are needed to better define the role of connective tissue in sCeAD pathogenesis. Although the current evidence is not enough to change the current guidelines, a better understanding of the connective tissue aberrations and the underlying genetic features is relevant to identifying people at risk of developing sCeAD. Skin biopsy and genetic testing should be considered particularly for patients with recurrent sCeAD and dissections in multiple vasculature beds. This is also important to develop future therapies targeting vessel wall strength aiming to prevent sCeAD occurrence and/or its complications such as disease recurrence and dissecting pseudoaneurysm formation. This may allow individualizing medical and endovascular treatments.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MG and ZK independently screened the titles and abstracts for systematic review inclusion. MG, RK, DK, AP, and ZK involved in assessing the discrepancies with the full text of the article and the manuscript writing. ZK had final responsibility for the decision to submit for publication. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The effect of balance and gait training on specific balance abilities of survivors with stroke: a systematic review and network meta-analysis

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Background: Stroke, which is a common clinical cerebrovascular disease, causes approximately 83% of survivors to suffer from balance impairments. Balance and gait training (BGT) is widely used to restore balance in patients with stroke. However, its wide variety presents clinicians with a dilemma when selecting interventions. This study aimed to compare and rank BGT interventions by quantifying information based on randomized controlled trials (RCTs).

Methods: We conducted a network meta-analysis (NMA) of non-gait-trained controls and head-to-head RCTs and compared the effects of 12 BGT interventions. A total of nine literature databases, including Medline, Embase, Cochrane Library, Web of Science, Scopus, SPORTDiscus, ClinicalTrials.gov, CNKI, and Chinese biomedical literature databases, were searched from their database inception to August 2023. Two authors independently selected studies and extracted data. The difference in outcomes, which were expressed as standardized mean differences and confidence intervals (CIs) of 95%, were explored in this meta-analysis.

Results: A total of 66 studies with 1,933 participants were included. Effect size estimates showed that not all BGT interventions were more effective than controls, with treadmill training as the least effective for balance test batteries (SMD=−0.41, 95% CI [−1.09, 0.27]) and proactive balance (SMD=−0.50, 95% CI [−1.14, 0.14]). Body-weight-supported treadmill training with external stimulation was most effective for proactive balance and dynamic steady-state balance (SMD=1.57, 95% CI [−0.03, 3.16]); SMD=1.18, 95% CI [0.67, 1.68]. Virtual reality gait training (SMD=1.37, 95% CI [0.62, 2.11]) had the best effect on improving balance test batteries, while dual-task BGT (SMD=1.64, 95% CI [0.50, 2.78]) had the best effect on static steady-state balance. After analyses for possible impact covariates, the findings through the outcomes did not change substantially. Confidence in the evidence was generally low or very low.

Conclusion: This NMA suggested that virtual reality gait training was the most effective BGT modality for improving balance test batteries. Body-weight support treadmill training with external stimulation was the most effective for improving active and dynamic balance. In addition, dual-task BGT was the best choice for improving static balance. However, balance is a multidimensional concept, and patients' different needs should be considered when selecting BGT.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022316057, ID: CRD42022316057.

KEYWORDS
stroke, balance, gait, rehabilitation, network meta-analysis

Introduction

Stroke is a common clinical cerebrovascular disease with high morbidity, mortality, and disability, and the second most common cause of death in the world (1–3). In 2019, approximately 100 million people suffered from stroke worldwide (4), with its global incidence increasing by 85% and mortality by 43% from 1990 to 2019, whose mortality rate in low- and middle-income countries is 3.6 times higher than that in high-income countries, placing a heavy burden on society and families (5).

Balance refers to the ability to hold the line of gravity within the point of support with minimal postural sway (6). Approximately 83% of stroke survivors are reported to suffer from balance disorders, one of the most common impairments for patients with stroke, which are associated with more severe physical impairments, disabilities, and a lower quality of life (7). In addition, balance disorders are strongly associated with a high rate of falls, which places a significant burden on patients with stroke and their families (7, 8). Several studies have shown that exercise training positively affects balance improvement (9–11) and that balance and gait training (BGT) is considered an essential aspect of fall prevention (12–14). Therefore, involving BGT in the balance rehabilitation program for patients with stroke has become particularly important.

Recently, more BGT interventions have been introduced to improve the balance of patients with stroke, such as dual-task gait training (15), virtual reality gait training (16), and robot-assisted gait training (17). The wide variety of BGT makes it a dilemma for clinicians to choose from available interventions. Those head-to-head intervention trials can be synthesized through traditional meta-analyses, providing some evidence. However, it is difficult to compare the efficacy of different BGT interventions, resulting in the inclusion of fewer bodies of literature (18), which does not allow for further exploration of the relative effectiveness among the various BGT interventions, while providing a ranking of priorities among different interventions. Moreover, previous meta-analyses had a high level of heterogeneity (17, 19), whose results might change with the inclusion of more kinds of literature.

Although there have been numerous studies demonstrating that BGT can be used to improve the balance of stroke survivors (17, 20, 21), they do not provide a comprehensive overview using network meta-analyses (NMAs) or compare the effect of BGT on various balance abilities. Through NMAs, these limitations are overcome by including a greater number of relevant trials while bringing together direct and indirect comparisons of all BGT interventions available (22, 23). Therefore, this network meta-analysis aimed to evaluate the effect of BGT on the balance of patients with stroke so as to examine the relative effect of various BGT interventions on the balance (balance test batteries, dynamic steady-state balance, static steady-state balance, proactive balance) of patients with stroke while further enhancing knowledge in this area. The pair meta-analyses and meta-regression analyses on control group (CON) data were also applied to examine patients' gender and age, timing and frequency of interventions, year of publication, and the time to study entry after a stroke to predict the extent of changes in their balance ability as well as to provide referable evidence for clinicians, patients, and caregivers.

Methods

Study protocol and registration

The study protocols for this systematic review were registered in the PROSPERO database (CRD42022316057) and meet the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extended statement criteria (24) [Appendix 2 (p. 6)].

Search strategy

A total of nine literature databases, namely, Medline, Embase, Cochrane Library, Web of Science, Scopus, SPORTDiscus, ClinicalTrials.gov, CNKI, and Chinese biomedical literature databases, were searched from their inception to August 2023, with no language restrictions. The combined Medical Subject Heading (MeSH) terms and keywords with Boolean operators were applied to search through the search strategy described in detail [Appendix 3 (p. 21)], which mainly includes the following terms: (stroke), (exercise OR training OR gait training), (randomized controlled trial, RCT), and (balance). We also performed a recursive search to identify relevant publications by manually filtering the bibliographic lists of similar reviews and large professional conferences. The results of all studies searched were initially screened by two independent reviewers (M.Z. and Zd. L.) through titles and abstracts based on the inclusion and exclusion criteria, and their full text, which met the initial screening requirements, was extracted. Two reviewers further independently screened studies that met the criteria and resolved differences through discussion with a third reviewer (T.L.), adjudicating when necessary.

Inclusion and exclusion criteria

The following were the inclusion criteria: (a) participants should be adults affected by stroke with an age of ≥18 years (according to the clinical definition); (b) the trials included at least two types of BGT intervention to be compared, or BGT intervention and control to

Abbreviations: CoP, Center of pressure; BGT, Balance and gait training; GRADE, The Grading of Recommendations Assessment, Development and Evaluation; MeSH, Medical Subject Heading; NMA, Network meta-analyses; NMAs, Network meta-analyses; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, Randomized controlled trial; SD, Standard deviations; SE, Standard errors; SIDE, Separate indirect evidence from direct evidence; SMD, Standardized mean difference; TUG, Timed up and go test; VR, Virtual reality.

TABLE 1 Interventions and abbreviations.

Abbreviation	Intervention
CON	No balance and walking training (usual care, keep daily or wait-list)
BGT	Balance and gait training without technical assistance (such as treadmill-assisted, robot-assisted, and body-weight support-assisted)
TT	Treadmill training without body-weight support
BWS-TT	Treadmill training with body-weight support
RA-GT	Robot-assisted gait training
VR-GT	Virtual reality gait training
AQE-BGT	Aquatic balance and gait training
BGT-ECA	Balance and gait training with external stimulation (includes visual stimulation, auditory stimulation, electrical stimulation)
TT-ECA	Treadmill training with external stimulation
BWS-TT-ECA	Body-weight support treadmill training with external stimulation
RA-GT-ECA	Robot-assisted balance and gait training with external stimulation
EC-BGT	Eye closed balance and gait training (gait training without visual aids, including closed-eye gait training, backward gait training)
DT-BGT	Dual-task balance and gait training (perform both types of training, at least one of the above-mentioned balance gait trainings)

be compared; see Table 1 for details of intervention and control; (c) according to Shumway-Cook and Woollacott (25), balance is a highly specific task that has to be divided into different categories: static/dynamic steady-state balance (maintaining a stable position while sitting, standing, and walking), proactive balance (anticipating disturbances), and reactive balance (compensation for disturbances). Concerning these findings, our study was focused on different balance categories: (1) balance test batteries (such as the Berg Balance Scale), (2) dynamic steady-state balance (such as the 10-m gait speed test), (3) static steady-state balance (such as the center of pressure (CoP) displacements during single-leg stance), (4) proactive balance (such as the Functional Reach-Test or Timed Up and Go (TUG) Test), and (5) reactive balance (such as the CoP displacements after an unexpected perturbation). At least one of the aforementioned five types of balance should be present in the results; (d) RCTs; (e) if the study data were missing, we emailed the authors to inquire about them, and the study was disqualified if we did not hear back.

Data extraction

Two investigators (M.Z. and Zd. L.) independently extracted data from the final studies included and entered them into a standardized data extraction spreadsheet through Excel. The following information was extracted: (1) author and year of publication; (2) relevant data on participants' characteristics (such as sample size, age, sex, degree of stroke, and time from stroke onset to study entry); and (3) details of interventions in the treatment and CON. The two investigators independently categorized the interventions in each included study, and any discrepancy was resolved through discussion, involving a third investigator if necessary. The total duration, intensity, and frequency of interventions were also extracted; (4) all information on balance outcomes (such as the Berg Balance Scale, 10-m walking speed test, CoP displacement during single-legged stance, and TUG) was analyzed across balance types. In this systematic review, two investigators independently assessed all studies (M.Z. and Zd. L.) based on the information extracted. If there was a disagreement on including a study, a third reviewer (T.L.) was consulted.

Risk of bias assessment

Two reviewers (M.Z. and Zd. L.) independently assessed the risk of bias in randomized controlled trials using the revised Cochrane Risk of Bias, version 2 (RoB 2) tool (26). Disagreements between the reviewers were settled by discussion, and if no consensus could be reached, a third reviewer (T.L.) made the final decision as an adjudicator (T.L.).

GRADE assessment

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the quality of evidence for the results of different BGT rankings based on NMA, including study limitations, indirectness and transitivity, statistical heterogeneity and inconsistency, and imprecision and publication biases (27). The GRADE method is used for each pairwise comparison, whose framework has been adapted to NMA (28, 29), in which all the studies included are RCTs, and it is assumed that each study would have the highest initial quality rating and, after assessing the above factors, would be rated as having a moderate, low, or very low quality where appropriate.

Data analysis

Assessment of the transitivity assumption

Transitivity is a critical underlying assumption of NMAs (30). To assess this hypothesis, we examined the distribution of possible effect modifiers by comparing intervention methods for further analyses, including baseline characteristics of participants, intervention duration, and intervention frequency (23, 31, 32).

Network meta-analysis

Network evidence was plotted using STATA15.1 (Stata Corp LLC, College Station, TX, United States) to represent the geometric structure of different BGT. The dots represent different intervention types, whose size represents the number of studies, and the line among each intervention type represents a direct comparison among interventions. We extracted baseline and endpoint mean differences and standard deviations (SD) for relevant outcomes; if SD was not reported in the study, standard errors (SE), 95% confidence intervals,

and interquartile intervals would be used for estimation (33). If a lower value represented a better study result, we would multiply the result by −1, as recommended in the Cochrane Handbook *for Systematic Reviews of Interventions* (33). If the study was a multi-arm RCT, then data would be extracted for all interventions and CONs of the study. Because different measures of outcomes were used for each type of balance, to ensure the comparability of results, the standardized mean difference (SMD) of the results of all continuous variables was used to estimate the effect. We used the "netmeta 1.5–0" package of R software (version 3.6.2, The R Foundation for Statistical Computing, Vienna, Austria) to perform a meta-analysis on the random-effects networks of a frequency-based framework (34). The heterogeneity of each network was assessed by statistics τ^2 and I^2, whose consistency (between direct and indirect evidence) was assessed using both global (Q statistics) and local methods (identifying inconsistent "hot spots" using the "node-split" function) (27, 35). We used the R "netmeta" package to separate indirect evidence from direct evidence (SIDE test) (35) to statistically assess global consistency (consistency across sources of evidence) (36). Inconsistencies were statistically tested and reported using z-scores and *p*-values, of which *p*-values < 0.05 were considered statistically significant (37, 38). The effect of different BGT interventions was assessed using a frequency ranking method, and the probability of ranking for each BGT was expressed as a P-score, which is a measure of the degree of certainty that one intervention is better than another, with higher *p* values representing better BGT interventions, together with an upper limit of 1 (39). To represent the results more visually, we created a heat map to summarize the ranking of the effect of all BGT on different balance abilities. A forest diagram was created to visually represent the effect of different BGTs compared to the CON.

Meta-regression: baseline predictors of changes in balance associated with balance and gait training

After screening analyses, the results suggested that age, gender, duration of illness, year of publication, frequency of interventions, and duration were factors most likely to influence outcomes. The "gemtc" package (1.0–1) in R was applied to investigate the effect of covariates on the balance ability of the subjects. We performed meta-regression analyses using CON group data to investigate the relationship between subjects' balance ability and their age, gender, duration of illness, year of publication, frequency of interventions, and duration of interventions (40, 41). In this analysis, if a study involved multiple subgroups, their estimates would be combined (33).

Results

Literature selection

A total of 5,208 articles were obtained by searching and screening the databases, of which 1,986 studies were excluded for the first time due to duplication. We excluded another 3,004 after reviewing titles and abstracts; another 71 were excluded because no report was retrieved; and finally, 147 studies were screened for the full text. We excluded 81 studies after full-text screening for the following reasons: 28 studies were not RCTs, 14 did not have appropriate outcomes or failed to provide analyzable data, 19 did not have an appropriate control group, and 20 had an intervention type other than the BGT defined in this study. Finally, 66 studies were included in our network meta-analysis, and details of exclusions and screening are shown in Figure 1.

Characteristics of the included studies

A total of 1,975 subjects participated in our study, with an age range of 44–74 years. The proportion of male participants was significantly higher than that of female participants (male participants: 1,236, 62.6% vs. female participants: 739, 37.4%). The study was completed mainly in Korean regions ($N = 29$, 43.9%). Patients' average time from stroke to entry into interventions was 2 years; the average intervention period was 5.2 weeks, and the frequency of interventions ranged from 1 to 7 times per week.

Of the included studies, six studies were three-armed controlled experiments, and the remaining studies were two-armed. The results on balance test batteries were reported in 47 studies; those on dynamic and static steady-state balance were reported in 64 and 21 studies, respectively; and the results related to proactive balance were reported in the additional 28 studies. Network graphs are shown in Supplementary Figure S1. The demographic characteristics of the included studies were summarized in Appendix 4 (p. 27), and the forest plots and funnel plots of all outcomes would be presented in Appendices 7, 11 (p. 42 and p. 70).

Results of the risk of biases

RoB 2 results showed that, for balance test batteries, dynamic steady-state balance, static steady-state balance, and proactive balance outcomes, 6.8%, 8.1%, 10%, and 3.7% of studies had a high risk; 27.3%, 30.6%, 30%, and 29.6% had some risk concerns; and 65.9%, 61.3%, 60%, and 66.7% had a low risk. Overall, we judged four balanced outcomes as having a high risk of bias. If raw, unadjusted scores of registered outcomes were reported, we considered the risk of selective reporting low. The risk of bias was not presented due to selective non-reporting or under-reporting, as this type of bias is not covered in RoB 2. The detailed process of risk assessment is shown in Supplementary Figures S2–S9 (justifications in Appendix 12).

Network meta-analysis

Balance test batteries

A total of 47 studies (1,360 participants) included the results of balance test batteries. The mixed comparisons in the league table showed that the balance test batteries of the VR-GT group improved significantly better than those of the RA-GT, DT-BGT, BWS-TT, BGT, TT, and CON groups, with a BWS-TT-ECA that was significantly better than that of the BWS-TT, BGT, TT, and CON groups. Other comparative details are shown in Table 2A. Following the ranking of the effects of the balance improvement scale, VR-GT had the best effect (P-score: 0.95) while TT had the worst (P-score: 0.04; Figure 2). The overall heterogeneity of the NMA model for balance test batteries

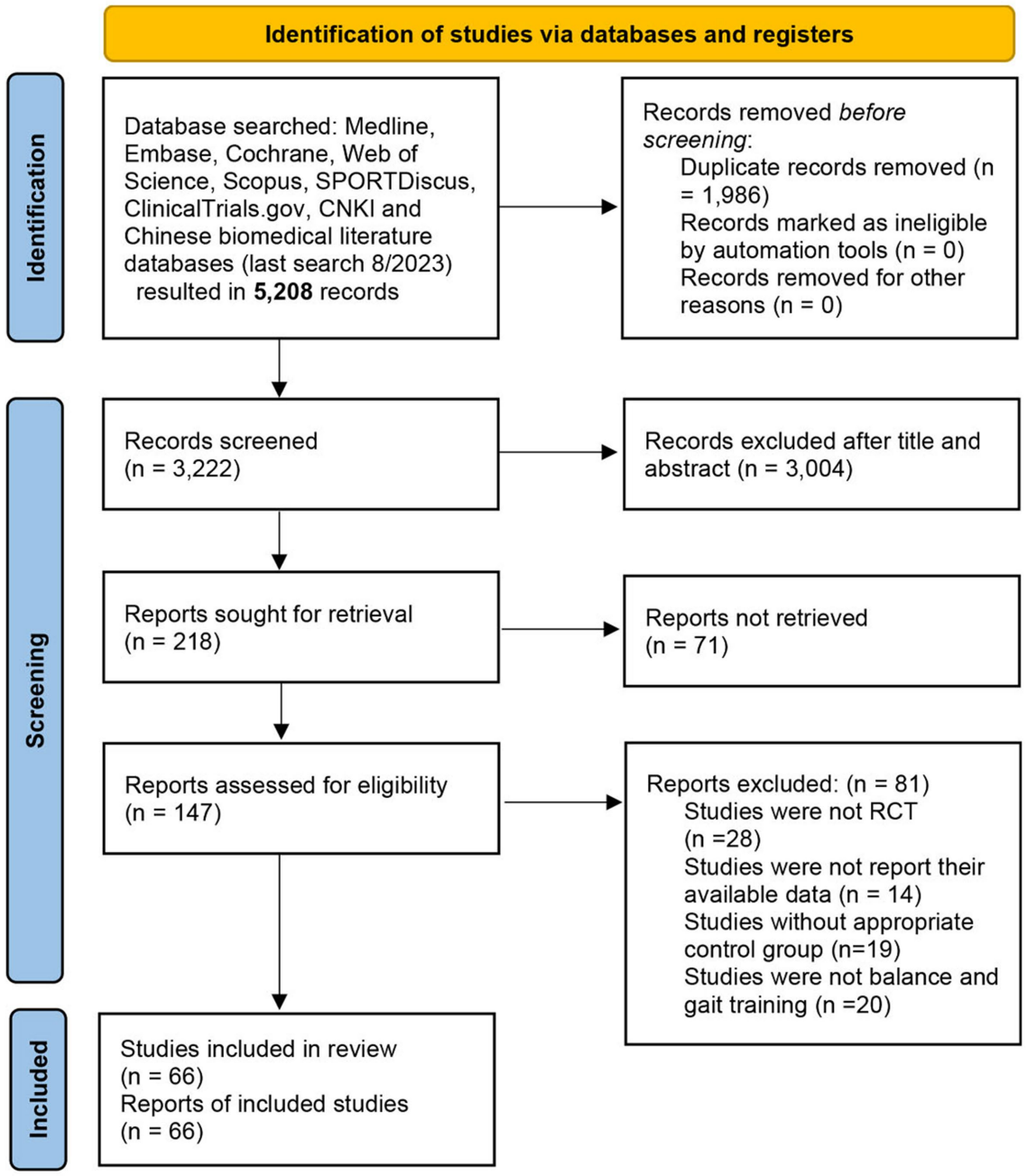

FIGURE 1
PRISMA flow diagram.

was significant ($\tau^2 = 0.29$, $I^2 = 65.5\%$, $p < 0.001$). The Q score of global inconsistency was 7.46 ($p = 0.9632$), and no hotspot of inconsistency was found in the models analyzed for inconsistency through the point-split method in Appendix 9 (p. 47).

Dynamic steady-state balance

The results on dynamic steady-state balance were reported in 64 studies (1,861 participants). Through a mixed comparison, we found that the dynamic balance of the BWS-TT-ECA group improved better than that of the RA-GT, BGT-ECA, BGT, DT-BGT, TT, and CON groups, and other comparative details are shown in Table 2B. In terms of the P-score ranking, BWS-TT-ECA had the best intervention effect (P-score: 0.93), while CON had the worst (P-score: 0.08; Figure 2). We found moderate overall heterogeneity in studies on dynamic balance ($\tau^2 = 0.13$, $I^2 = 45.2\%$, $p < 0.001$). The Q score of the global inconsistency assessment was 27.11 ($p = 0.2514$). However, after analyzing inconsistency using the point-split method, two hotspots of inconsistency were found and shown in Appendix 9 (p. 49), indicating a disagreement between direct and indirect evidence.

TABLE 2A League table of balance test batteries.

VR-GT	.	.	0.71 (−0.66, 2.09)	.	.	.	.	.	.	.	**1.32 (0.32, 2.32)**	**1.85 (0.93, 2.78)**
0.37 (−0.87, 1.61)	EC-BGT	0.49 (−0.91, 1.89)	.	.	.	.	.	.	.	0.74 (−0.77, 2.24)	0.80 (−0.60, 2.20)	.
0.51 (−0.48, 1.50)	0.14 (−0.91, 1.19)	BWS-TT-ECA	.	.	.	.	.	.	**0.79 (0.04, 1.54)**	0.50 (−0.82, 1.82)	0.71 (−0.22, 1.64)	.
0.76 (−0.18, 1.71)	0.39 (−0.84, 1.63)	0.26 (−0.74, 1.25)	RA-GT-ECA	.	0.16 (−1.25, 1.57)	.	.	.	.	.	0.61 (−0.30, 1.53)	.
0.74 (−0.93, 2.41)	0.37 (−1.43, 2.17)	0.23 (−1.41, 1.87)	−0.02 (−1.70, 1.65)	AQE-BGT	.	.	.	.	.	.	0.59 (−0.90, 2.08)	.
0.92 (0.11, 1.74)	0.55 (−0.48, 1.59)	0.42 (−0.32, 1.15)	0.16 (−0.64, 0.96)	0.18 (−1.37, 1.73)	RA-GT	.	.	.	−0.36 (−1.84, 1.12)	0.59 (−0.03, 1.21)	0.19 (−0.35, 0.73)	**1.33 (0.11, 2.54)**
0.92 (−0.03, 1.87)	0.55 (−0.57, 1.67)	0.41 (−0.44, 1.26)	0.15 (−0.79, 1.10)	0.18 (−1.43, 1.78)	−0.01 (−0.68, 0.67)	BGT-ECA	.	.	.	0.46 (−0.40, 1.31)	0.32 (−0.41, 1.06)	.
1.03 (−0.17, 2.23)	0.66 (−0.85, 2.18)	0.53 (−0.80, 1.85)	0.27 (−1.07, 1.61)	0.29 (−1.60, 2.19)	0.11 (−1.08, 1.30)	0.12 (−1.18, 1.41)	TT-ECA	.	.	.	.	0.74 (−0.20, 1.68)
1.14 (0.10, 2.17)	0.77 (−0.55, 2.09)	0.63 (−0.45, 1.71)	0.38 (−0.77, 1.52)	0.40 (−1.36, 2.16)	0.22 (−0.73, 1.16)	0.22 (−0.85, 1.29)	0.11 (−1.14, 1.35)	DT-BGT	−0.06 (−1.38, 1.26)	.	.	0.66 (−0.28, 1.60)
1.13 (0.26, 1.99)	0.76 (−0.28, 1.79)	0.62 (−0.03, 1.26)	0.36 (−0.52, 1.24)	0.39 (−1.19, 1.96)	0.20 (−0.35, 0.75)	0.21 (−0.50, 0.92)	0.09 (−1.13, 1.32)	−0.01 (−0.94, 0.91)	BWS-TT	0.13 (−0.51, 0.77)	0.22 (−0.53, 0.96)	.
1.26 (0.40, 2.12)	0.89 (−0.11, 1.88)	**0.75 (0.05, 1.44)**	0.49 (−0.37, 1.35)	0.52 (−1.05, 2.08)	0.33 (−0.14, 0.80)	0.34 (−0.28, 0.96)	0.22 (−1.00, 1.45)	0.12 (−0.85, 1.09)	0.13 (−0.36, 0.63)	BGT	1.32 (−0.09, 2.73)	.
1.33 (0.58, 2.09)	0.96 (−0.04, 1.96)	**0.82 (0.15, 1.50)**	0.57 (−0.19, 1.32)	0.59 (−0.90, 2.08)	0.41 (−0.01, 0.83)	0.41 (−0.18, 1.01)	0.30 (−0.88, 1.47)	0.19 (−0.73, 1.12)	0.20 (−0.30, 0.71)	0.07 (−0.41, 0.55)	CON	−0.28 (−1.56, 1.00)
1.77 (1.03, 2.51)	**1.40 (0.21, 2.59)**	**1.27 (0.34, 2.19)**	**1.01 (0.05, 1.97)**	1.03 (−0.61, 2.68)	**0.85 (0.13, 1.57)**	0.86 (−0.03, 1.75)	0.74 (−0.20, 1.68)	0.63 (−0.18, 1.45)	0.65 (−0.13, 1.43)	0.52 (−0.26, 1.30)	0.44 (−0.25, 1.14)	TT

The effects of different BGT Interventions were assessed using a frequency ranking method, and the probability of ranking for each BGT was expressed as a P-score. Results of the network meta-analysis are presented in the left lower half and results from pairwise comparisons in the upper right half, if available. Comparisons between Interventions should be read from left to right and the estimate is in the cell in common between the column-defining Intervention and the row-defining Intervention. In the left lower half, standard mean differences (SMDs) higher than 0 favor the column-defining Intervention, in the upper right half SMDs higher than 0 favor the row defining Intervention. Cells in bold print indicate significant results "." = not available.

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TABLE 2B League table of dynamic steady-state balance.

BWS-TT-ECA	.	.	.	0.43 (−0.07, 0.93)	.	.	.	0.68 (−0.02, 1.38)	.	.	.	0.83 (−0.11, 1.76)
0.20 (−0.53, 0.92)	TT-ECA	.	.	.	.	.	0.95 (−0.24, 2.14)	.	.	.	**0.87 (0.34, 1.40)**	1.12 (−0.04, 2.28)
0.20 (−0.49, 0.90)	0.01 (−0.68, 0.69)	EC-BGT	.	0.58 (−0.54, 1.69)	.	.	.	1.25 (−0.06, 2.56)	.	.	**0.77 (0.07, 1.47)**	**0.94 (0.10, 1.78)**
0.39 (−0.25, 1.03)	0.19 (−0.45, 0.83)	0.19 (−0.45, 0.82)	VR-GT	.	0.49 (−0.58, 1.55)	−0.41 (−1.46, 0.63)	.	0.02 (−0.86, 0.90)	.	.	**1.02 (0.35, 1.69)**	**1.06 (0.28, 1.85)**
0.43 (−0.03, 0.89)	0.23 (−0.38, 0.85)	0.23 (−0.34, 0.80)	0.04 (−0.47, 0.56)	BWS-TT	.	−0.21 (−1.41, 1.00)	.	**0.61 (0.18, 1.04)**	−0.01 (−1.02, 0.99)	.	.	**0.70 (0.23, 1.18)**
0.61 (−0.26, 1.48)	0.42 (−0.48, 1.31)	0.41 (−0.47, 1.29)	0.22 (−0.55, 0.99)	0.18 (−0.60, 0.96)	RA-GT-ECA	0.07 (−1.05, 1.19)	.	.	.	.	.	0.70 (−0.34, 1.74)
0.61 (0.07, 1.14)	0.41 (−0.17, 1.00)	0.40 (−0.15, 0.96)	0.22 (−0.24, 0.68)	0.18 (−0.20, 0.55)	−0.00 (−0.73, 0.72)	RA-GT	.	0.11 (−0.34, 0.55)	.	.	**1.23 (0.41, 2.04)**	**0.37 (0.02, 0.72)**
0.63 (0.06, 1.21)	0.44 (−0.18, 1.05)	0.43 (−0.18, 1.04)	0.24 (−0.30, 0.78)	0.20 (−0.24, 0.64)	0.02 (−0.78, 0.82)	0.03 (−0.39, 0.44)	BGT-ECA	0.15 (−0.27, 0.57)	.	.	.	**0.59 (0.02, 1.16)**
0.74 (0.25, 1.23)	0.54 (−0.04, 1.13)	0.54 (−0.01, 1.09)	0.35 (−0.12, 0.82)	0.31 (−0.02, 0.64)	0.13 (−0.63, 0.89)	0.13 (−0.18, 0.44)	0.11 (−0.24, 0.45)	BGT	.	0.06 (−1.04, 1.16)	.	**1.37 (0.55, 2.20)**
0.84 (0.07, 1.62)	0.65 (−0.11, 1.40)	0.64 (−0.12, 1.40)	0.45 (−0.27, 1.18)	0.41 (−0.25, 1.07)	0.23 (−0.72, 1.19)	0.24 (−0.44, 0.91)	0.21 (−0.51, 0.93)	0.10 (−0.57, 0.77)	DT-BGT	.	0.12 (−0.59, 0.83)	.
0.91 (−0.01, 1.83)	0.71 (−0.25, 1.67)	0.70 (−0.24, 1.65)	0.52 (−0.38, 1.42)	0.48 (−0.36, 1.32)	0.29 (−0.78, 1.37)	0.30 (−0.53, 1.12)	0.27 (−0.58, 1.13)	0.17 (−0.63, 0.97)	0.06 (−0.95, 1.08)	AQE-BGT	.	0.16 (−0.96, 1.28)
1.17 (0.57, 1.78)	**0.98 (0.49, 1.46)**	**0.97 (0.45, 1.49)**	**0.79 (0.31, 1.26)**	**0.74 (0.28, 1.20)**	0.56 (−0.23, 1.35)	**0.57 (0.15, 0.98)**	**0.54 (0.05, 1.04)**	**0.43 (0.00, 0.87)**	0.33 (−0.27, 0.93)	0.27 (−0.61, 1.14)	TT	0.14 (−0.59, 0.86)
1.18 (0.67, 1.68)	**0.98 (0.42, 1.54)**	**0.97 (0.44, 1.50)**	**0.79 (0.34, 1.23)**	**0.74 (0.41, 1.08)**	0.56 (−0.17, 1.29)	**0.57 (0.29, 0.84)**	**0.54 (0.17, 0.92)**	**0.43 (0.13, 0.73)**	0.33 (−0.32, 0.99)	0.27 (−0.53, 1.07)	0.00 (−0.39, 0.40)	CON

The effects of different BGT Interventions were assessed using a frequency ranking method, and the probability of ranking for each BGT was expressed as a P-score. Results of the network meta-analysis are presented in the left lower half and results from pairwise comparisons in the upper right half, if available. Comparisons between Interventions should be read from left to right and the estimate is in the cell in common between the column-defining Intervention and the row-defining Intervention. In the left lower half, standard mean differences (SMDs) higher than 0 favor the column-defining Intervention, in the upper right half SMDs higher than 0 favor the row defining Intervention. Cells in bold print indicate significant results "." = not available.

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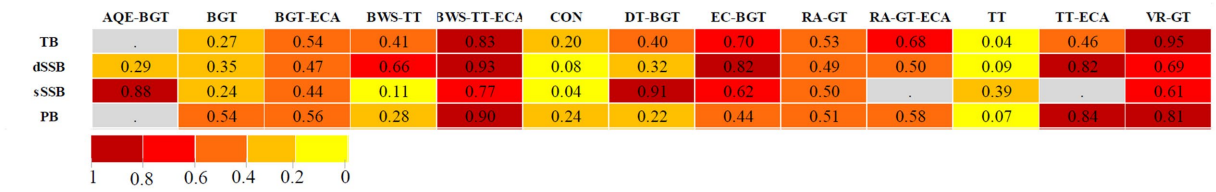

FIGURE 2
Heat map of balance and gait training interventions. A heat map of balance and gait training interventions ranked according to associated degree of alteration in balance test batteries, dynamic steady-state balance, static steady-state balance, and proactive balance numbers reflect P-scores, which rank interventions on a continuous scale from 0 to 1. A higher P-score indicates a greater increase in the balance parameter. Gray squares indicate that data were not available. AQE-BGT, aquatic balance and gait training; BGT, balance and gait training; BGT-ECA, balance and gait training with external cues; BWS-TT, body weight-supported treadmill training; BWS-TT-ECA, body weight-supported treadmill training with external cues; CON, control group; dSSB, dynamic steady-state balance; DT-BGT, dual-task gait training; EC-BGT, eyes closed gait training; PB, proactive balance; sSSB, static steady-state balance; RA-GT, robotic-assisted gait training; RA-GT-ECA, robotic-assisted gait training with external cues; TB, balance test battery; TT, treadmill gait training; TT-ECA, treadmill gait training with external cues; VR-GT, virtual reality gait training.

Static steady-state balance

Studies on static steady-state balance outcomes were the fewest, with a total of 21 studies involving a total of 609 patients with stroke. According to the league table of static balance, we found that the DT-BGT group was significantly better than the TT, BGT, BWS-TT, and CON groups; the AQE-BGT group was significantly better than the RA-GT, BGT, BWS-TT, and CON groups; and the other comparisons are shown in Table 2C. Additionally, no significant improvement effect of TT, BGT, or BWS-TT was found for static balance. In the overall effect ranking, DT-BGT had the best effect with a P-score of 0.91, and CON was the worst with a P-score of 0.04 (Figure 2). In the heterogeneity analysis, the overall heterogeneity was shown to be good ($\tau^2 = 0.01$, $I^2 = 7.3\%$, $p = 0.3735$). The global Q score of inconsistency was 11.25 ($p = 0.1282$). In the inconsistency test, we found no hotspots of inconsistency in Appendix 9 (p. 52), indicating a relatively good consistency of the study.

Proactive balance

Results on proactive balance were reported in 28 studies, in which a total of 749 patients with stroke participated. A mixed comparison of the league table showed that the active balance of the BWS-TT-ECA group improved significantly better than that of the BWS-TT and TT groups; the active balance of the TT-ECA group was significantly better than that of the DT-BGT, TT and CON; and other comparative details are shown in Table 2D. In the overall effect ranking for improving balance, the best intervention was BWS-TT-ECA (P-score: 0.90), while TT was the worst performer (P-score: 0.07; Figure 2). The heterogeneity was moderate ($\tau^2 = 0.15$, $I^2 = 46.2\%$, $p < 0.05$), and the Q score of global inconsistency was 7.06 ($p = 0.5306$). Using the nodal split method for local inconsistency testing, we found no hotspots of inconsistency in Appendix 9 (p. 54), indicating good consistency between direct and indirect evidence.

Meta-regression

After regression analysis, we found no significant effect of all covariates on these four balance outcomes, indicating that the heterogeneity of the study did not stem from the age and sex of participants, the duration and frequency of interventions, the year of publication, or the time of entry into the study after stroke [Appendix 8 (p. 46)].

GRADE assessment

The GRADE approach was used to assess the quality of evidence from studies on the effect of different BGTs on the different balance abilities of patients with stroke through an NMA. Table 3 presents a summary of the certainties of evidence based on four balance types [all details of the GRADE assessment for all pairwise comparisons are presented in Appendix 10 (p. 56)]. The main reasons for downgrading were imprecision, inconsistency, and the risk of bias. However, two hotspots were found through a local inconsistency check of the dynamic steady-state balance, indicating differences in regional direct and indirect comparisons, contributing to the downgrade. The funnel plot was roughly symmetrical, indicating no significant publication bias (Supplementary Figures S14–S17).

Discussion

This NMA is the first network meta-analysis to comprehensively assess the effect of various BGTs on the balance of stroke patients. The results found that the effect of different BGT on the different balance abilities of patients with stroke was apparently different, with specific details as follows: VR-GT was the most effective for the balance test batteries of patients with stroke; BWS-TT-ECA was the most effective for their dynamic steady-state balance and proactive balance; and DT-BGT was the most effective for their static steady-state balance. In addition, we did not find that age, gender, duration of illness, year of publication, frequency of interventions, and duration of interventions have a regulatory effect on the BGT effect. Our study provides more clinical options for balance rehabilitation in stroke patients.

The present study showed that VR-GT (SMD: 1.37, 95% CI: 0.62–2.11; P-score: 0.95) was the most effective for the balance test batteries of stroke survivors compared to the CON, which was significantly more effective than many other types of exercise. We found several virtual reality studies on stroke survivors (19, 42, 43), which suggest that virtual reality (VR) training can be more effective in improving balance or gait in stroke patients, which is consistent with our findings.

TABLE 2C League table of static steady-state balance.

DT-BGT	.	.	.	.	.	.	**1.04 (0.24, 1.84)**	.	.	.
0.16 (−1.17, 1.50)	AQE-BGT	.	.	.	.	.	.	0.64 (−0.27, 1.55)	.	**2.27 (1.08, 3.46)**
0.44 (−0.58, 1.47)	0.28 (−0.79, 1.35)	EC-BGT	.	.	.	.	**0.78 (0.08, 1.49)**	0.43 (−0.59, 1.45)	.	.
0.73 (−0.31, 1.78)	0.57 (−0.40, 1.54)	0.29 (−0.52, 1.09)	VR-GT	.	.	0.27 (−0.53, 1.07)	0.10 (−0.65, 0.85)	.	.	**1.36 (0.24, 2.49)**
0.75 (−0.48, 1.98)	0.59 (−0.28, 1.46)	0.31 (−0.61, 1.23)	0.02 (−0.81, 0.85)	BGT-ECA	.	.	.	**0.51 (0.06, 0.96)**	.	.
0.92 (−0.28, 2.13)	0.76 (−0.09, 1.61)	0.48 (−0.43, 1.39)	0.19 (−0.59, 0.97)	0.17 (−0.49, 0.83)	BWS-TT-ECA	.	.	0.15 (−0.60, 0.89)	0.64 (0.14, 1.14)	**1.05 (0.38, 1.72)**
0.99 (−0.15, 2.13)	**0.83 (0.01, 1.65)**	0.55 (−0.30, 1.39)	0.26 (−0.36, 0.88)	0.24 (−0.43, 0.91)	0.07 (−0.52, 0.65)	RA-GT	.	0.58 (−0.27, 1.43)	.	**0.59 (0.20, 0.98)**
1.04 (0.24, 1.84)	0.88 (−0.19, 1.95)	0.60 (−0.04, 1.24)	0.31 (−0.36, 0.98)	0.29 (−0.65, 1.22)	0.12 (−0.79, 1.02)	0.05 (−0.76, 0.86)	TT	.	.	.
1.26 (0.11, 2.41)	**1.10 (0.36, 1.84)**	**0.82 (0.01, 1.62)**	0.53 (−0.17, 1.23)	**0.51 (0.06, 0.96)**	0.34 (−0.15, 0.82)	0.27 (−0.22, 0.76)	0.22 (−0.60, 1.04)	BGT	0.16 (−0.51, 0.83)	−0.08 (−0.91, 0.74)
1.50 (0.30, 2.70)	**1.33 (0.49, 2.17)**	**1.05 (0.16, 1.95)**	**0.76 (0.00, 1.53)**	**0.74 (0.10, 1.39)**	**0.57 (0.12, 1.02)**	0.50 (−0.06, 1.07)	0.45 (−0.44, 1.35)	0.23 (−0.23, 0.70)	BWS-TT	−0.03 (−0.67, 0.61)
1.64 (0.50, 2.78)	**1.48 (0.71, 2.25)**	**1.20 (0.36, 2.03)**	**0.91 (0.27, 1.55)**	**0.89 (0.26, 1.52)**	**0.72 (0.21, 1.23)**	**0.65 (0.30, 1.00)**	0.60 (−0.21, 1.41)	0.38 (−0.06, 0.82)	0.15 (−0.34, 0.64)	CON

The effects of different BGT Interventions were assessed using a frequency ranking method, and the probability of ranking for each BGT was expressed as a P-score. Results of the network meta-analysis are presented in the left lower half and results from pairwise comparisons in the upper right half, if available. Comparisons between Interventions should be read from left to right and the estimate is in the cell in common between the column-defining Intervention and the row-defining Intervention. In the left lower half, standard mean differences (SMDs) higher than 0 favor the column-defining Intervention, in the upper right half SMDs higher than 0 favor the row defining Intervention. Cells in bold print indicate significant results "." = not available. AQE-BGT, Aquatic balance and gait training; BGT, balance and gait training; BGT-ECA, balance and gait training with external cues; BWS-TT, body weight supported treadmill training; BWS-TT-ECA, body weight supported treadmill training with external cues; CON, Control group; DT-BGT, dual-task gait training; EC-BGT, eyes closed gait training; RA-GT, robotic-assisted gait training; RA-GT-ECA, robotic-assisted gait training with external cues; TT, treadmill gait training; VR-GT, virtual reality gait training.

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TABLE 2D League table of proactive balance.

BWS-TT-ECA	.	.	.	.	.	.	.	**1.61 (0.47, 2.75)**	.	.	.
0.53 (−1.17, 2.23)	TT-ECA	.	.	0.40 (−0.79, 1.59)	.	.	.	.	1.17 (−0.04, 2.38)	.	**1.50 (0.82, 2.17)**
0.63 (−1.03, 2.28)	0.10 (−0.73, 0.93)	VR-GT	0.66 (−0.46, 1.78)	.	−0.04 (−0.98, 0.90)	.	.	.	**1.51 (0.38, 2.64)**	.	**1.59 (0.64, 2.55)**
1.04 (−0.71, 2.78)	0.51 (−0.50, 1.52)	0.41 (−0.46, 1.28)	RA-GT-ECA	.	.	0.03 (−1.14, 1.20)	.	.	0.85 (−0.24, 1.94)	.	.
1.08 (−0.51, 2.67)	0.55 (−0.20, 1.31)	0.45 (−0.28, 1.18)	0.04 (−0.85, 0.94)	BGT-ECA	0.31 (−0.26, 0.89)	.	.	.	−0.00 (−0.71, 0.71)	.	.
1.11 (−0.41, 2.63)	0.58 (−0.19, 1.36)	0.48 (−0.17, 1.14)	0.08 (−0.78, 0.93)	0.03 (−0.44, 0.51)	BGT	0.06 (−0.78, 0.91)	.	0.49 (−0.51, 1.50)	0.59 (−0.21, 1.38)	.	.
1.14 (−0.47, 2.76)	0.62 (−0.16, 1.39)	0.51 (−0.19, 1.22)	0.11 (−0.69, 0.90)	0.06 (−0.55, 0.68)	0.03 (−0.51, 0.57)	RA-GT	.	.	0.37 (−0.23, 0.96)	.	**1.11 (0.00, 2.21)**
1.29 (−0.74, 3.31)	0.76 (−0.69, 2.20)	0.66 (−0.75, 2.07)	0.25 (−1.23, 1.73)	0.21 (−1.14, 1.56)	0.17 (−1.16, 1.51)	0.14 (−1.19, 1.48)	EC-BGT	.	0.28 (−0.97, 1.53)	.	.
1.61 (0.47, 2.75)	1.08 (−0.19, 2.34)	0.98 (−0.22, 2.18)	0.57 (−0.75, 1.89)	0.53 (−0.59, 1.64)	0.49 (−0.51, 1.50)	0.46 (−0.68, 1.60)	0.32 (−1.35, 1.99)	BWS-TT	.	.	.
1.57 (−0.03, 3.16)	**1.04 (0.31, 1.76)**	**0.94 (0.28, 1.59)**	0.53 (−0.26, 1.32)	0.48 (−0.02, 0.99)	0.45 (−0.02, 0.93)	0.42 (−0.04, 0.89)	0.28 (−0.97, 1.53)	−0.04 (−1.15, 1.07)	CON	.	−0.23 (−1.40, 0.94)
1.78 (−0.20, 3.76)	**1.26 (0.03, 2.48)**	1.16 (−0.11, 2.43)	0.75 (−0.66, 2.16)	0.70 (−0.58, 1.99)	0.67 (−0.60, 1.94)	0.64 (−0.62, 1.90)	0.50 (−1.26, 2.26)	0.18 (−1.44, 1.80)	0.22 (−1.02, 1.46)	DT-BGT	0.28 (−0.78, 1.34)
2.07 (0.40, 3.74)	**1.54 (0.92, 2.16)**	**1.44 (0.74, 2.13)**	**1.03 (0.10, 1.96)**	**0.99 (0.26, 1.71)**	**0.95 (0.26, 1.65)**	**0.92 (0.25, 1.60)**	0.78 (−0.63, 2.19)	0.46 (−0.76, 1.68)	0.50 (−0.14, 1.14)	0.28 (−0.78, 1.34)	TT

The effects of different BGT Interventions were assessed using a frequency ranking method, and the probability of ranking for each BGT was expressed as a P-score. Results of the network meta-analysis are presented in the left lower half and results from pairwise comparisons in the upper right half, if available. Comparisons between Interventions should be read from left to right and the estimate is in the cell in common between the column-defining Intervention and the row-defining Intervention. In the left lower half, standard mean differences (SMDs) higher than 0 favor the column-defining Intervention, in the upper right half SMDs higher than 0 favor the row defining Intervention. Cells in bold print indicate significant results "."= not available. BGT, balance and gait training; BGT-ECA, balance and gait training with external cues; BWS-TT, body weight supported treadmill training; BWS-TT-ECA, body weight supported treadmill training with external cues; CON, Control group; DT-BGT, dual-task gait training; EC-BGT, eyes closed gait training; RA-GT, robotic-assisted gait training; RA-GT-ECA, robotic-assisted gait training with external cues; TT, treadmill gait training; TT-ECA, treadmill gait training with external cues; VR-GT, virtual reality gait training.

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TABLE 3 Summary of certainty of evidence (GRADE approach) for network meta-analysis in a study examining the effect of different gait training on different balance abilities in stroke patients.

Outcome	Certainty of evidence	Reason for downgrade
Balance test batteries	Very low	Imprecision, risk of bias
Dynamic steady-state balance	Very low	Imprecision, risk of bias, inconsistency
Static steady-state balance	Very low	Imprecision, risk of bias
Proactive balance	Very low	Imprecision, risk of bias

GRADE, Grading of Recommendations Assessment, Development and Evaluation.

For stroke survivors, optimizing and strengthening the compensatory mechanisms of their brain is crucial for motor impairments (44), and a virtual environment that promotes the illusion of body movements can be created using VR technology, which can enhance the neural activation of motor brain areas, mobilize plastic changes in the neurology of their brain, aid in the recovery of neurological cell synapses, and enable direct training for the central nervous system, which is essential for the reorganization and recovery of neural structures in stroke survivors (45, 46). It is well known that patients with different levels of stroke can undergo different BGT; only those who can walk can undergo traditional treadmill training; those who can walk some distance can undergo weight-supported BGT; and those who cannot walk are more suitable for electromechanical or robot-assisted training (47–49). The type of VR-GT BGT also has all the advantages of VR training, which is more acceptable to patients with stroke, especially for patients with more severe stroke in the early stages of recovery, where the potential for balance recovery is more pronounced. This type of exercise is a valid reason for the additional improvement of the balance test batteries of patients with stroke, which may have contributed to the study's findings. This NMA also showed a marked effect of BWS-TT-ECA and RA-GT-BGT compared to the CON, which has been included in the interest. Another interesting observation is that TT is the least effective in restoring the balance test batteries of patients with stroke and in studies on proactive balance. One possible explanation is that patients with stroke have reached a new homeostatic state of balance when performing TT BGT, which only maintains their balance, and that to effectively apply BGT in improving patients' balance, it is necessary to add challenging exercises without reducing their freedom, such as BWS-TT-ECA or BGT-ECA (50, 51).

Dynamic steady-state balance refers to the ability to maintain a stable position while walking, while proactive balance means an equilibrium ability to predict disturbances (52). Research has shown that a habitual gait speed ≤ 1 m/s (dynamic steady-state balance) and the time to complete a Timed Up and Go Test ≥ 13.5 s (proactive balance) increase the risk of falling by 2–3 times (53, 54), and dynamic and static steady-state balance, as well as proactive balance, may be independent of each other (55). Interestingly, the results of the BGT rankings for dynamic steady-state and proactive balance showed a high degree of similarity, with specific details as follows: first, BWS-TT-ECA was the best for both balances (SMD: 1.18, 95% CI: 0.67–1.68; P-score: 0.93); (SMD: 1.57, 95% CI: −0.03–3.16; P-score: 0.90), while the results of proactive balance were not exceptionally stable, with a 95% CI spanning "0"; second, there was some similarity in the order of the remaining rankings of the BGT effect, with both TT-ECA and VR-GT ranking higher; and finally, compared to the CON, both TT-ECA and VR-GT were more effective for dynamic steady-state and proactive balance, both of which were highly significant, suggesting that if both types of balance needed to be rehabilitated simultaneously, similar BGT interventions could be chosen. Although there are many similarities, dynamic steady-state balance is undeniably very different from proactive balance. For dynamic steady-state balance, there are more BGT intervention types available, and in addition to BWS-TT-ECA, TT-ECA, EC-BGT, VR-GT, BWS-TT, RA-GT, BGT-ECA, and BGT also have meaningful effects. However, for proactive balance, TT-ECA and VR-GT were the only two BGT exercises that had a noteworthy effect, with much fewer BGT options. Although they are a specific task in balance performance, for patients with stroke, various balances need to work together to prevent falls.

Compared to CON, DT-BGT, AQE-BGT, EC-BGT, VR-GT, BGT-ECA, BWS-TT-ECA, and RA-GT, we have had significant efficacy for rehabilitating static steady-state balance, indicating that the above BGT was the most promising. DT-BGT had the best therapeutic effect (SMD: 1.64, 95% CI: 0.50–2.78; P-score: 0.91). Previous studies have shown that DT-BGT is effective in improving stride length, stride frequency, cadence, and 10-m walk tests for patients with stroke (15, 56). However, possible advantages in improving the balance function are uncertain, and our study bridges this gap. Regarding static steady-state balance, DT-BGT has an obvious advantage over the other BGT types we have included, but there is no substantial advantage for other balances. Notably, BGT was much more selective (and more pronounced than CON) for improving dynamic and static steady-state balance than improving balance test batteries and proactive balance. For the latter two types of balance, although most BGT has a positive effect on balance, a wide CI crosses "0," indicating uncertainties in the treatment effect. Previous studies have shown that, after stopping training for 3 months, the ability of healthy older fallers and non-fallers to stand on one leg is significantly reduced (57), which may be more severe for patients with stroke. Although, through a variety of BGT interventions, the static balance of patients with stroke is effectively improved, long-term adherence to training is necessary for obtaining long-term benefits.

Strengths and limitations

This NMA has several advantages over previous relevant studies. A systematic and comprehensive search strategy for published and unpublished studies based on many databases was applied. Meanwhile, the search was not restricted by publication date or language, and the studies included were not limited to specific types of interventions or comparators; the NMA allows comparisons on the efficacy of different exercise therapies, takes into account the results of direct and indirect comparisons, improves statistical efficiency, and included all relevant studies, which allow us to include a considerable number of RCTs (66 trials; 1,933 patients) and provide a ranking of priorities among different BGT in terms of the efficacy of various balance rehabilitation.

There are still several limitations. First, although we conducted regression analyses with some possible influence as covariates, we did

not obtain meaningful results, indicating, on the one hand, that our statistics were relatively stable, while, on the other hand, we did not find a source of heterogeneity. We found high heterogeneity in the results of balance test batteries ($\tau^2 = 0.29$, $I^2 = 65.5\%$, $p < 0.001$), which we attributed through discussion to the variability of the outcome, which was a major limitation. Second, the stroke grade or site of onset was reported in only a few studies. Thus, we could not tell whether patients were homogeneous at the time of the initial intervention, and the initial disease grade or the stroke site might have influenced the outcome (58), which might also be an essential source of heterogeneity for this study. Third, we included only each study's mean and standard deviation rather than the raw data on each patient. Undoubtedly, more precise estimates of different effects could be made based on the data on individual patients, but this was beyond our ability. Fourth, the studies we included did not involve indicators related to the reactive balance of patients with stroke. The specific contribution of reactive balance to falls was undisputed; interventions to improve the balance response due to an unexpected loss of balance were thought to have a more critical impact on the risk of falls (59), and we hoped that, in the future, some investigators would undertake a study in this area. Fifth, when analyzing dynamic steady-state balance inconsistency, we found two hotspots indicating the ambiguity between direct and indirect evidence, illustrating the instability of the results of the outcomes and the need for further validation through high-quality RCTs. Finally, according to the GRADE assessment, our study evidence was of low quality, and the size and ranking of the treatment effect might change as more evidence becomes available. Therefore, more trials need to be included for further investigation.

Conclusion

This NMA provides evidence that the effect of various BGTs on the balance of patients with stroke is different. Balance is a multidimensional concept, and patients' needs should be fully considered when selecting BGT. A more effective BGT should be selected to improve patients' balance ability and reduce adverse falls for them. BGTs that are not statistically meaningful should be cautiously selected because their effectiveness has a higher degree of uncertainty. All findings may help clinicians, patients, and healthcare providers choose more appropriate BGT while recognizing that the quality of the evidence is shallow and that the findings should be interpreted cautiously.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

MZ served as principal author and had full access to all the data in the study, taking responsibility for the accuracy of the data analysis, and the integrity of the data. MZ and ZL contributed to the conception and design. MZ, ZL, YL, XJ, and BX contributed to data acquisition and interpretation and draft of the manuscript. TL contributed to revising the article and final approval. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1234017/full#supplementary-material

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Effect of magnesium sulfate on cerebral vasospasm in the treatment of aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis

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Introduction: The use of magnesium sulfate for treating aneurysmal subarachnoid hemorrhage (aSAH) has shown inconsistent results across studies. To assess the impact of magnesium sulfate on outcomes after aSAH, we conducted a systematic review and meta-analysis of relevant randomized controlled trials.

Methods: PubMed, Embase, and the Cochrane Library were searched for relevant literature on magnesium sulfate for aSAH from database inception to March 20, 2023. The primary outcome was cerebral vasospasm (CV), and secondary outcomes included delayed cerebral ischemia (DCI), secondary cerebral infarction, rebleeding, neurological dysfunction, and mortality.

Results: Of the 558 identified studies, 16 comprising 3,503 patients were eligible and included in the analysis. Compared with control groups (saline or standard treatment), significant differences were reported in outcomes of CV [odds ratio (OR) = 0.61, $p = 0.04$, 95% confidence interval (CI) (0.37–0.99)], DCI [OR = 0.57, $p = 0.01$, 95% CI (0.37–0.88)], secondary cerebral infarction [OR = 0.49, $p = 0.01$, 95% CI (0.27–0.87)] and neurological dysfunction [OR = 0.55, $p = 0.04$, 95% CI (0.32–0.96)] after magnesium sulfate administration, with no significant differences detected in mortality [OR = 0.92, $p = 0.47$, 95% CI (0.73–1.15)] and rebleeding [OR = 0.68, $p = 0.55$, 95% CI (0.19–2.40)] between the two groups.

Conclusion: The superiority of magnesium sulfate over standard treatments for CV, DCI, secondary cerebral infarction, and neurological dysfunction in patients with aSAH was demonstrated. Further randomized trials are warranted to validate these findings with increased sample sizes.

KEYWORDS

magnesium sulfate, aneurysmal subarachnoid hemorrhage, cerebral vasospasm, delayed cerebral ischemia, secondary cerebral infarction, mortality, rebleeding, neurological dysfunction

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is caused by the rupture of intracranial aneurysms and has a high morbidity rate of 6–9 per 100,000 persons and a mortality rate of approximately 35% (1). Previous data has revealed that more than 30% of patients with aSAH die within the first few days to weeks after initial bleeding, and most survivors experience long-term neurological dysfunction (2). The leading causes of disability and death are post-aSAH complications, including cerebral vasospasm (CV), delayed cerebral ischemia (DCI), secondary cerebral infarction, and rebleeding (3).

Although calcium antagonists such as nimodipine are commonly used to prevent CV, DCI, secondary cerebral infarction, and rebleeding in patients with aSAH (1), magnesium sulfate may provide an alternative for preventing such complications. A few studies have shown that magnesium sulfate is considered safe in treating aSAH (4); the higher the serum magnesium concentration, the lower the probability of CV (5). Hypomagnesemia can be observed in approximately 38% of patients upon admission (6), suggesting that serum magnesium concentrations may be closely related to CV after aSAH. Although several randomized controlled trials (RCTs) have recently evaluated the prophylactic use of magnesium sulfate in patients with aSAH, whether magnesium sulfate can improve the prognosis of aSAH remain controversial (6–13). Therefore, we performed a systematic review and meta-analysis to determine whether magnesium sulfate treatment could reduce the risk of CV and other poor outcomes in patients with aSAH.

2. Methods

2.1. Search criteria

We conducted this systematic review and meta-analysis according to the PRISMA guidelines (14). PubMed, Embase, and the Cochrane Library were searched for relevant articles written in English that were published from database inception to March 20, 2023. Full-text RCTs that compared the incidence of CV, DCI, secondary cerebral infarction, rebleeding, neurological dysfunction, and mortality between magnesium sulfate and control groups (saline or standard treatment) after aSAH in published studies were included. Case reports, comments, non-randomized studies, editorials, protocols, letters, guidelines, and animal studies were excluded. Unpublished studies were excluded from the analysis. The databases were searched using the appropriate MeSH terms and thw keywords "magnesium sulfate" and "subarachnoid hemorrhage." We also searched the titles, abstracts, and subject headings of all potentially relevant articles. The reference lists of all included articles and review papers were carefully reviewed to obtain additional publications.

2.2. Outcome measures

We assessed the effects of magnesium sulfate and saline/standard treatment on poor patients outcomes, including CV, DCI, secondary cerebral infarction, rebleeding, neurological dysfunction, and mortality. The primary outcome of this meta-analysis was CV, which was defined as recurrence of aSAH symptoms after improvement of aSAH symptoms or increased velocity of cerebral blood flow, as detected by angiography and/or transcranial Doppler (3). The secondary outcomes included DCI (defined as symptoms or signs of neurological deficits relieved within 24 h), secondary cerebral infarction (defined as symptoms or signs of neurological deficits that persisted for more than 24 h or low-density lesions confirmed on head computed tomography (CT) with corresponding new symptoms or signs) (3), rebleeding, neurological dysfunction and mortality.

2.3. Statistical analysis

Review Manager software version 5.4 (The Cochrane Collaboration,2020; Nordic Cochrane Centre, Copenhagen, Denmark) for statistical analysis. Dichotomous data were summarized as odds ratios (ORs) and 95% confidence intervals (CIs). Continuous data were displayed as mean differences (MDs) and standard deviations (SDs). Where appropriate, SDs were calculated based on the reported standard errors. Cochran's Q test was used to assess study heterogeneity. An $I^2 > 50\%$ or $p < 0.1$ was said to represent significant heterogeneity. Due to the heterogeneity in treatment duration and definitions of neurological dysfunction between the included studies, a meta-analysis of random effects was utilized to pool the data for more robust results (15). Categorical variables were analyzed using the dominant ORs, and continuous variables using MDs. Additionally, a meta-analysis of random effects was used to combine the results of the original studies. If there was significant heterogeneity, a sensitivity analysis using the leave-one-out method was carried out to evaluate the robustness of the results and check if any single study included in the meta-analysis might have a significant effect on the final results. To achieve this test, data for each study was removed and meta-analyses were then recalculated for the remaining studies, so that the impact of the removed data on the overall study can be ascertained. The Cochrane Collaboration Tool was used to assess bias. p-values <0.05 were considered statistically significant.

3. Results

3.1. Literature search results

We identified 558 studies across the databases reporting magnesium sulfate in aSAH, of which 373 published studies were obtained after removing duplicate records. After screening the titles and abstracts, 238 unrelated studies were excluded. The full texts of the remaining 135 studies were reviewed; eventually, 16 studies (3, 5–13, 16–21) with a total of 3,503 participants (1,764 and 1,739 in the magnesium sulfate and control groups, respectively) comparing the incidence of related complications in patients with aSAH treated with magnesium sulfate and control groups were included in the analysis (Figure 1). Eight studies (7, 8, 11, 12, 17–20) were conducted in Europe, six (3, 6, 9, 10, 16, 21) in Asia, one (13) in the Americas, and one (5) in Australia. The treatment duration in the 16 studies (3, 5–13, 16–21) was 10–21 days, and the follow-up time of most studies (5–7, 9–13, 16, 17, 19, 21) was more than 3 months. The baseline characteristics and the primary and secondary outcome indicators of each study are shown in Table 1.

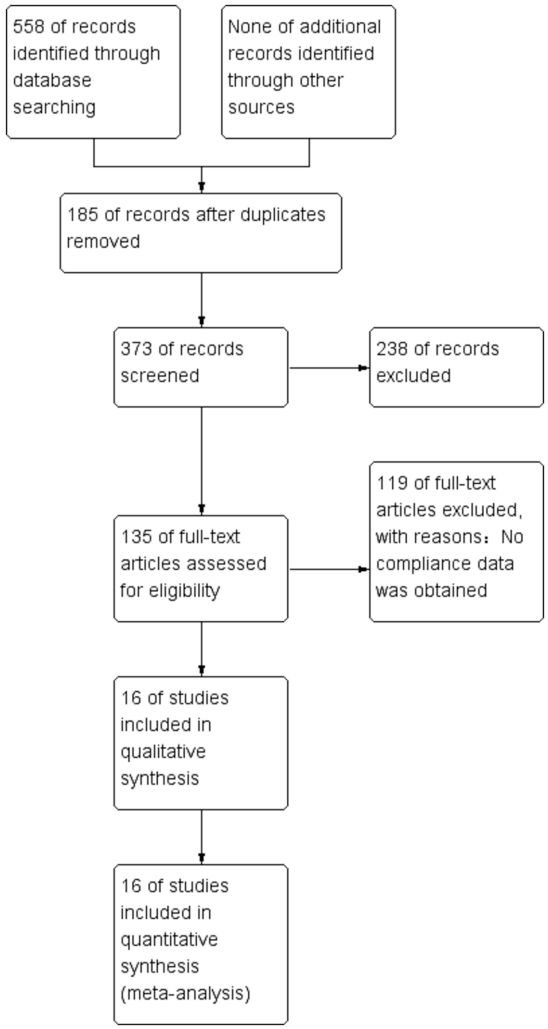

FIGURE 1
Literature search scheme.

3.2. Analysis of the quality of eligible studies

We evaluated the qualification standard for the 16 included studies using the Cochrane Collaboration tool. Quality analysis of the studies is shown in Figures 2A,B. All studies (3, 5–13, 16–21) described randomization methods, and seven studies (3, 5–7, 10, 13, 20) had sufficient allocation concealment. Regarding the blinding method, except for one study (11) with a single-blinded design, the remaining studies were double-anonymized (3, 5–10, 12, 13, 16–21). Finally, no study has selectively reported these results.

3.3. Outcomes

3.3.1. CV

A total of 973 patients in nine studies (3, 5, 6, 11–13, 16, 20, 21) were evaluated for CV after aSAH. The results showed that compared with patients in control groups, the incidence of CV in aSAH patients treated with magnesium sulfate was significantly lower [OR = 0.61, $p = 0.04$, 95% CI (0.37–0.99)] (Figure 3A). Owing to significant heterogeneity ($p = 0.02$, $I^2 = 55\%$), we used sensitivity analysis to evaluate the robustness of the results. After excluding a trial by Wong et al. (6), heterogeneity was significantly decreased ($p = 0.33$, $I^2 = 13\%$), with no changes to the significant difference in favor of magnesium sulfate [OR = 0.52, $p = 0.001$, 95% CI (0.35–0.77)] (Figure 3B).

3.3.2. DCI

DCI was recorded in 11 studies (3, 6, 8, 10–13, 16, 19–21) with 1,760 patients. Compared with the control group, the incidence of DCI in the magnesium sulfate group was significantly lower [OR = 0.57, $p = 0.01$, 95% CI (0.37–0.88)] (Figure 4). After sensitivity analysis, no exact source of heterogeneity was detected.

3.3.3. Secondary cerebral infarction

Seven studies (3, 6, 9, 11, 18–20) assessed 1,072 patients with secondary cerebral infarctions. Compared with the control group, the incidence of secondary cerebral infarction in the magnesium sulfate group was reduced [OR = 0.49, $p = 0.01$, 95% CI (0.27–0.87)] (Figure 5A). Owing to significant heterogeneity ($p = 0.04$, $I^2 = 55\%$) across the studies, we used sensitivity analysis to evaluate the robustness of the results. After excluding a trial by van den Bergh et al. (19), heterogeneity was significantly decreased ($p = 0.14$, $I^2 = 39\%$), with no changes to the significant difference in favor of magnesium sulfate [OR = 0.40, $p = 0.004$, 95% CI (0.21–0.74)] (Figure 5B).

3.3.4. Mortality

The pooled results from 11 studies (3, 6, 7, 9–11, 13, 16, 19–21) with 2,389 patients showed that there was no significant difference in mortality between the magnesium sulfate group and the control group in the treatment of aSAH [OR = 0.92, $p = 0.47$, 95% CI (0.73–1.15)] (Figure 6).

3.3.5. Rebleeding

Among the 16 studies, only two (3, 17) documented data on rebleeding in 329 patients. The pooled data showed no significant difference in the occurrence of rebleeding between the magnesium sulfate and control groups [OR = 0.68, $p = 0.55$, 95% CI (0.19–2.40)] (Figure 7).

3.3.6. Neurological dysfunction

Seven studies (3, 6, 11, 13, 17, 18, 20) evaluated neurological dysfunction in 964 patients. There was no significant difference in neurological dysfunction between the magnesium sulfate and control groups [OR = 0.67, $p = 0.16$, 95% CI (0.39–1.16)] (Figure 8A). Further sensitivity analysis was performed due to the significant heterogeneity ($p = 0.02$, $I^2 = 60\%$). After excluding a study by Wong et al. (6), the heterogeneity was significantly decreased ($p = 0.11$, $I^2 = 45\%$) with a significant difference detected in favor of magnesium sulfate [OR = 0.55, $p = 0.04$, 95% CI (0.32–0.96)] (Figure 8B).

4. Discussion

CV, DCI, secondary cerebral infarction, and rebleeding mainly occurs within 2 weeks after aSAH onset, in which the incidence of CV and DCI are 30%–90% and 17%–40%, respectively; the high incidence of complications suggests the need for prevention (2, 3, 7). Although

TABLE 1 Characteristics of the included studies.

Studies	Patients (*n*)		Gender		Average age, y		CV		DCI		SCI		Mortality		Rebleeding		Neurological dysfunction	
	MG	CG	Male	Female	MG	CG	MG	CG	MG	CG	MG	CG	MG	CG	MG	CG	MG	CG
Akdemir et al. (16)	40	43	32	51	53.4	53.9	10	14	10	14	NA	NA	8	6	NA	NA	NA	NA
Boet et al. (10)	23	22	8	37	NA	NA	NA	NA	6	12	NA	NA	3	3	NA	NA	NA	NA
Bradford et al. (5)	79	78	NA	NA	55.8	56.6	40	50	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dorhout et al. (7)	604	596	362	838	57.0	57.0	NA	NA	NA	NA	NA	NA	91	85	NA	NA	NA	NA
Huenges et al. (17)	107	102	44	165	53.7	55.7	NA	NA	NA	NA	NA	NA	NA	NA	0	1	53	51
Kunze et al. (18)	54	53	41	66	50.0	52.0	NA	NA	NA	NA	0	9	NA	NA	NA	NA	9	23
Leijenaar et al. (8)	307	309	175	441	56.2	57.9	NA	NA	81	75	NA	NA	NA	NA	NA	NA	NA	NA
Muroi et al. (11)	31	27	43	15	52.1	53.6	12	10	3	6	3	6	4	6	NA	NA	4	4
Takeuchi et al. (12)	12	13	11	14	60.8	57.1	1	8	1	7	NA	NA	NA	NA	NA	NA	NA	NA
van den Bergh et al. (19)	139	144	99	184	54.8	54.4	NA	NA	22	36	63	67	27	31	NA	NA	NA	NA
Veyna et al. (13)	20	16	10	26	46.0	51.0	6	5	6	5	NA	NA	4	2	NA	NA	6	5
Westermaier et al. (20)	54	53	66	41	50.0	52.0	36	45	12	27	12	27	6	10	NA	NA	9	15
Wong et al. (21)	30	30	18	42	58.0	62.0	11	17	7	13	NA	NA	4	5	NA	NA	NA	NA
Wong et al. (6)	169	158	119	208	57.0	57.0	42	29	42	29	17	18	22	28	NA	NA	42	29
Yamamoto et al. (9)	35	35	23	47	59.1	59.5	NA	NA	NA	NA	5	9	1	1	NA	NA	NA	NA
Zhang et al. (3)	60	60	62	58	43.5	42.9	4	12	3	10	2	8	5	8	4	5	3	11
Total	1,764	1,739	1,113	2,233	NA	NA	162	190	193	234	102	144	175	185	4	6	126	138

y, years; CV, cerebral vasospasm; DCI, delayed cerebral ischemia; SCI, secondary cerebral infarction; MG, magnesium sulfate group; CG, control group (saline/standard treatment); NA, not available.

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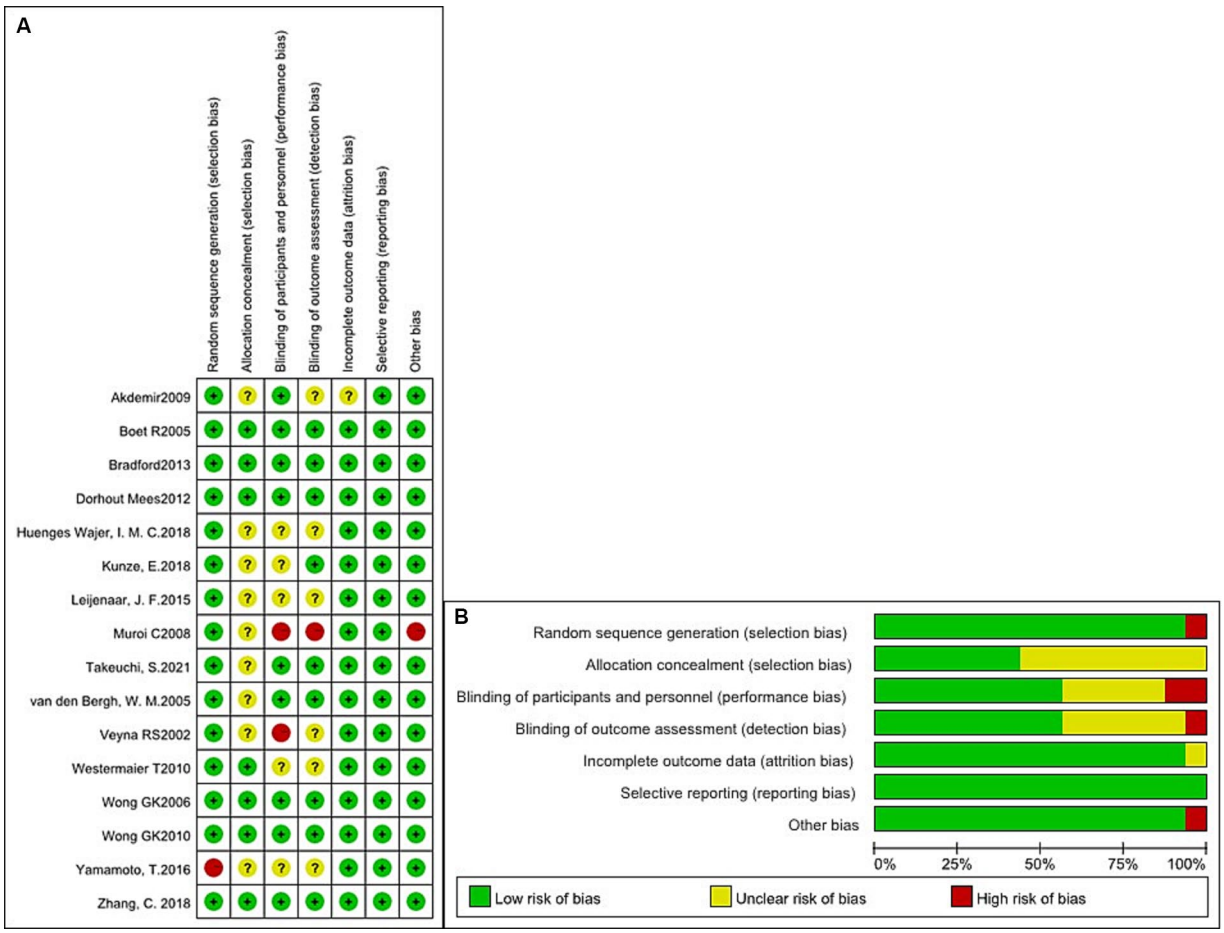

FIGURE 2
Quality analysis of the studies. **(A)** Summary of the risk of bias in all included studies. **(B)** Risk of bias graph: judgments about each risk of bias item presented as percentages across all included studies.

the calcium channel blocker nimodipine is currently the first-line treatment for aSAH (1), some studies have suggested that magnesium sulfate, which is inexpensive, has similar or even better efficacy in the treatment of aSAH; its safety and tolerability have been confirmed in the treatment of eclampsia (4, 11, 16).

Theoretically, magnesium ions may exert neuroprotective effects in preventing and improving CV and other complications in patients with aSAH via three mechanisms. First, as natural calcium channel antagonists, magnesium ions block the influx of calcium ions, inhibiting blood vessel contraction and preventing CV. Second, after the onset of aSAH, the role of the vasoconstrictor nitric oxide is weakened; however, magnesium ions can enhance the role of nitric oxide, thereby preventing CV. Third, magnesium sulfate prevents brain cells from releasing excitatory amino acids and acts as a vasodilator in cerebral arteries (3, 21, 22) (Figure 9).

Nine studies (3, 5, 6, 11–13, 16, 20, 21) recorded the influence of magnesium sulfate on CV. The incidence rates of CV in the magnesium sulfate group and in the control group were 32.7% and 39.7%, respectively, demonstrating that magnesium sulfate significantly reduced the incidence of CV. However, due to the presence of substantial heterogeneity among the included studies, a sensitivity analysis was performed, showing that the significant difference in magnesium sulfate treatment remained unchanged. This was inconsistent with previous studies (6, 13, 16, 21), which may have been due to the different infusion days and maintenance doses of soluble magnesium sulfate in the included studies.

Regarding DCI, 11 studies (3, 6, 8, 10–13, 16, 19–21) recorded relevant outcomes. The incidence rates of DCI in the magnesium sulfate and control groups were 21.8% and 26.6%, respectively, showing a significant difference in favor of magnesium sulfate, consistent with most previous studies (3, 19, 20, 23). This may be because magnesium ions can act as vasodilators to reduce the occurrence of DCI by improving vasospasms and ischemia tolerance (20). Due to significant heterogeneity, the results need to be interpreted with caution.

Seven studies (3, 6, 9, 11, 18–20) reported secondary cerebral infarction outcomes. The incidence rates of secondary cerebral infarction in the magnesium sulfate group and in the control group were 18.8% and 27.2%, respectively, indicating a considerable difference between the two groups. Due to the presence of significant heterogeneity, another sensitivity analysis was performed. After excluding the study by van den Bergh et al. (19), the significant difference observed with magnesium sulfate treatment did not change. This may be because magnesium sulfate can reduce the area of cerebral infarction by improving the CV and shortening the total ischemic time, thereby preventing secondary cerebral infarction (13).

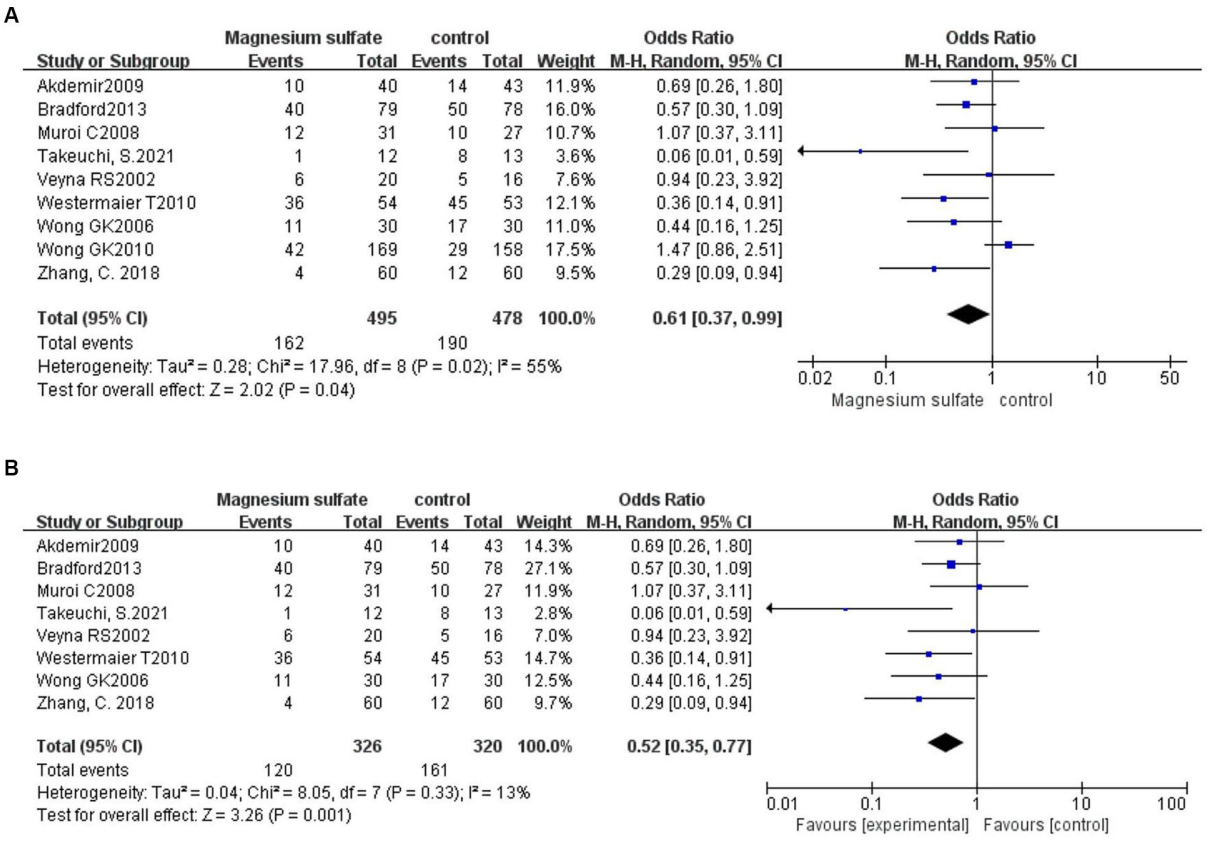

FIGURE 3
Forest plots showing the occurrence of cerebral vasospasm between magnesium sulfate and the control group before **(A)** and after **(B)** sensitivity analysis.

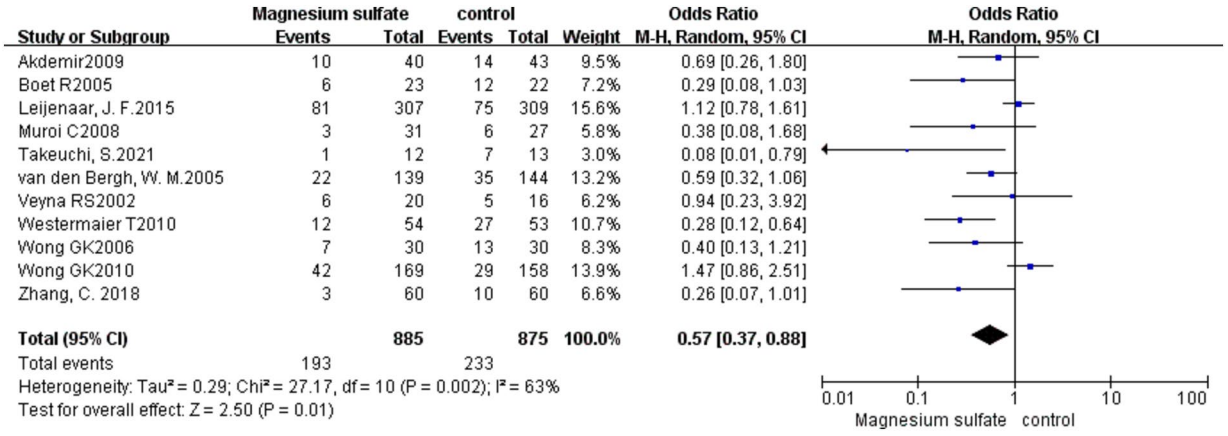

FIGURE 4
Forest plot showing the occurrence of delayed cerebral ischemia between magnesium sulfate and the control group.

Eleven (3, 6, 7, 9–11, 13, 16, 19–21) of the 16 studies analyzed patient mortality. The mortality rates in the magnesium sulfate and control groups were 14.5% and 15.6%, respectively, with no significant differences detected between the two groups. Limited by the relatively small sample sizes, further studies are warranted to determine whether magnesium sulfate reduces mortality in patients with aSAH.

Two studies (3, 17) reported the effect of magnesium sulfate on rebleeding. The incidence of rebleeding in the magnesium sulfate and control groups was 2.4% and 3.7%, respectively, with no significant difference between the two groups, indicating that magnesium sulfate may not reduce rebleeding in patients with aSAH. Due to the scarcity of available data, future studies with larger sample sizes are needed to verify this finding.

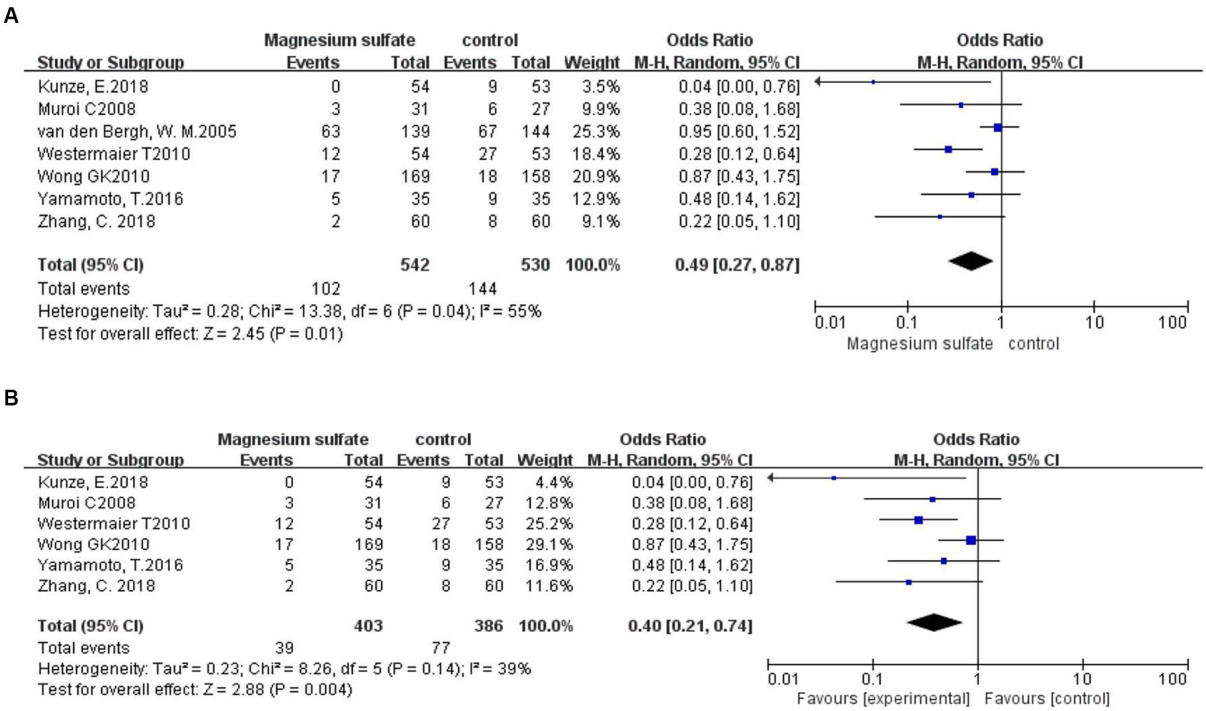

FIGURE 5
Forest plots showing the occurrence of secondary cerebral infarction between magnesium sulfate and the control group before **(A)** and after **(B)** sensitivity analysis.

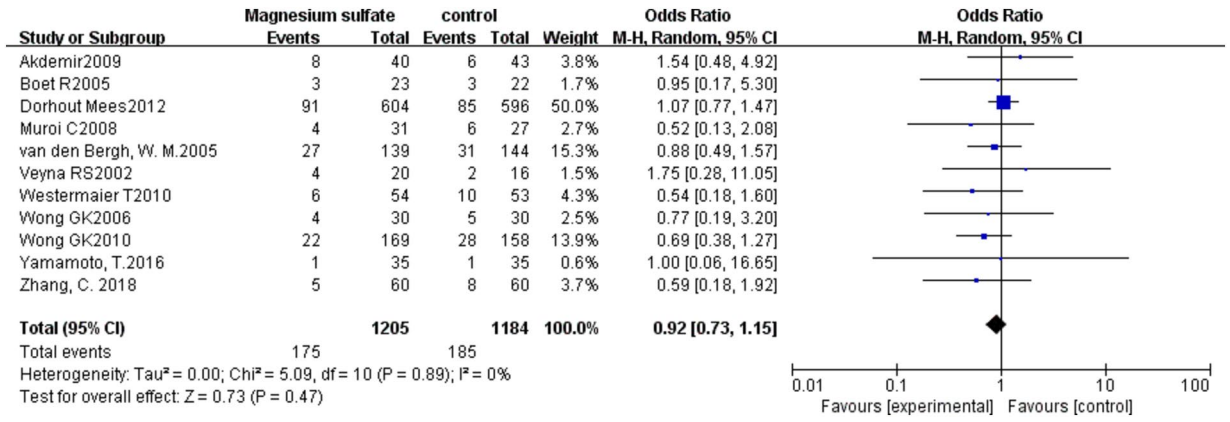

FIGURE 6
Forest plot showing the mortality between magnesium sulfate and the control group.

Neurological dysfunction was recorded in seven (3, 6, 11, 13, 17, 18, 20) studies. There was no significant difference in the incidence of neurological dysfunction between the two groups initially; however, there was substantial heterogeneity. After conducting the sensitivity analysis, there was a significant difference in favor of magnesium sulfate, indicating that patients in the magnesium sulfate group had better neurologic and functional outcomes. However, in the included studies, the definitions of neurological dysfunction differed and multiple assessment scales were used, including the National Institutes of Health Stroke Scale (3), the modified Rankin scale (6, 17), and the Glasgow Outcome Scale (6, 11, 13, 18, 20), which may have affected the validity of our results.

Despite recent publications regarding magnesium sulfate in the treatment of aSAH, whether magnesium sulfate can improve CV and other poor outcomes remains controversial (3, 5–7, 12, 18–20). Some studies (3, 12, 18–20) have reported that magnesium sulfate treatment for aSAH can reduce the incidence of CV, DCI, secondary cerebral infarction, and neurological dysfunction, while other studies (5–7) have concluded that magnesium sulfate treatment for aSAH is not beneficial. In the present study, compared to standard treatments, magnesium sulfate was shown to reduce the incidence of these

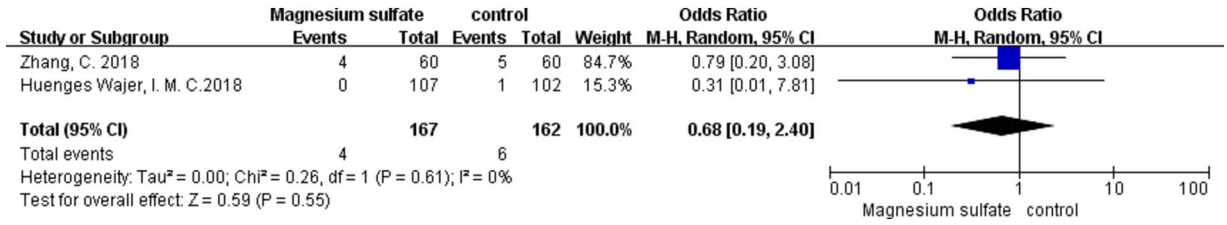

FIGURE 7
Forest plot showing the occurrence of rebleeding between magnesium sulfate and the control group.

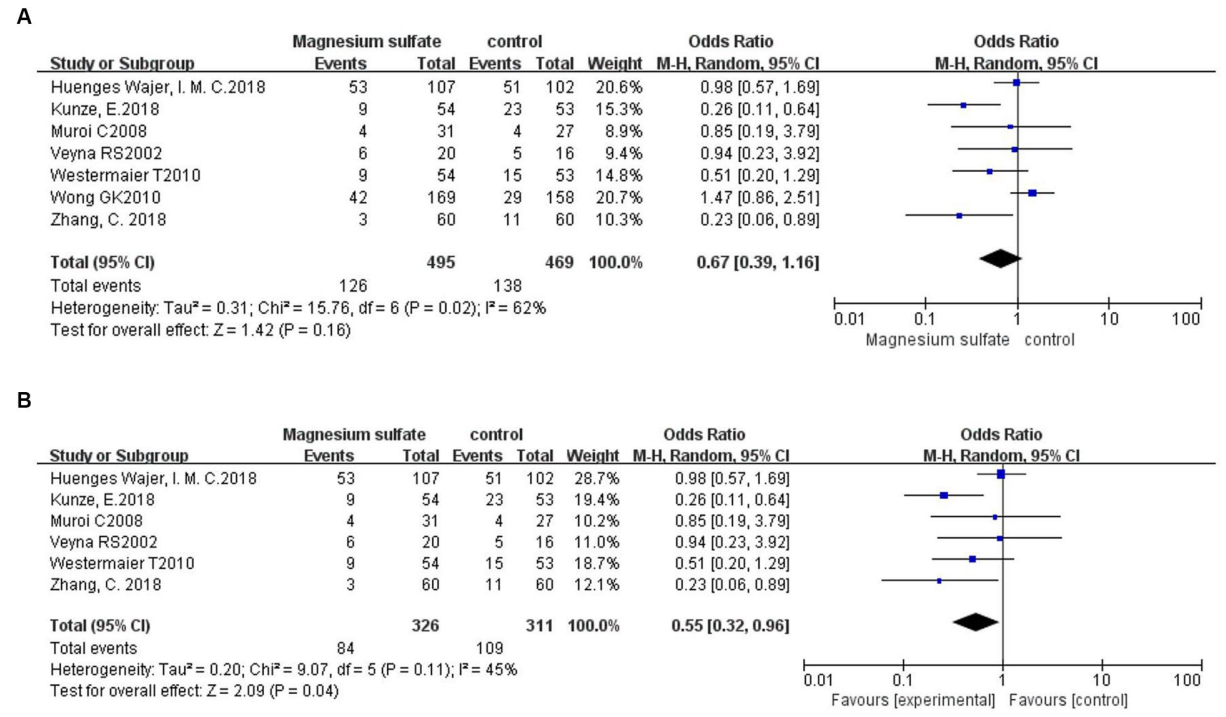

FIGURE 8
Forest plots showing the occurrence of neurological dysfunction between magnesium sulfate and the control group before **(A)** and after **(B)** sensitivity analysis.

post-aSAH outcomes. Further studies are warranted to verify these findings.

Our study had some limitations. First, in the included studies, the infusion days and maintenance doses of magnesium sulfate were different, which may have affected the results of our analysis. Second, although the number of patients exceeded 3,000, the number of patients with some outcomes was relatively small, especially for the rebleeding outcome, making it difficult to obtain statistical differences. Third, the length of follow-up varied between the included studies, subacute and late complications were more likely to be reported in studies with longer follow-up periods.

In conclusion, the present meta-analysis provides evidence supporting the superiority of magnesium sulfate over standard treatments for reducing the occurrence of CV, DCI, secondary cerebral infarction, and neurological dysfunction in patients with aSAH. Limited by the differences between the studies and the relatively small sample sizes included, no significant differences were observed in the outcomes of rebleeding and mortality between magnesium sulfate and standard treatment groups. Further randomized trials with larger sample sizes are required to confirm these findings.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

HZ, XG, XH, and YX: drafting the original manuscript and interpretation of the data. ZP and FZ: critical revision of the

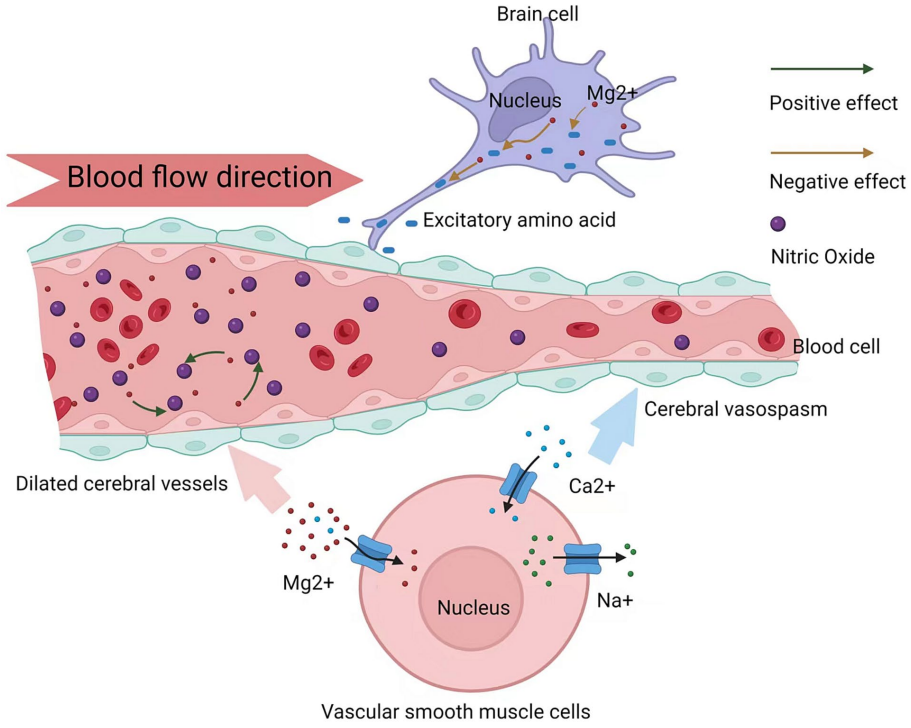

FIGURE 9
Mechanism plot of magnesium sulfate in preventing poor outcomes of aneurysmal subarachnoid hemorrhage.

manuscript. LW and LY: conception and design of the study. WG and CK: literature search. CC: data extraction. WH: drafting the figures and tables. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association between inflammatory bowel disease and risk of stroke: a systematic review and meta-analysis of cohort studies

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Background/objectives: Recently, four meta-analyses have explored the association between inflammatory bowel disease (IBD) and the risk of stroke. These studies have demonstrated that people with IBD may be at an increased risk of stroke. However, some limitations such as high heterogeneity and the lack of uniformity in the types of research, especially the reuse of some sample sizes, cannot be neglected. These factors reduce the credibility of their research conclusions. Therefore, we conducted a meta-analysis to explore this possible association.

Methods: PubMed, Embase, and Web of Science were searched from inception to 30 June 2023. A random effects model with the generic inverse variance method was used in this meta-analysis. The Review Manager software was used to obtain all relative risks (RRs) and their 95% confidence intervals (CIs). Publication bias was tested, and sensitivity and subgroup analyses were conducted to explore possible heterogeneities.

Results: This meta-analysis included 12 cohort studies (involving 4,495,055 individuals). Meta-analysis of these data has shown that IBD was associated with an increased risk of stroke (RR = 1.19, 95%CI:1.14-1.24, $p < 0.00001$). Our results were stable and robust in subgroup and sensitivity analyses.

Conclusions: Our results suggest that IBD is associated with an increased risk of stroke. To reduce the incidence of stroke, patients with IBD are encouraged to undergo stroke risk assessments, especially for young female patients; assessing the risk of ischemic stroke is of particular importance. Prospective studies considering stroke subtypes, IBD severity and treatments, regions, and other confounding factors are needed to further explore the nature of each association.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, identifier CRD42022373656.

KEYWORDS

IBD, stroke, risk, meta-analysis, systematic review

1 Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disease in the gastrointestinal tract, with Crohn's disease (CD) and ulcerative colitis (UC) being types of the condition. The epidemiology of IBD has changed significantly compared to the past. The highest rate of inflammatory bowel disease (IBD) is observed in the Western world, yet in newly industrialized countries in Asia, Africa, and Latin America, the incidence of IBD is increasing at a rapid rate (1–3). With its continual growth on a global scale, IBD has become an immense economic strain on health systems and a major healthcare issue across the world (4).

According to the Global Burden of Disease 2019, stroke has become the second leading cause of death and the third leading cause of disability and death combined globally. From 1990 to 2019, the total number of stroke events rose by 70.0%, epidemic stroke increased by 85.0%, and stroke deaths increased by 43.0% (5). The World Stroke Report indicates that in 2019, more than 120 million people died from stroke and related diseases (6, 7), resulting in a huge economic burden and psychological distress for families and society (8). Furthermore, according to some studies, it has been estimated that ∼2 million adolescents suffer from ischemic strokes annually, which makes up 15–18% of all ischemic strokes globally, with the stroke rate among the younger generation also increasing (9–12). It is yet to be determined precisely what causes stroke, however, some studies have demonstrated that an immune inflammatory response can be detrimental to the pathophysiology of stroke (13–15).

Studies have revealed a close association between IBD and a range of neurological disorders, including Parkinson's disease, dementia, multiple sclerosis, and depression (16–19). Given the growing prevalence of stroke, it is worth investigating whether IBD could be a potential risk factor for stroke. Previously, four meta-analyses have found that IBD is a risk factor for stroke (20–23). Although these studies have reached consistent conclusions, we also found that these studies have high heterogeneity, a small or incomplete number of included articles, and a lack of uniformity in the types of research. These reasons led to the conclusion that these articles should be treated with caution. Therefore, to establish whether IBD is a contributing factor for stroke, we conducted a systematic review and meta-analysis by scrutinizing all the cohort studies in the relevant databases and analyzing the data collected.

2 Methods

2.1 Protocol and registration

We performed the systematic review and meta-analysis in accordance with the PRISMA (the Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (24) reporting guidelines. This review protocol was prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO Registration Number: CRD42022312797).

2.2 Search strategy

We conducted a comprehensive search of PubMed, Embase, and Web of Science from inception to 30 June 2023 to identify all studies related to the association between inflammatory bowel disease (IBD) and stroke. The following keywords were used in our search strategies: (inflammatory bowel disease OR ulcerative colitis OR Crohn's disease) AND (stroke OR cerebrovascular disorder OR cerebral infarction OR cerebral hemorrhage). We conducted our search combining MeSH terms with text word searching, without any language restriction. The online Supplementary material (Supplementary Table 1) presents the details of the retrieval strategy for PubMed. In addition, we manually searched the reference lists of all relevant articles to ensure completeness.

2.3 Study selection

The included studies met the following inclusion criteria: (1) cohort studies; (2) the exposure was IBD and the outcome was stroke appearing after the diagnosis of IBD; and (3) studies reported relative risk (RR), hazard ratio (HR), or incidence rate ratio (IRR) with 95% confidence interval (CI) for stroke incidence or provided the original data for the calculation. The exclusion criteria were as follows: (1) laboratory studies, abstracts, reviews, meta-analyses, comments, letters, and case reports; (2) articles without sufficient data; (3) IBD appearing after the diagnosis of stroke; and (4) the study did not provide sufficient data to calculate the RR, HR or IRR and 95% CI. Studies were independently screened by two reviewers who read titles and abstracts and obtained the full text of potentially relevant articles based on the inclusion and exclusion criteria. Any differences were resolved by consensus.

2.4 Data extraction

We extracted the following information from each eligible study: the first author, the year of publication, districts, study subjects, sample size, follow-up duration, type of IBD and stroke, mean age or age of the group, sex, the proportion of males, and RR or HR (adjusted and unadjusted) with their 95%CI. Discrepancies were settled with mutual agreement by two reviewers who independently extracted the data from each included study.

2.5 Assessment of quality

The Newcastle-Ottawa Scale (NOS) (25), which is specially designed for observational and non-randomized studies, was used to evaluate the quality of the included articles. It uses a star system (ranging from 0 to 9 stars) to assess the quality of a study based on three domains: selection (four stars), comparability (two stars), and outcome/exposure (three stars). The number of stars signifies the quality of an article: 7–9 stars being high-quality, 4–6 stars being moderate quality, and 1–3 stars being low-quality.

2.6 Statistical analysis

This study aimed to investigate the association between IBD and the occurrence of ischemic stroke, hemorrhagic stroke, and unclassified stroke. Meta-analyses were performed using the Review Manager 5.3 (Cochrane Collaboration, Copenhagen, Denmark). RR and 95% CI from each study were calculated using a random-effects model, the generic inverse variance method of DerSimonian and Laird. We used Cochran's Q-test and I^2 statistic to evaluate heterogeneity among studies. Cochran's Q-test was used to evaluate the heterogeneity, $P < 0.10$ for the Q-test was considered statistically significant and I^2 value was used to assess the degree of heterogeneity. If I^2 values were <25%, we considered low heterogeneity, values in the range of 26%-50% were considered as having medium heterogeneity, and above 50% as having high heterogeneity. When the heterogeneity was >50%, it was necessary to employ a random effects model to combine the data; otherwise, a fixed effects model was used. Sensitivity/subgroup analyses were performed according to the type of IBD and stroke, race, age, and sex of study participants, follow-up period, and adjustment for confounders to explore the potential sources of heterogeneity. Additionally, the funnel plot and Egger's regression asymmetry were used to evaluate the potential of publication bias with the STATA/SE software (Version 12.0, STATA Corporation, Texas, USA).

3 Results

3.1 Selection

As specified in the PRISMA flow diagram, there were 3,431 potentially relevant articles retrieved from the three electronic databases using the initial search strategy. A total of 1,269 duplicates were excluded. By reading the titles and abstracts, we obtained 68 records, of which 12 articles were finally included after reading the full texts (Supplementary Figure 1).

3.2 Study characteristics

A total of 12 cohort studies (26–37) met our inclusion criteria; the main characteristics of the included studies were listed in Table 1. The meta-analysis involved a total of 4,495,055 individuals. The sample size among the included studies varied widely, from 8,060 participants (28) in a Canadian study to 455,950 participants (26) in the United Kingdom Biobank study. The average age ranged from 36.51 to 56.7 years, and the proportion of males ranged from 41.5% to 61%, except for one study (37) that did not mention the male-to-female ratio. The follow-up period also varied from 1 to 16.6 years. Two of the articles (27, 29) did not classify IBD as CD or UC. While only four articles (28, 31, 35, 37) defined the type of stroke. The studies were conducted in different regions, with eight studies (26, 27, 29, 32, 33, 35–39) being conducted in Europe, one study in North America (28), and three studies in Asia (30, 31, 34, 40, 41). According to the quality evaluation of the Newcastle-Ottawa Scale (NOS) results, three articles were of medium quality and nine articles were of high quality (see Supplementary Table 4).

3.3 Association between IBD and risk of stroke

In all, 12 studies confirmed the link between IBD and stroke risk. A pooled analysis showed that IBD was significantly associated with an increased stroke risk ($n = 17$, RR = 1.19, 95%CI:1.14–1.24, $p < 0.00001$ Supplementary Figure 2). Due to the relatively high heterogeneity ($I^2 = 59\%$, $p = 0.001$, see Supplementary Figure 2), to further explore the potential sources of heterogeneity, we performed several subgroup analyses. Details of all subgroup analyses are provided (see Table 2 and Supplementary Figures 3–9). In a subgroup analysis stratified by type of IBD, we found that stroke was positively associated with the risk of CD ($n = 11$, RR = 1.30, 95%CI:1.20–1.41, $p < 0.00001$; $I^2 = 65\%$ Supplementary Figure 3), UC($n = 11$, RR = 1.11, 95%CI:1.06–1.16, $p < 0.00001$; $I^2 = 36\%$ Supplementary Figure 3) and any IBD subgroups ($n = 9$, RR = 1.18, 95%CI:1.14–1.21, $p < 0.00001$; $I^2 = 0\%$ Supplementary Figure 3). In subgroup analysis stratified by the follow-up period, we found significant positive association between IBD and stroke risk for patients with a follow-up period of less than 5 years ($n = 8$, RR = 1.21, 95%CI:1.17–1.24, $p < 0.00001$; $I^2 = 73\%$ Supplementary Figure 4) and more than or equal to 5 years ($n = 9$, RR = 1.14, 95%CI:1.10–1.17, $p < 0.00001$; $I^2 = 0\%$ Supplementary Figure 4). It is well known that age, sex, and race are also risk factors for stroke, so we performed subgroup analyses of patients stratified by these variables. In subgroup analysis stratified by age, we found a significant positive association between IBD and risk of stroke with the following results: those aged more than or equal to 40 years ($n = 12$, RR = 1.22, 95%CI:1.10–1.35, $p = 0.0001$; $I^2 = 80\%$ Supplementary Figure 5) and those aged under 40 years old ($n = 8$, RR = 1.46, 95%CI:1.17–1.82, $p = 0.0007$; $I^2 = 63\%$ Supplementary Figure 5). In subgroup analysis stratified by sex, we found a significant positive association between IBD and risk of stroke with the following results: females ($n = 10$, RR = 1.30, 95%CI:1.18–1.42, $p < 0.00001$; $I^2 = 68\%$ Supplementary Figure 6) and males ($n = 10$, RR = 1.12, 95%CI:1.06–1.19, $p < 0.0001$; $I^2 = 31\%$ Supplementary Figure 6). In the subgro up analysis by race, we found a significant positive association between IBD and stroke risk in Caucasians ($n = 12$, RR = 1.21, 95%CI:1.16–1.27, $p < 0.00001$; $I^2 = 64\%$ Supplementary Figure 7) and Asians ($n = 5$, RR = 1.10, 95%CI:1.02–1.19, $p = 0.02$; $I^2 = 17\%$ Supplementary Figure 7). In the subgroup analysis stratified by adjustment for confounders, we found a significant positive association between IBD and stroke with adjusted RR ($n = 15$, aRR = 1.17, 95%CI:1.14–1.19, p < 0.00001; $I^2 = 63\%$ Supplementary Figure 8) and crude RR ($n = 4$, cRR = 2.69, 95%CI:2.61–2.78, $p < 0.00001$; $I^2 = 99\%$ Supplementary Figure 8). When exploring the relationship between IBD subtypes and stroke subtypes, we found that CD and UC were associated with the incidence of ischemic stroke (CD $n = 2$, RR = 1.23, 95%CI:1.14–1.32, $p < 0.00001$; $I^2 = 22\%$; UC $n = 2$, RR = 1.14, 95%CI:1.03–1.27, $p = 0.009$; $I^2 = 76\%$ Supplementary Figure 9), but they were not associated with hemorrhagic stroke (CD $n = 2$, RR = 1.38, 95%CI:0.83–2.30, $p = 0.21$; $I^2 = 93\%$; UC $n = 2$, RR = 1.16, 95%CI:0.85–1.58, $p = 0.35$; $I^2 = 87\%$ Supplementary Figure 9). No evidence of publication bias was found in our analysis of the association between IBD and the risk of stroke; the visual inspection of the funnel plot and the Egger's test (P = 0.119 Supplementary Figures 10, 11)

TABLE 1 Main characteristics of included studies.

References	Region	Study design	Follow-up duration (years)	Type of IBD	Type of stroke	Sample size	Mean age or age group (years), male (%)
Alayo et al. (26)	UK	Cohort	12.4	CD/UC	Unspecified	455,950	56.7 (45.4)
Baean-Diez et al. (27)	Spain	Cohort	6	IBD	Unspecified	9,544	56 (44%)
Bernstein et al. (28)	Canada	Cohort	16.1-16.6	CD/UC	Subarachnoid-hemorrhage, intracranial hemorrhage, ischemic stroke	8,060	CD:36.51 (41.5%) UC:42.42 (48.7%)
Choi et al. (30)	Republic of Korea	Cohort	4.9	CD/UC	Unspecified	37,696	39.4 (61.0%)
Tanislav et al. (36)	Germany	Cohort	1-5	CD/UC	Unspecified	23,894	47 (45.5%)
Huang et al. (31)	Taiwan	Cohort	7	CD/UC	Ischemic stroke	18,392	44.8 (45.1%)
Kirchgesner et al. (32)	France	Cohort	3.5	CD/UC	Unspecified	210,162	45 (46.2%)
Kwon (34)	Republic of Korea	Cohort	8-11	CD/UC	Unspecified	2,746,988	55.65 (61.31%)
Sun et al. (35)	Sweden	Cohort	12	CD/UC	Ischemic and hemorrhagic stroke	491,993	43 (48.57%)
Kristensen et al. (33)	Denmark	Cohort	6.8	CD/UC	Unspecified	260,774	43 (46.5%)
Card et al. (29)	UK	Cohort	5.9	IBD	Unspecified	185,587	45 (47.7%)
Zöller et al. (37)	Sweden	Cohort	4	CD/UC	Ischemic and hemorrhagic stroke	43,832	NR

both provided support for this conclusion. Moreover, no significant changes were observed in the direction and magnitude of the pooled estimates after excluding studies one by one from the meta-analysis. This suggests that the meta-analysis results are reliable and stable (Supplementary Table 5, Supplementary Figure 12).

4 Discussion

Our research was aimed at synthesizing the best available evidence on the association between IBD and stroke risk. Compared with patients without IBD, our meta-analysis of 12 cohort studies revealed that patients with IBD have a significantly higher incidence rate of stroke (random-effects RR = 1.19, 95%CI 1.14–1.24; I^2 = 59%). Our results remained consistent after subgroup analyses by race, sex, age, and year of follow-up, underscoring the robustness of our results. Furthermore, our results are also in line with previous research findings (20–23). To the best of our knowledge, our team conducted, for the first time, further research on the relationship between the IBD subtype and the risk of stroke subtype.

Of the five observational studies included in the previous meta-analysis, Singh et al. (23) reported that individuals with IBD were 18% more likely to suffer from stroke (adjusted OR, 1.18; 95%CI, 1.09–1.27). Moreover, the risk of stroke was higher in female patients (adjusted OR, 1.28; 95%CI, 1.17–1.41) compared to male patients (adjusted OR, 1.11; 95%CI, 0.98–1.25). Additionally, younger individuals (adjusted OR, 1.84; 95%CI, 1.28–2.66) were more likely to experience stroke than older patients (adjusted OR, 1.11; 95%CI, 1.02–1.21). This study only included four case-control studies and one cohort study. Case-control studies are more prone to recall bias, selection bias, and reverse causation, making them less reliable for establishing causality than cohort studies. Furthermore, their research only included Caucasians. Given these reasons, their conclusions need to be further verified. A meta-analysis that included eight articles (one case-control and seven cohorts) conducted by Xiao et al. (22) showed that, when compared to male, older, UC-type, and Caucasian IBD patients, female, younger, CD-type, and Asian patients had a higher risk of stroke. These results are basically consistent with our results and partially match the Yuan and Chen studies when it comes to race. However, Yuan et al. (21) conducted a subgroup analysis that revealed that the risk of stroke was higher in UC patients (adjusted RR, 1.32; 95%CI, 1.17–1.50) than in CD patients (adjusted RR, 1.17; 95%CI, 0.95–1.45), which is a contrast to our and Xiao's findings. The reason for this risk difference may have been observed by Ha et al. (42), who found no elevation of cerebrovascular occlusion risk in IBD patients (both UC and CD), however, this conclusion should be taken with caution. The authors suggested that cerebrovascular occlusion is the same as stroke, yet we held that a stroke must cause necrosis of brain tissue. Due to the presence of compensatory mechanisms in cerebral blood vessels, cerebrovascular occlusion does not always result in a stroke. The discrepancy between the findings of Yuan et al. and our study may be attributed

TABLE 2 Subgroup analyses of the association between IBD and risk of stroke.

Subgroup	No. of studies	RR (95%CI)	$P_{association}$	I^2 (%)	$P_{heterogeneity}$
Overall studies	17	1.19 (1.14–1.24)	P < 0.00001	59%	P = 0.001
Type of IBD					
Any IBD	9	1.18 (1.14–1.21)	P < 0.00001	0%	P = 0.83
CD	11	1.30 (1.20–1.41)	P < 0.00001	65%	P = 0.002
UC	11	1.11 (1.06–1.16)	P < 0.00001	36%	P = 0.11
Follow-up period					
Less than 5 years	8	1.21 (1.17–1.24)	P < 0.00001	73%	P = 0.0005
More than or equal to 5 years	9	1.14 (1.10–1.17)	P < 0.00001	0%	P = 0.72
Adjustment for confounders					
cRR	4	2.69 (2.61–2.78)	P < 0.00001	99%	P < 0.00001
aRR	15	1.17 (1.14–1.19)	P < 0.00001	63%	P = 0.0005
Age					
<40 years	8	1.46 (1.17–1.82)	P = 0.0007	63%	P = 0.009
≥40 years	12	1.22 (1.10–1.35)	P = 0.0001	80%	P < 0.00001
Race					
Caucasian	12	1.21 (1.16–1.27)	P < 0.00001	64%	P = 0.001
Asian	5	1.10 (1.02–1.19)	P = 0.02	17%	P = 0.30
Sex					
Male	10	1.12 (1.06–1.19)	P < 0.0001	31%	P = 0.16
Female	10	1.30 (1.18–1.42)	P < 0.00001	68%	P = 0.0008
Type of IBD and stroke					
CD (IS)	2	1.23 (1.14–1.32)	P < 0.00001	22%	P = 0.26
UC (IS)	2	1.14 (1.03–1.27)	P = 0.009	76%	P = 0.04
CD (HS)	2	1.38 (0.83–2.30)	P = 0.21	93%	P = 0.0001
UC (HS)	2	1.16 (0.85–1.58)	P = 0.35	87%	P = 0.006

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis; HS, hemorrhagic stroke; IS, ischemic stroke; cRR, crude relative ratio; aRR, adjustment relative ratio; CI, confidence interval.

to the varying sample sizes of stroke patients included in each study. Given these reasons, our conclusion may be more credible. All in all, compared with the article of Singh et al. (23), the other three articles (20–22) increased the number of cohort studies and expanded the scope of the population, making their conclusions more credible and increasing the scope of application of the conclusions.

However, compared with the previous four articles, our research has the largest number of cohort studies ($n = 12$) and the largest sample size ($n = 4{,}495{,}055$), especially by including newer cohort studies (26, 34–36, 43) published in 2021 and 2023, and a more thorough statistical analysis was conducted (e.g., preselected subgroup analyses of the types of IBD, sex, age, race/ethnicity, and duration of follow-up were conducted, and the Egger test was used to evaluate publication bias). Although the findings of our research are in line with the previously published meta-analyses on IBD and stroke, based on these advantages, our study provides relatively strong evidence that IBD is significantly associated with an increased risk of stroke.

Although the mechanisms underlying the link between IBD and stroke risk are not yet fully understood, some hypotheses exist. First, as is well known, IBD is a chronic non-specific intestinal inflammatory disease. Some studies found that C-reactive protein, adherent molecules, and inflammatory cytokines are overexpressed in patients with IBD (44–46); these chronic inflammatory factors contribute to vascular endothelial dysfunction, carotid intimal thickening, and abnormal carotid atherosclerosis, all of which eventually lead to stroke (47–49). Second, the destruction of the normal intestinal microenvironment may aggravate this kind of inflammatory reaction (50, 51); due to intestinal absorption dysfunction, insufficient absorption of vitamin B6 can lead to an increase in homocysteine, which can also promote the

occurrence of stroke (52–54). Third, our study shows that the incidence of stroke in women is higher than that in men (women: RR = 1.30, 95%CI, 1.18–1.42; men: RR = 1.12, 95%CI, 1.06–1.19), which is contrary to our traditional view. The reason for this is that the level of C-reactive protein is higher in women than in men, and the oral contraceptive pill, a blood clotting agent, is used by young women with IBD (55).

Our results revealed considerable heterogeneity (random-effects RR = 1.19, 95%CI, 1.14–1.24; I^2 = 59%), so we conducted subgroup analyses to identify the sources of this heterogeneity. However, after considering the IBD and stroke subtypes, age, follow-up time, sex, and race, we concluded that they were not the main sources of heterogeneity. In addition, to evaluate the stability of pooled results, we conducted a sensitivity analysis with the omission method (i.e., omitting one study at a time); the results of our meta-analysis for IBD and stroke were observed to be relatively stable by this method.

This study has some strengths and limitations that should be acknowledged. First, compared with previous meta-analyses on this topic, our research encompasses the newest and most extensive set of literature, and the estimated effect sizes were the same in all the included studies, which can minimize heterogeneity. Second, our team found that some articles (11, 29, 31, 33, 38–41) featured sample sizes from the same database, which could compromise the accuracy of the results. Therefore, we conducted a thorough analysis of the sources of the sample size included in the article and excluded any articles that utilized duplicate databases, thus ensuring the authenticity and credibility of our conclusions. Third, we performed an extensive literature search and applied strict inclusion/exclusion criteria and rigorous quality assessment. Fourth, most of the included studies were of good quality and provided high-quality evidence on the topic. Lastly, due to the results with apparent heterogeneity, we conducted subgroup analyses by age, sex, race, duration of follow-up, and type of IBD and stroke to examine potential sources of heterogeneity. All these features make the conclusion more credible and convincing. While it has several strengths, we also acknowledge that some limitations should be pointed out. First, these articles are from various medical register databases, which may lead to incomplete or inaccurate extraction of important information, due to the patients having different social environments, educational experiences, and cultural customs. This information may result in the overestimation or underestimation of the association between IBD and stroke risk. Second, risk factors of cerebrovascular disease include uncontrolled risk factors, such as race, age, sex, heredity, and climate change, and controllable risk factors such as hypertension, diabetes, smoking, drinking, and obesity. However, the studies we included did not uniformly adjust all confounding factors, which may make the results difficult to interpret or confound associations. Third, most of the articles included in the discussion highlighted the relationship between IBD subtypes and stroke risk, however, only two articles (35, 37) discussed the relationship between IBD subtypes and stroke subtypes. There is a need for more research to confirm the specific relationship between the IBD subtype and stroke subtype. Fourth, IBD is a typical inflammatory disease, and an inflammatory reaction plays an important role in the pathogenesis of stroke. However, these articles did not mention the severity and treatment of IBD. It is necessary to further examine the relationship between the severity and treatment of IBD and the occurrence of stroke. Finally, we included eight articles (61.5%) from Europe, featuring the largest sample size, three (23.07%) from Asia, featuring a medium sample size, and only two (15.38%) from North America, featuring the smallest sample size. Therefore, the conclusion of this article is more suitable for European and Asian populations. Whether these observed findings can be extrapolated to other regions needs further verification.

5 Conclusions

Our findings point to a link between IBD and an elevated risk of stroke. To lessen the risk of stroke, it is recommended that patients with IBD have a stroke risk evaluation, especially young female patients; assessing the risk of ischemic stroke is of particular importance. To gain a fuller understanding of the association between the two, further research is necessary that takes into account factors such as stroke subtype, IBD severity and treatment, region, and other potential confounders.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

J-SF and MW performed the literature search, drafted the manuscript, and designed the systematic review. MW and B-cS screened the literature. NC, Q-BZ, and J-SF extracted data and assessed the quality. M-JH and YL analyzed and interpreted the data. MW, J-SF, and NC were responsible for the research design, data analysis, and manuscript revision. All authors gave their approval for the submission of the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1204727/full#supplementary-material

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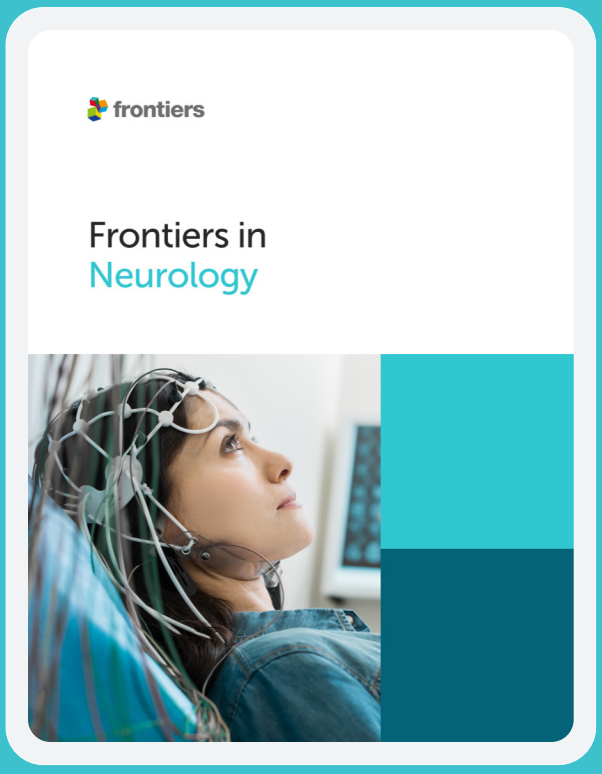

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